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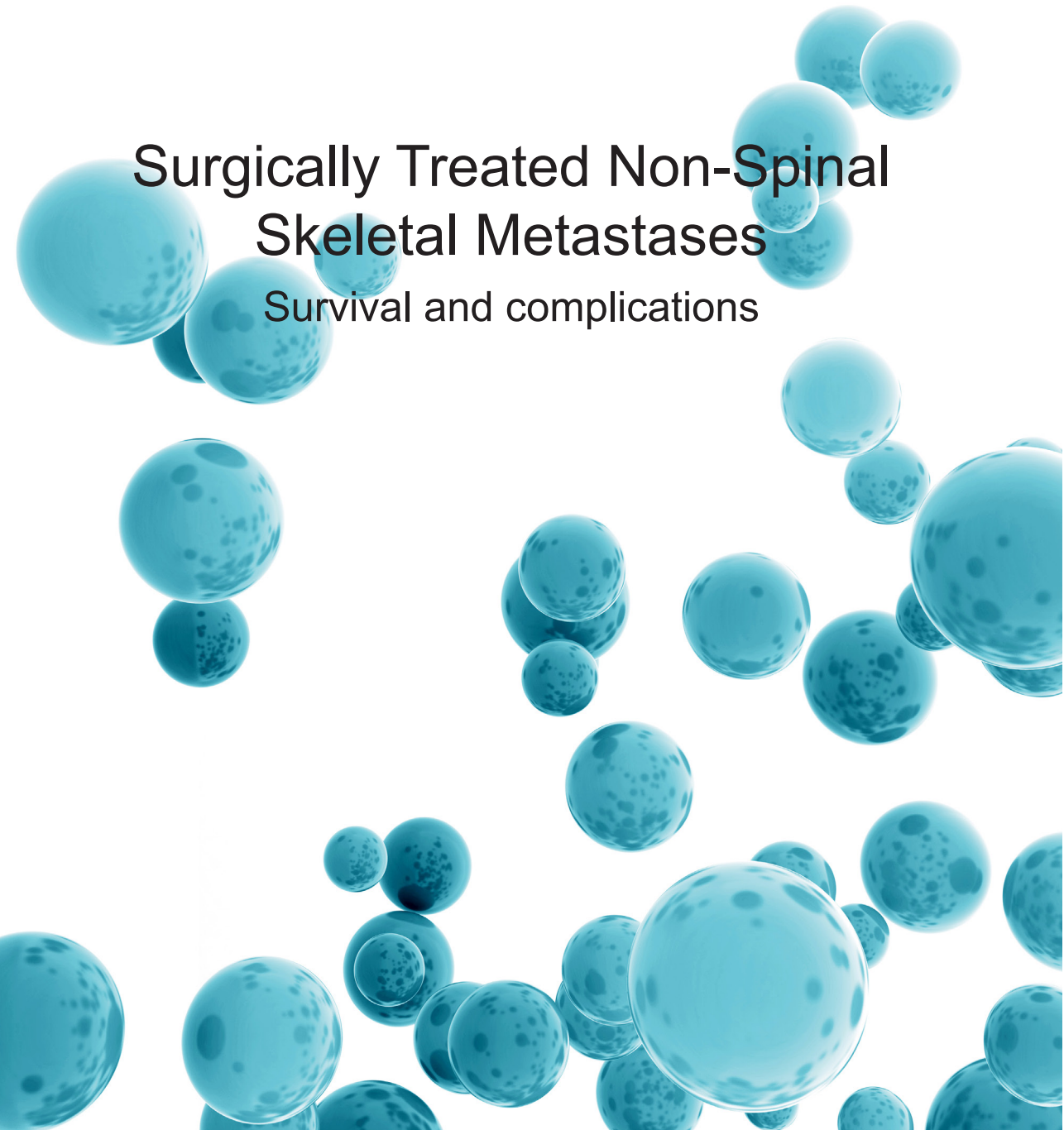
MAIRE RATASVUORI

Surgically Treated Non-Spinal Skeletal Metastases

Survival and complications



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ACADEMIC DISSERTATION
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the Board of the School of Medicine of the University of Tampere,
for public discussion in the small auditorium of building M,
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UNIVERSITY OF TAMPERE

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Dedicated to patients suffering from skeletal metastases

ABSTRACT

BACKGROUND The cancer burden is increasing, and although the treatment of different primary cancers has become very specialized and effective, the disease will eventually disseminate in some patients. Metastatic disease is the leading cause of death in cancer patients, with bone as one of the most common sites of metastasis after the lungs and liver. Skeletal metastases can dramatically decrease patients´ quality of life due to sharp pain and pathological fracture. Treatment of skeletal metastases is most often non-surgical, but when surgery is needed it varies from simple excisions to excessive resections and reconstructions with prostheses. Estimating survival is important in choosing the scope of treatment. This is the first thesis concerning surgical treatment of non-spinal skeletal metastases in Finland.

PATIENTS AND METHODS Patient data for the first and second study were based on the Scandinavian Sarcoma Group Skeletal Metastases Registry, world's largest metastases registry. A total of 1195 operated non-spinal skeletal metastases in 1107 patients were included in the first study. The scope of the second study was to study factors affecting survival in bone-seeking cancers, investigating patients with breast, lung, prostate, and kidney cancer. In the third study, the focus was on skeletal metastases in renal cell carcinoma and the effects of pre-operative embolization. In the fourth study, the focus was on venous thromboembolic events among patients who underwent surgery for pathological fractures.

RESULTS In 14% of patients, skeletal complications were the first sign of cancer. The overall patient survival rate after operating on metastases was 58% at 6 months, 41% at 1 year, and 2% after 5 years. Primary cancer, metastatic load, and overall health status could robustly estimate the survival. A scoring system was developed to improve to estimate the survival. Marginal resection in solitary

metastases in renal cell carcinoma increased survival compared to the intralesional surgery. Larger tumours had more intra-operative bleeding but, unexpectedly, we did not find pre-operative embolization beneficial. Reported complications were few, but there was an increased risk of thromboembolic events, which can be fatal.

CONCLUSION Survival depends on the primary tumour, metastatic load and surgical margins. Surgical treatment should be well designed. We need further collaboration between radiologists, oncologists, surgeons, and hematologists and in the future, we hope to create more accurate clinical practice guidelines and prevent complications, which can lead to premature death.

TIIVISTELMÄ

TAUSTA Syövän hoito on hyvin kehittynyttä, mutta osalla potilaista tauti lopulta leviää. Luusto on yksi yleisimmistä syövän leviämispaikoista keuhkojen ja maksan jälkeen. Luustoetäpesäkkeitä hoidetaan kipulääkityksin ja sädetyksellä, mutta joskus voimakas kipu tai patologinen murtuma edellyttää kirurgista hoitoa. Kirurgiset tekniikat vaihtelevat yksinkertaisimmista naulauksista isoihin resektioihin ja tuumoriproteesien laittoon. Potilaan eliniän arvioiminen on tärkeää valittaessa eri hoitolinjojen välillä. Tämä on ensimmäinen väitöskirja luustoetäpesäkkeiden kirurgisesta hoidosta Suomessa.

POTILAAT JA MENETELMÄT Tutkimus perustuu laajaan skandinaaviseen rekisteriin syöpäpotilaista, jotka ovat joutuneet leikkaukseen luuston etäpesäkkeen vuoksi (Scandinavian Sarcoma Group Skeletal Metastases Registry). Ensimmäisessä tutkimuksessa tarkasteltiin tietoja kaikista rekisterissä olevista 1107 leikatusta potilaasta. Toisessa tutkimuksessa vertailtiin eloonjäämistä neljässä yleisimmässä luustoetäpesäkkeitä aiheuttavassa syövässä, rinta-, keuhko-, eturauhas- ja munuaissyövässä. Kolmannessa tutkimuksessa fokus oli munuaissyövässä ja leikkausta edeltävässä embolisaatiohoidossa. Neljännessä tutkimuksessa tutkittiin leikkauksen jälkeisten tromboembolisten komplikaatioiden yleisyyttä.

TULOKSET Patologinen murtuma oli ensimmäinen merkki syövästä 14 %:lla potilaista. Kokonaiseloonjääminen ortopedisen leikkauksen jälkeen oli 58 % kuuden kuukauden kohdalla, 41 % vuoden kohdalla ja vain 2 % viiden vuoden kohdalla. Primaaridiagnoosin, etäpesäketaakan ja yleistilan perusteella voidaan karkeasti arvioida eloonjäämisennustetta. Munuaissyövässä marginaalinen resektio yksittäisten etäpesäkkeiden kohdalla voi ennustaa parempaa selviytymistä. Isot etäpesäkkeet aiheuttivat enemmän leikkauksenaikaista verenvuotoa, mutta yllättäen leikkausta edeltävästä

embolisaatiohoidosta ei ollut tilastollista hyötyä. Raportoituja komplikaatioita oli vähän, mutta riski vakaviin tromboembolisiin komplikaatioihin on merkittävä.

YHTEENVETO Potilaita pitää hoitaa yksilöllisesti. Eloonjäämisennuste leikkauksen jälkeen on riippuvainen primaaridiagnoosista, etäpesäketaakasta ja leikkausmarginaaleista. Tarvitsemme lisää yhteistyötä ortopedien, onkologien, hematologien ja radiologien kanssa, jotta tulevaisuudessa voitaisiin tehdä tarkempia hoitosuunnitelmia, ja estää komplikaatioita, jotka voivat johtaa ennenaikaiseen kuolemaan.

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the original articles listed below. The publications are reprinted with permission from their copyright holder.

I Ratasvuori M, Wedin R, Keller J, Nottrott M, Zaikova O, Bergh P, Kalen A, Nilsson J, Jonsson H, Laitinen M. (2013) "Insight opinion to surgically treated metastatic bone disease: Scandinavian Sarcoma Group Skeletal Metastasis Registry report of 1195 operated skeletal metastasis." Surg Oncol. Jun;22(2):132-8

II Ratasvuori M, Wedin R, Hansen BH, Keller J, Trovik C, Zaikova O, Bergh P, Kalen A, Laitinen M. (2014) "Prognostic role of en-bloc resection and late onset of bone metastasis in patients with bone-seeking carcinomas of the kidney, breast, lung, and prostate: SSG study on 672 operated skeletal metastases." J Surg Oncol. 110:460-365

III Ratasvuori M, Sillanpää N, Wedin R, Trovik C, Hansen B, Laitinen M (2016) "Surgery of non-spinal skeletal metastases in renal cell carcinoma No effect of embolization?" Acta Orthop. Apr; 87(2):183-8.

IV Ratasvuori M, Lassila R, Laitinen M. (2016) "Venous Thromboembolism after Surgical Treatment of Non-Spinal Skeletal Metastases An Underdiagnosed Complication." Thromb Res. May; 141:124-8.

ABBREVIATIONS

ALP serum alkaline phosphatase
CT computed tomography
CI cumulative interval
BMI body mass index
CatK cathepsin K
DOAC direct oral antigoaculants
DVT deep venous thrombosis
EBRT external beam radiotherapy
EPR endoprosthetic replacement
HR hazard ratio
IBL intraoperative estimated blood loss
IFN interferon
IL interleukin
K-M Kaplain-Meier analysis
LMWH low molecular weight heparin
MRI magnetic resonance imaging
MWA microwave ablation
PET positron-emission tomography
PE pulmonary embolism
Qol quality of life
RANK receptor activator of NF-kappaB
RCC renal cell carcinoma
RFA radiofrequency ablation
RR risk ratio
RT radiotherapy
SRE skeletal related event
SSG Scandinavian Sarcoma Group
THA total hip arthroplasty
VTE venous thromboembolic event

1 INTRODUCTION

The cancer burden is increasing. In the USA, cancer has surpassed heart disease as the primary cause of death in all but the very elderly. (Twombly 2005) In Nordic countries, the prevalence of cancer has increased 100 cases per 100 000 people year and more people overall are living with a cancer diagnosis. (Engholm, Ferlay et al. 2010)

Although the treatment of different primary cancers has become very specialized and effective, the disease will eventually disseminate in some patients. Metastases are the leading cause of death in these cancer patients. Metastasis results from haematogenous or lymphagenous spreading of tumour cells from their site of origin to other organs. The organ distribution of metastases depends on the type and location of the primary tumour; for example, breast and prostate cancer often metastasize to bone. (Chambers, Groom et al. 2002) Overall, bone is one of the most common sites of metastasis, along with the lungs and liver. (Mundy 1997) Diagnosis of skeletal metastasis indicates that the disease is incurable, which may cause anxiety. Other reasons why skeletal metastases can decrease the quality of life (QoL) are sharp pain, hypercalcaemia, anaemia, neurological deficiencies including paraparesis, and pathological fracture, otherwise known as skeletal-related events (SREs). (Hansen, Keller et al. 2004, BH Hansen 2009) Skeletal metastases are primarily treated with different cancer medications and with radiotherapy. If the pain is infernal despite these treatments, or if there is pathological or impending fracture, surgery may be needed. The surgical options vary from intramedullary nailing without tumour removal to excessive resection and reconstruction with the customized tumour prosthesis. In surgery, immediate pain relief and improved functional status are particularly important.

Estimating survival is important in choosing the extent of treatment. Overtreatment is not allowed in patients with short life expectancy, but some patients have prolonged survival. Several articles have addressed surgical treatment of skeletal metastases (Nathan, Healey et al. 2005, Wedin and Bauer 2005, Bickels, Dadia et al. 2009) and survival,

(Hansen, Keller et al. 2004, Saad, Lipton et al. 2007, Katagiri, Okada et al. 2014) but there is still a lack of universal treatment recommendations. The indications for surgery are debated, among other aspects, including whether impending fractures should be operated on, surgical methods (nailing versus prosthesis), and operation strategy (marginal or intralesional removal). Current clinical practice relies on strong expert opinions and literature with several limitations, especially a low number of surgical patients.

In addition, surgical treatment has a risk of complications, such as infections and mechanical failures, which can be disastrous in this fragile patient group. Reported complication rates are approximately 17%, (Wood, Racano et al. 2014) but there may be some inaccuracies in reports as venous thromboembolic events (VTEs) have had little attention given how well-known a risk factor cancer is for VTEs. VTEs do not only increase morbidity but also mortality among cancer patients. Patients who are treated with chemotherapy and have metastatic disease have additional risks for VTE. (Lip, Chin et al. 2002, Blom, Vanderschoot et al. 2006) The management of skeletal metastases is no longer a simple task of fixing a fracture, but involves multidisciplinary coordination between radiologists, oncologists, and surgeons. Cancer patients consume progressively more hospital resources as metastatic disease and subsequent SREs develop. (Pockett, Castellano et al. 2010) A significant increase in median charges is associated with surgery. (Antczak, Trinh et al. 2014)

More information is needed on surgical treatment so the most suitable treatment strategies can be planned for suffering patients and health care funds could be targeted correctly. Metastatic disease is no longer a death sentence condemning patients to "terminal care." (Agarwal and Nayak 2015) The treatment should be well designed, and high-standard surgical services should be offered.

This doctoral thesis was initiated to investigate survival and complications of surgery in non-spinal skeletal metastases. We have a large database on surgical patients with skeletal metastases and are grateful to have collaborations with other Scandinavian units. The first study was to gain insight into skeletal metastases. The second study evaluated four common primary tumours inducing skeletal metastases, how they differ, and to point out that, patients with skeletal metastases cannot be treated as a single patient population. The third study

investigated survival after surgical management of skeletal metastases of renal cell carcinoma (RCC) and the role of pre-operative embolization. The fourth study addressed the under-diagnosed complication in skeletal metastases surgery, VTEs. This is the first thesis in Finland concerning surgical treatment of non-spinal skeletal metastases.

2 REVIEW OF LITERATURE

2.1 Biology of skeletal metastases

In cancer, some of the body's cells begin to divide without stopping and spread into surrounding tissues. Cancer is a highly diverse disease characterized by mutations influencing angiogenesis and apoptosis. There are differences between cancers originating from different organs or tissues, and even among cells within a single tumour. (Aktipis and Nesse 2013) Nonetheless, all cancerous tumours are malignant, which means that they can not only spread into nearby tissues, but can also break off and travel to distant sites in the body through the blood or lymph system and form new tumours (i.e., metastasize). Bone provides an especially attractive site for metastasis for a variety of reasons, including that the bone matrix contains a rich storehouse of growth factors (e.g. insulinlike growth factor -1, transforming growth factor-beta) released during bone turnover, factors that are important in the metastatic process. (Bussard, Gay et al. 2008)

Metastasis to bone is a complicated process. In the last decade, crucial research into skeletal metastasis has been conducted in the field of molecular and cellular biology, identifying various genes involved in bone remodelling and revealing genetic determinants involved in tumour progression and metastasis. Metastasis consists of a series of sequential steps. (Chambers, Groom et al. 2002) To put it more simply, metastatic tumour cells must first escape from a primary tumour, invade blood vessels, survive in the circulation, and travel by the development of new blood vessels to form a macroscopic tumour at the distant site. (Chambers, Groom et al. 2002) Thus, cancer cells must adapt their phenotype and behaviour to enable detachment from the primary tumour and subsequent colonization of bone. (Ottewell, O'Donnell et al. 2015)

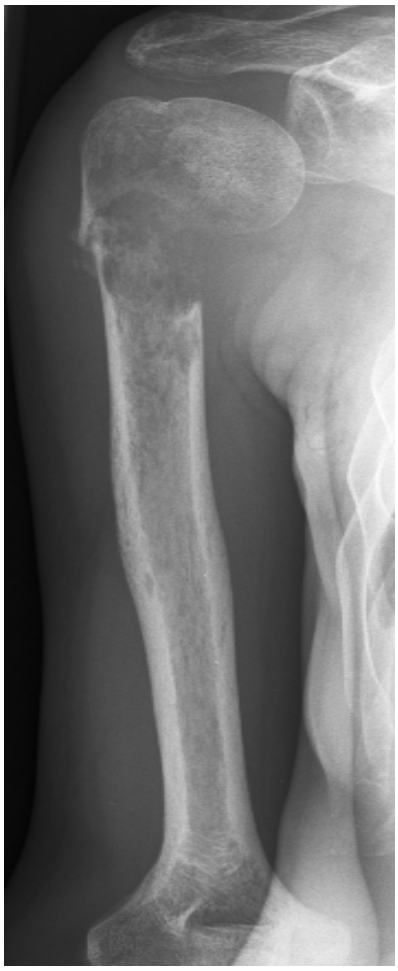


Figure 1. Osteolytic tumour lesion in the humerus of a lung cancer patient.

Osteoclasts are primary bone-resorbing cells in both normal and pathological states. Both locally produced cytokines and systemic hormones can regulate normal osteoclast formation. (Hofbauer, Rachner et al. 2014) Tumour cells secrete osteoclast-stimulating factors, as well as factors that inhibit osteoblast activity, leading to the formation of osteolytic metastatic lesions (Fig. 1). Interleukin (IL)-1, IL-6, parathyroid hormone-related protein (PTHrP), receptor activator of NF- kappaB (RANK ligand), and macrophage inflammatory protein-1-alpha have been implicated as mediating enhanced osteoclast formation and bone destruction. For example, in breast cancer PTHrP seems to be the major factor inducing osteoclast formation through upregulation of RANK ligand, which is a key factor for osteoclast differentiation and activation. (Roodman 2001) In addition, bone resorption is thought to increase tumour growth. (Zheng, Zhou et al. 2008)

Cancer cells may also promote the formation of metastatic lesions by releasing substances to manipulate osteoblast differentiation. When osteoblastic bone formation displaces osteoclastic bone resorption, osteoblastic lesions similar to sclerosis occur. Excessive bone growth then leaves bulges in the mineralized tissue (Fig. 2). (Clement-Demange and Clezardin 2015, Krzeszinski and Wan 2015) The differences are likely to reside in the differential interaction between tumour cells from different primary tumours and the bone environment, and both osteoblast and osteoclast activities can be advantageously modulated by cancer cells. (Bussard, Gay et al. 2008)

There is a high predilection to skeletal metastasis among several primary cancers, including RCC, lung cancer, thyroid cancer, prostate cancer, and breast cancer. (Roodman 2001) Research has attempted to understand the nuances of this organotropic spread. (Thobe, Clark et al. 2011) Bone has a large reserve of the above-mentioned growth factors, which are released and activated during bone resorption, creating fertile ground for tumour cells to grow. In addition, blood flow is high in areas of the bone marrow, allowing various cells to easily enter and exit. (Roodman 2001, Bussard, Gay et al. 2008) Tumour cells that metastasize to bone also usually use the same physiological mechanisms as hematopoietic stem cells homing to bone. (Ottewell, O'Donnell et al. 2015)

Furthermore, there is evidence that the frequency of evident skeletal metastases in hormone-independent prostate and breast cancer is determined by growth initiating influences within the bone microenvironment, not by the number of tumour cells initially seeding these sites. (Wang, Reeves et al. 2015)

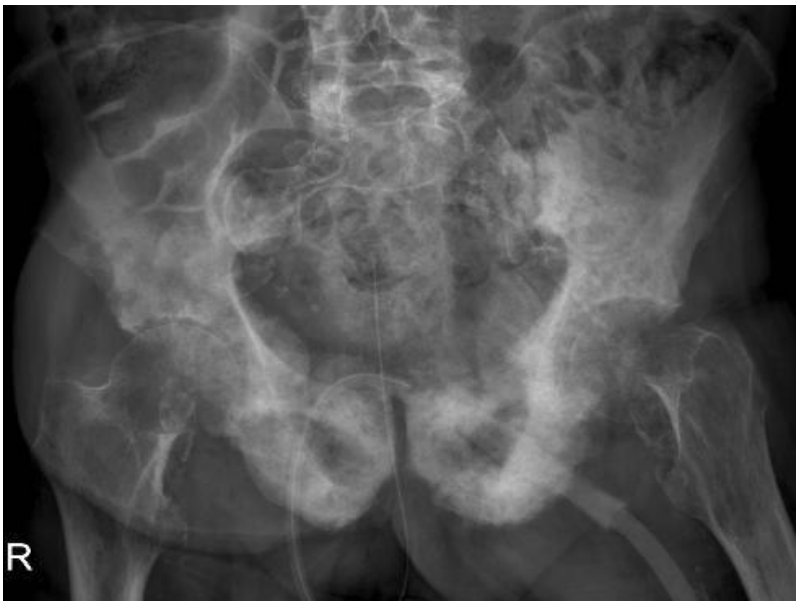


Figure 2. Osteoblastic tumour lesion in the pelvis of a prostate cancer patient.

2.2 Skeletal-related events

Cancer patients with skeletal metastases are at increased risk of experiencing severe morbidity due to complications, such as severe pain, nerve compression, pathological fracture, or hypercalcemia (i.e., SREs). (Roodman 2001, Ford, Jones et al. 2013) The main SRE is usually intractable pain, which results in a significantly decreased QoL. (Harris, Chow et al. 2009) Some patients paint the situation as "worse than death". (van den Hout, van der Linden et al. 2003) Pain can be caused by several mechanisms. Pressure can be increased due to tumour, microfractures, stretching of the periosteum, reactive muscle spasm, nerve root infiltration, or nerve compression. (Mercadante 1997) Nerve irritation can also be caused by the release of chemical mediators, such as the production of factors by osteoclasts. (Goblirsch, Zwolak et al. 2006)

Skeletal metastases weaken bones and can lead to pathological fracture. Twenty years ago lytic lesions destroying 50% or more of the diaphyseal cortex were determined to result in a 60-90% reduction in strength, thereby increasing the risk of fracture significantly. (Hipp, Springfield et al. 1995) Ten years later, a biomechanical study examining the effect of the location of metastatic lesions on proximal femoral strength showed that the strength of specimens with inferomedial femoral neck defects was less than of those in other locations. Anteromedial defects have been shown to be weakest at the lesser trochanter. (Keyak, Kaneko et al. 2007) The quality of skeletal metastases plays an important role, as breast cancer patients, who usually have lytic skeletal metastases, have higher rates of pathological fracture than patients with prostate cancer, in whom metastatic lesions are more often blastic. (Saad, Lipton et al. 2007)

Cancer-induced hypercalcemia is rare but can be a serious complication of skeletal metastases. (Jick, Li et al. 2015) Signs and symptoms of hypercalcaemia are non-specific, and clinicians should suspect this condition. Common symptoms include nausea, vomiting, fatigue, anorexia, and constipation. (Bickels, Dadia et al. 2009) Evidence suggests that the primary mechanism responsible for humoral and osteolytic hypercalcaemia is increased osteoclast resorption activity leading to the release of calcium with subsequent elevation of serum calcium levels. (Diel, Body et al. 2015)

The concept of skeletal symptomatic events (SSEs) is defined for skeletal metastases for which active treatment, such as radiotherapy (RT), surgery for symptomatic pathological fracture, or decompression for symptomatic spinal cord compression, is needed. Skeletal events that are symptomatic and identified clinically are thought to be clinically more relevant endpoints than SREs, which include asymptomatic radiologically detected events. (Smith, Coleman et al. 2015)

2.3 Incidence of skeletal-related events

Reported incidence and prevalence rates for skeletal metastases are inconsistent. The reported rates vary between 7 and 70%. (Sathiakumar, Delzell et al. 2012, Santini, Procopio et al. 2013, Kuchuk, Kuchuk et al. 2015) A few large studies have been conducted on the incidence of SREs, such as Pockett´s study concerning 28 167 patients from Spain and Oster´s study concerning data on 1819 patients from two large US health care systems in a 14-year period. Based on these studies, it has been estimated that over half of all cancer patients with skeletal metastases will suffer from SREs. (Pockett, Castellano et al. 2010, Oster, Lamerato et al. 2013)

In Pockett's study, 10% of breast cancer patients were subsequently admitted to secondary care for the development of skeletal metastases within 3 years of their index admission. Furthermore, 21% of these patients later developed SREs requiring hospital admission. (Pockett, Castellano et al. 2010) In Oster´s study, 62% of breast cancer patients with skeletal metastases had evidence of SREs either at the time of or subsequent to the diagnosis of skeletal metastases. SREs were present at the time of diagnosis of skeletal metastasis in 22% of the patients. The cumulative incidence of SREs was 39% at 6 months and 45% at 12 months. (Oster, Lamerato et al. 2013) In a study based on a large population of women with breast cancer (98 260 patients), 7% had skeletal metastases. Among these patients, SREs occurred in 46% of the patients, and of them 1% needed bone surgery. (Sathiakumar, Delzell et al. 2012)

Pockett et al reported that 16% of lung cancer patients were admitted to secondary care for the development of skeletal metastases within 3

years of their index admission. Twenty-six percent of the patients later developed a SRE. (Pockett, Castellano et al. 2010) In Oster's study, 59% of the patients had a SRE at the time of or subsequent to the diagnosis of skeletal metastases. SREs were present at the time of the diagnosis of skeletal metastasis in 22% of patients. The cumulative incidence of SREs was 41% at 6 months and 45% at 12 months. (Oster, Lamerato et al. 2013) In one study from France including 554 patients, 25% had SREs and 9% of these patients needed surgery. (Decroisette, Monnet et al. 2011) In another study from Canada, 40% (118/269) of patients had bone disease and 61% of these patients developed a SRE. (Kuchuk, Kuchuk et al. 2015)

Pockett et al reported that 17% of prostate cancer patients were subsequently admitted to secondary care for the development of skeletal metastases, and 16% of these patients later developed a SRE requiring hospital admission. (Pockett, Castellano et al. 2010) In Oster's study, the cumulative incidence of SREs was 22% at 6 months and 30% at 12 months. (Oster, Lamerato et al. 2013) In a study based on the Nationwide Inpatient Sample (NIS) database including 443 929 visits by patients with skeletal metastases, 16% of the patients experienced at least one SRE. (Roghmann, Antczak et al. 2015)

In RCC, studies have shown that 30-40% of patients have bone metastases at the initial presentation of the disease or develop them later. (1994, Schlesinger-Raab, Treiber et al. 2008, Woodward, Jagdev et al. 2011) In one study of more than 1800 patients, 398 patients with skeletal metastasis were identified: 124 (31%) had skeletal metastases at the time of RCC diagnosis and 269 (68%) developed skeletal metastases after RCC diagnosis. Seventy-one percent of the patients experienced at least one SRE. (Santini, Procopio et al. 2013)

Only a few studies have examined the risk factors for skeletal metastases or the risk of SREs in patients with skeletal metastasis. However, in Colleoni's study, nodal status, tumour size, receptor status, and young age predicted differences in the incidence of skeletal metastases in breast cancer patients. Moreover, patients with lymph node metastases at the time of the diagnosis of their primary tumour were more likely to develop skeletal metastases. (Colleoni, O'Neill et al. 2000) Recent studies from Antczak, Roghmann, and their study groups showed that the incidence of SREs is slightly decreasing in developed countries. New anti-bone remodelling therapy, such as with

bisphosphonates, may have influenced this. However, charges for SRE-associated hospitalizations have increased alarmingly. (Antczak, Trinh et al. 2014)

2.4 Diagnosing skeletal metastases

2.4.1 Imaging

If a patient with a history of diagnosed cancer reports pain anywhere in the skeleton, the possibility of metastatic bone disease should be in mind. Plain radiographs should be taken of the affected sites. As skeletal metastasis varies in appearance, variable radiological findings are possible. In osteolytic metastases, excessive bone degradation leaves cavities in the mineralized tissue, which are recognized as a defect in the medullary or cortical area. (Krzeszinski and Wan 2015) Osteoblastic, often referred as osteosclerotic, metastases appear denser than the surrounding bone. Osteoporotic metastases appear as "faded" bone without discrete areas of cortical destruction or increased density on the radiograph. The fourth possibility is a mix of these findings. (Theriault and Theriault 2012) Computed tomography (CT) is sometimes required to detect metastases located at complex anatomical sites, such as the shoulder girdle, spine, and pelvis. (Bickels, Dadia et al. 2009) In asymptomatic patients, skeletal scintigraphy is highly sensitive in the detection of osseous metastases, as it allows overall assessment of the skeleton (Fig. 3). (Costelloe, Rohren et al. 2009)

The bone scan with labelled phosphonates enables visualization of local bone metabolism, which is activated in an early phase of metastasis of, for example, prostate cancer and breast cancer, which are associated with marked reactive hypermetabolism of bone. In contrast, the scan is relatively insensitive to tumours, which are active in destructive osteolysis or isolated bone marrow infiltration, such as in RCC or musculoskeletal lymphoma. (Heindel, Gubitz et al. 2014)

Whole-body magnetic resonance imaging (MRI) detects more bone metastases than scintigraphy. (Costelloe, Rohren et al. 2009) The high soft tissue contrast and spatial resolution of MRI reveal metastases in the bone marrow and adjacent soft tissues before any changes in

internal bone structure that could be detected by CT arise. (Costelloe, Rohren et al. 2009, Heindel, Gubitz et al. 2014) If MRI and CT cannot detect the disease and bone metastasis is still suspected, positron emission tomography (PET) CT can be used.

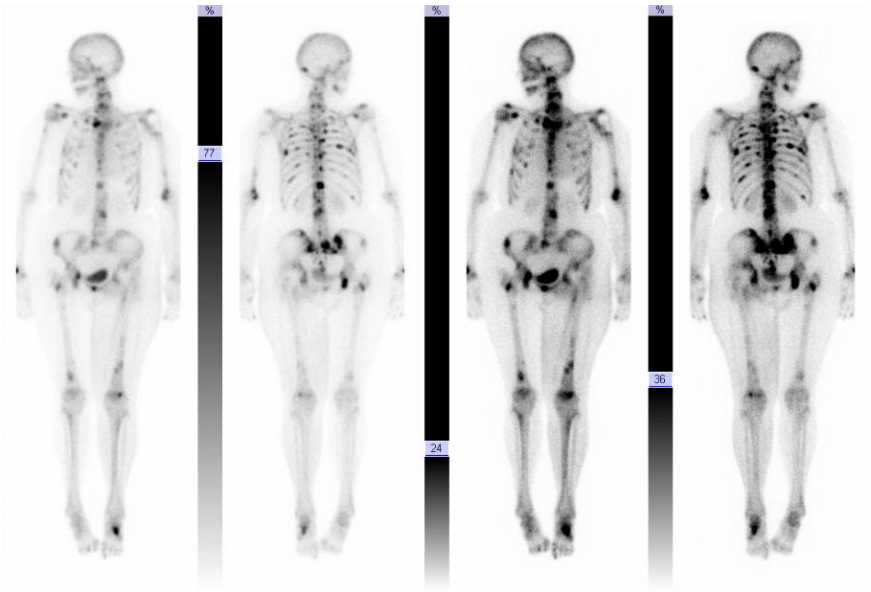


Figure 3. Bone scan showing metastatic lesions in breast cancer.

PET is a nuclear medicine technique that produces high-resolution tomographic images through the detection of high-energy photon pairs emitted during positron decay of a radioisotope. (Costelloe, Rohren et al. 2009) PET-CT is based on the visualization of glucose metabolism using 18F-fluorodeoxyglucose and is now a standard diagnostic technique in oncology. (Heindel, Gubitz et al. 2014)

2.4.2 Pathology and laboratory tests

A bone lesion in a patient with no history of cancer should be assumed to be a primary bone sarcoma until proven otherwise. A solitary lesion should be investigated by biopsy prior to being distinguished as a metastatic carcinoma, haematological malignancy, primary sarcoma,

chemotherapy or especially radiation-induced secondary malignancy. (Mark, Poen et al. 1994, Cheung 2014, Sun, Lin et al. 2015) A bone lesion might also be due to previous chemotherapy, like osteonecrosis or bone infarct. (Kadan-Lottic NS 2008) If multiple bony lesions typical of skeletal metastases are seen in a patient with a history of bone-seeking cancer, such as prostate or breast cancer, the lesion in question can be treated as metastasis. However, if the primary cancer rarely metastasizes to bone (e.g., colon cancer), more accurate diagnosis of the lesion should be carried out prior to making a treatment decision.

Interactions between tumours and bone typically result in increased rates of bone metabolism, which can be detected by increased levels of biochemical markers. (Jung and Lein 2014) Their determination in the serum and/or urine could help in diagnostics. (Joerger and Huober 2012) For example, serum alkaline phosphatase (ALP) is secreted by osteoblasts and the serum level of ALP has been shown to be higher in patients with prostate cancer with skeletal metastases than in patients without skeletal metastases. However, as an enzyme associated with the plasma membrane of cells, ALP is also found in the liver, intestines, and placenta, all of which may contribute to the total amount of ALP found in blood.

ALP also accumulates in the circulation in, for example, hepatobiliary disease and heart failure. (Kamiya, Suzuki et al. 2012) Other examples of investigated markers are the N-telopeptide of type I collagen (NTX), a sensitive marker of osteolysis, (Brown, Cook et al. 2005) and the cross-linked non-isomerized form of the carboxy-terminal telopeptide of type I collagen (αα-CTX), which reflects dysregulation of bone turnover. (Barnadas, Manso et al. 2014) Studies have shown the connection between elevated levels of these bone markers and disease progression and increased mortality. (Coleman, Costa et al. 2011, Barnadas, Manso et al. 2014, Jung and Lein 2014)

In prostate cancer patients, increasing prostate specific antigen (PSA) level is an important factor in the prediction of the risk of bone metastases. (Briganti, Suardi et al. 2014)

In addition, uncertainties exist, particularly in the diagnostic application of bone markers, because of high spread of values in different malignancies. The current consensus is that the diagnostic sensitivity and specificity of bone markers are not sufficient for integration into routine screening protocols. However, the field of bone

marker science is rapidly expanding, providing important insights into the evaluation of a patient's risk of worsening skeletal health and hopefully giving more information in the future. (Coleman, Costa et al. 2011)

2.5 Non-surgical treatment of skeletal-related events

In general, cancers are incurable once they have metastasized to the bone. The treatment of skeletal metastases is aimed at palliation of symptoms, with non-surgical treatments varying according to the underlying disease. Skeletal metastases can be treated conservatively by influencing tumour cell growth (e.g., radiation therapy, chemotherapy, or hormone therapy) or by influencing factors that are secondary to tumour cells (e.g., osteoclast activation). The proper care of patients with skeletal metastasis requires interdisciplinary care among radiologists, oncologists, surgeons, pain medicine specialists, and palliative care professionals.

2.5.1 Pharmacological therapy

2.5.1.1 Pain management

Pharmacological therapies are the foundation of cancer pain management. Non-opioids, paracetamol alone or with combination with codein, and non-steroidal anti-inflammatory drugs are the primary choices. Side effects, such as gastrointestinal ulcers and hepatic toxicity, may become problematic with long-time use. Opioids affect the central nervous system and are effective in providing necessary analgesia, but they have several complications, some of which may be severe: nausea, constipation, vomiting, sedation, and even respiratory depression. Adjuvant analgesics, such as tricyclic antidepressants, provide analgesia by inhibiting the re-uptake of norepinephrine and serotonin. (Paice and Ferrell 2011) As metastatic pain is not only nociceptive but also neuropathic, the pain may be relieved by adjuvants such as antidepressants and antiepileptics. (Nishihara, Arai et al. 2013)

The true role of antiepileptic medicament like pregabalin needs to be further studied as a recent report has questioned the role of pregabalin in cancer-induced bone pain. (Fallon, Hoskin et al. 2016)

2.5.1.2 Bisphosphonates and denosumab

Bisphosphonates and denosumab are said to act as anti-bone remodelling therapy. (Rusz and Kahan 2013) Bisphosphonates are especially useful in preventing and delaying SREs. Osteoclast activation can be down-regulated by bisphosphonates. They bind hydroxyapatite and impede osteoclast-mediated bone resorption. (Clement-Demange and Clezardin 2015) Currently licensed bisphosphonates include zoledronic acid (indicated in any advanced malignancy involving bone), disodium pamidronate (indicated in breast cancer or multiple myeloma), sodium clodronate (indicated in breast cancer or multiple myeloma), and ibandronic acid (indicated in breast cancer). (Ford, Jones et al. 2013)

Denosumab is a fully human monoclonal antibody targeting RANKL and inhibits osteoclast formation and activity. (Clement-Demange and Clezardin 2015) Denosumab significantly delays the time to first onset SRE in breast cancer, prostate cancer, and other solid tumours. (Lipton, Fizazi et al. 2012) In a recent meta-analysis of nine studies with 2806 patients with breast cancer with skeletal metastases, both bisphosphonates and denosumab reduced the risk of SREs and delayed the time to SREs. In this study, reduced pain and improved QoL were observed. (Wong, Stockler et al. 2012) In one study, denosumab was superior to zoledronic acid in preventing SREs with favourable safety and convenience. (Lipton, Fizazi et al. 2012) Denosumab has also been shown to be more efficacious in delaying or preventing hypercalcemia. (Diel, Body et al. 2015) However, no differences were found between denosumab and zoledronic acid in reducing overall mortality, or in the frequency of overall adverse events. (Ford, Jones et al. 2013, Peddi, Lopez-Olivo et al. 2013) Adverse effects are typically associated with gastrointestinal problems, including nausea, indigestion, heartburn, vomiting, and retrosternal pain, leading to interrupted treatment in up to 20% of patients. (Reid 2011)

Bisphosphonates and denosumab are also associated with serious side effects, such as atypical femoral fractures (Shane, Burr et al. 2014) and osteonecrosis of the jaw, complications that not only impair the QoL, but also potentially affect the treatment of the underlying disease. (Otto, Schreyer et al. 2012) A common oncological guideline is to have a dental examination with appropriate preventive dentistry prior to starting the treatment. Other documented adverse effects include renal toxicity (reported more in oledronic acid), hypocalcaemia (reported more in denosumab), and anaemia. (Lipton, Fizazi et al. 2012, Peddi, Lopez-Olivo et al. 2013)

The routine use of bisphosphonates in combination with other systemic therapy in patients with skeletal metastases from breast or prostate cancer is supported by the literature. (Liu, Huang et al. 2015)

2.5.1.3 Tumour-specific therapies

Therapies to treat advanced cancer metastasized to the bone should target both the growth of vascularized metastases and progression of micrometastases to a vascularized area. These growth stages can be targeted by anti-growth therapies, such as cytotoxic chemotherapies and molecular-based strategies designed to block specific growth pathways. (Chambers, Groom et al. 2002) In addition treatment should also target to primary cancer.

Primary cancers with advanced staging are treated individually. For example, in breast cancer, patients with hormone receptor-positive disease may benefit from agents such as tamoxifen and aromatase inhibitors, if disease causes just minimal symptoms. Patients with aggressive disease benefit from chemotherapy, usually with anthracycline or taxane-based regimens; for example, trastuzumab is used in human epidermal growth factor receptor 2-positive disease. Patients who undergo chemotherapy and/or treatment with aromatase inhibitors are at increased risk of osteoporosis because of oestrogen deprivation. (Bjarnason, Hitz et al. 2008) Calcium/vitamin D supplements are added to improve bone health.

Metastatic RCC has been shown to be resistant to chemotherapy and hormonal therapy. Cytokines, such as interferon-a (IFN-a) and IL-2, have been used in the past. (Adiga, Dutcher et al. 2004) The

development of therapeutic agents that angiogenetic block pathways typically involved in RCC progression, such as the vascular endothelial growth factor pathway (e.g. axitinib, sunitinib, sorafenib, pazopanib, and bevacizumab) or the mammalian target of rapamycin pathway (temsirolimus, everolimus), has established molecular targeted therapy as the preferred first-line therapeutic approach for most patients with advanced RCC. (Waalkes 2012) Sunitinib is now considered a reference standard of care and results in significant overall survival than IFN-a. (Oudard, Beuselinck et al. 2011) Reported side effects include hypertension, neutropenia, hand-foot syndrome, fatigue, thrombocytopenia and bleeding events. (Elice and Rodeghiero 2012, Donskov, Michaelson et al. 2015)

In prostate cancer hormone therapy is the standard of treatment and in castrate resistant disease chemotherapy is used. If disease has not viscerally metastasized Radium-223 can be used. Radium-223 is a first-in-class alfa -particle-emitting radioisotope that homes to areas of high bone turnover, making it ideal to target metastatic bone disease. (Nilsson, Strang et al. 2012) It is thought to decrease tumour volume and pressure on the richly innervated periosteum. (Heidenreich, Bastian et al. 2014)

The field of anti-growth therapies is broad and developing all the time.

2.5.1.4 Future aspects in medical therapy

Thanks to a more thorough understanding of the biology of skeletal metastases, novel bone-targeted therapies are emerging. Understanding of the molecular mechanisms responsible for osteoclast activation in cancer has led to the development of novel therapeutic possibilities like cathepsin K (CatK) inhibitor, odanacatib, and sipuleucel-T. Odanacatib decreases bone resorption and maintains bone formation, indicating that this compound has an advantage over other antiresorptive agents (e.g., bisphosphonates, denosumab) in the treatment of diseases associated with bone loss. (Clement-Demange and Clezardin 2015) Some studies support the role of CatK in breast cancer skeletal metastasis, and it may represent a novel oral therapy for the treatment of metastatic breast cancer. (Duong le, Wesolowski et al. 2014) In

United States is approved autologous vaccine called sipuleucel-T (consisting individually collected antigen-presenting cells), which is delivered to the patient in three biweekly infusions. It is said to have effect on survival. (Heidenreich, Bastian et al. 2014)

Overall, the development of these new drugs may significantly reduce the frequency of skeletal lesions in patients with advanced disease in the near future.

2.5.2 Radiation therapy

External beam radiotherapy (EBRT) plays an important role in the treatment of skeletal metastases, and its effectiveness in pain control has been shown in many studies. EBRT provides effective and time-efficient pain control with few side effects. However, the provision of pain relief by EBRT is thought to be more complex than resultant tumour cell death, given that the timing of the relief often precedes a time frame that would be necessary for tumour cell death. (Lutz, Berk et al. 2011) Radiobiology studies suggest that EBRT may alter the cellular behaviour of tumour cells or osteoclasts that cause discomfort to adjacent nerves. (Vakaet and Boterberg 2004)

EBRT can provide significant palliation of painful bone metastases in 50 80% of patients, with up to one-third of patients achieving complete pain relief at the treated site. (Chow, Harris et al. 2007) (Johnstone and Lutz 2014) There is strong evidence that pain relief lasts for at least 6 months in at least 50% of patients. (Falkmer, Jarhult et al. 2003) Over 100 different fractionation regimens are in use worldwide to treat metastatic bone pain. (Fairchild, Barnes et al. 2009) Overall response rates were similar in one study, with 1696 of 2818 (60%) patients in the single fraction arm and 1711 of 2799 (61%) patients in the multiple fraction arm achieving a good response. (van der Linden, Steenland et al. 2006) Single and multiple fraction regimens provided equal pain relief; however, significantly higher retreatment rates occurred in those receiving single fractions. (Chow, Zeng et al. 2012) In patients with painful bone metastases requiring repeated radiation therapy, treatment with 8 Gy in a single fraction seems to be non-inferior and less toxic than 20 Gy in multiple fractions. (Chow, van der Linden et al. 2014) However, a longer course of radiotherapy is

recommended for patients with relatively prolonged life expectancy. In the Dutch Bone Metastasis Study, the mean time to the onset of pain relief was 3 weeks in both arms. (van der Linden, Lok et al. 2004) Patients who get response to re-irradiation might live longer. (Wong, Hoskin et al. 2014)

The main systemic side effects from EBRT have been reported to be skin irritation or mild sunburn. Gastrointestinal complaints, such as nausea or diarrhoea, may result from radiation around the spine or pelvis, and esophagitis or mucositis can result from radiation to mucosal surfaces adjacent to the treated bone lesion. One recognized side effect is fatigue, though it is typically less than the fatigue associated with the disease or other treatment modalities. Side effects occur acutely, sub-acutely, and in the long-term and are affected by both the daily dose of radiation, size of the volume irradiated and the total dose delivered. Less acute side effects have been associated with single fraction palliative radiation compared to multi-fraction regimens. (Hartsell, Scott et al. 2005, Foro Arnalot, Fontanals et al. 2008)

In a review of 25 randomized controlled trials (RCTs), the risk of pathological fracture was not significantly different between single fraction and multiple fraction arms. (Chow, Zeng et al. 2012) According to one small study of 102 patients, the incidence of pathological fracture could be decreased by radiotherapy, (Harada, Katagiri et al. 2010) but the prevention of pathological fracture by radiotherapy has not been scientifically proven in larger studies or reviews. Yet, radiotherapy is the mainstay for the treatment of painful, uncomplicated bone metastases.

2.5.3 Other therapies

Modern therapies are available for the palliative management of patients with metastatic bone disease. Radiofrequency ablation (RFA), microwave ablation (MWA), high intensity focus ultrasound and magnetic resonance imaging (MRI) guided focused ultrasound are all based on the thermal effect. With a rapid temperature increase, they can induce irreversible cell death via coagulation necrosis. (Mavrogenis, Angelini et al. 2015) RFA and MWA appear to be similarly effective for the treatment of painful skeletal metastases. The main difference is that

MWA achieves the same clinical result faster, but in a more expensive way. (Botsa, Mylona et al. 2014)

MRI guided focused ultrasound enables real-time three-dimensional monitoring of thermal damage in the target zone. (Napoli, Anzidei et al. 2013) These treatments are in clinical use merely for treating liver and lung metastases. (Petre, Sofocleous et al. 2015)

Selective embolization is a safe and effective palliative treatment for metastatic bone lesions of various primary cancers, but the pain relief is temporary. Different techniques can be used for embolization of the target vessel, such as those employing gelatin sponge, polyvinyl alcohol particles, alcohol emulsions, coils, or tissue adhesives. Embolization provides devascularization, tumour size reduction, calcification of margins, and pain relief. (Forauer, Kent et al. 2007) In one study, the mean duration of pain relief was 8.1 months (range 1–12 months). (Rossi, Mavrogenis et al. 2011) Although several authors reported decades ago that transcatheter arterial embolization is effective in relieving bone pain, (Nagata, Nakano et al. 1989, Chiras, Adem et al. 2004) it has not regained popularity in Finland.

2.6 Surgical treatment of skeletal-related events

In oncologic orthopaedics, the skeletal metastasis population does not represent a major service burden; surgery is needed in only a few cases. In different studies, 1-9.2% of patients suffering from skeletal metastases needed surgery. (Decroisette, Monnet et al. 2011, Sathiakumar, Delzell et al. 2012, Katagiri, Okada et al. 2014) Considering the number of patients with skeletal metastases, the rate is low. However, orthopaedic interventions may be underutilized because of a lack of awareness of their benefits. (Kelly, Lee et al. 2012) There may be situations in which patients are left untreated because of a lack of experience in advanced surgical reconstructions. (Bauer 2005)

In 1958, Bremner and Jelliffe made a statement that is still valid today: "*Most patients suffering long-bone pathological fracture have widespread disease, but it is wrong and unkind to regard this misfortune as a terminal event warranting only the simplest of symptomatic treatment. Recognition of this state of affairs demands the greatest expedition in*

returning the patient to comfort and mobility, that he may better enjoy his remaining months." (Bremner and Jelliffe 1958) Surgery is most commonly needed for mechanical complications, such as impending or existing pathological fracture or intractable pain. Palliative surgery is often sufficient, but occasionally curative intent may be attempted for, for example, solitary skeletal metastases. The goal of surgery is to relieve pain, achieve structural stability at the surgically treated site, and control tumour growth locally with the minimum possibility of morbidity. (Bickels, Dadia et al. 2009)

Surgery should improve the patient's QoL and maintain their independence as long as possible. (Bauer 2005) Patients should be able to complete the rehabilitation protocol after the operation as quickly and easily as possible. Overall, the patient's survival should be longer than their recovery and rehabilitation from the surgery. (Nathan, Healey et al. 2005) In a study of 55 patients with acetabular metastases, 34 (76%) had less pain than after surgery than before surgery based on their decreased use of narcotics. (Marco, Sheth et al. 2000) In a review of 18 studies evaluating pain and another review of 30 studies evaluating function after surgical management for metastatic disease of the femur, the proportion of patients experiencing pain relief was 91%, and 89% of patients had maintained or improved ambulatory status. Similar rates have been found after operations on the humerus and pelvis. (Wood, Racano et al. 2014)

Recently, studies have indicated that surgical metastasectomy may improve survival in different cancers. (Casiraghi, Maisonneuve et al. 2015, Charalampoudis, Mantas et al. 2015, Gadde, Tamariz et al. 2015, Rossfeld and Carson 2015) The survival benefit of the resection of skeletal metastases is debatable, but there are a few studies supporting it. (Colman, Kirkwood et al. 2014) (Kato, Murakami et al. 2013)

2.6.1 Question of impending fracture

Impending fracture is defined as a pathological condition of imminent fracture risk on a pre-existent bone lesion. (Piccioli, Spinelli et al. 2014) Edwards et al diagnosed an impending pathological fracture when X-rays showed a destructive lesion at least 3 cm in diameter, a lytic lesion with destruction of more than 50% of the cortical bone, avulsion of the

lesser trochanter, or persistent pain. (Edwards, Pandit et al. 2001) The prediction of pathological fracture risk has been of great interest, as it would facilitate choosing the right treatment for patients.

Different ranking systems have been developed to evaluate risk, of which the most quoted is Mirel's. (Mirels 1989) Mirel's assessment is based on four variables thought to contribute to pathological fracture risk: lesion location, pain level, radiographic appearance, and size. Evans et al reported that the Mirel's rating system is reproducible and valid in humeral lesions, but in femoral lesions its sensitivity and specificity was too low. (Evans, Bottros et al. 2008) This rating system has been criticized because it is based on only 38 patients, two-thirds of whom had breast cancer. Several studies have shown that Mirel's guidelines would potentially result in unnecessary procedures. (Van der Linden, Dijkstra et al. 2004, Piccioli, Spinelli et al. 2014, Nazarian, Entezari et al. 2015)

In a study from the Dutch group, only axial cortical involvement of more than 30 mm and circumferential cortical involvement of more than 50% have had significant value in predicting fractures. (Van der Linden, Dijkstra et al. 2004) Recently, a technique called computed tomography-based structural rigidity analysis (CTRA) was developed to accurately predict fracture risk based on the quantification of changes in bone geometry and density (Anez-Bustillos, Derikx et al. 2014) and has been reported to be more accurate than Mirel's. (Damron, Nazarian et al. 2015, Damron, Nazarian et al. 2016) There is increasing debate about stabilizing impending fractures prior to actual fracture. The actual fracture risk is very hard to evaluate, as discussed above, so the question of operating on an impending fracture is even more complex. The indication for surgery is not clear in the literature.

Some studies prefer early treatment for impending fractures, such as Keyak's study, in which the location of a lesion in the inferomedial cortex of the femur was prone to stabilization. (Keyak, Kaneko et al. 2007) It is stated that surgery for impending fractures increases survival rates, has fewer hardware failures, and fewer complications compared to surgically treated existing pathological fractures. (Edwards, Pandit et al. 2001) Arvinius et al stated that prophylactic operations require transfusions less often, provide earlier ambulation, and result in shorter hospital stays, improving oncology patients' QoL. (Arvinius, Parra et al. 2014) Furthermore, elective fixation may prevent the intense

pain and loss of function associated with a pathological fracture, and it is easier to perform than fixation of an existing pathological fracture. (Bickels, Dadia et al. 2009)

On the other hand, it has been argued that good results are based on the patients usually being younger and less progressive disease, leading to a better prognosis. (Arvinius, Parra et al. 2014) In addition, there is a risk of major complications, such as thromboembolic events and death, which is why some orthopaedic surgeons think that operating on pathological fractures prophylactically is too hazardous. (Bauer 2005)

2.6.2 Operation methods and strategies

The improved survival of disseminated cancer patients due to advances in overall cancer management imposes the requirement that surgical constructs should be able to withstand prolonged loading despite poor bone quality and healing capacity. The operating methods vary from intramedullary nailing to excessive resections and reconstruction with endoprosthetic replacements (EPRs). The indications for choosing one surgical implant option over another are not clear, and surgical options depend greatly on the anatomical site of the lesion and expected survival. (Eastley, Newey et al. 2012)

Surgery for skeletal metastases is usually palliative, and local control has not been the main primary objective of treatment. In primary sarcomas, adequate margins with wide or marginal margins have been the cornerstone of surgery. The definition of adequate margins is difficult and there is a lack of international consensus on the definition of margin descriptions. Historically, the Enneking classification from the 1980s has been widely used; margins are classified based on the concept of a reactive zone around sarcomas. A marginal margin means resection through this layer, a wide margin means surgery outside the layer, in radical excision a whole compartment is resected, and in intralesional excision the tumour itself is breached at any stage. (Enneking, Spanier et al. 1980)

With improvements in pre-operative planning, sufficient margins have become more narrow. Simple definitions are used, such as "tumour at the inked margin" taken as positive and all other margins as negative, (O'Donnell, Griffin et al. 2014) and margins being more or less

than 2 mm. There is evidence that margins may affect local recurrence, but the effect on survival is unclear. (Willeumier, Fiocco et al. 2015) In metastatic surgery, marginal resection is used when the intent is to remove the whole tumour and intralesional excision when the tumour is left in place.

2.6.2.1 Surgical management of lower extremity fractures

Surgical management of lower extremity fractures includes different surgical techniques. Internal fixation with intramedullary nailing, plates, and screws has traditionally been the primary method. However, it carries a very high failure rate (Yazawa, Frassica et al. 1990) and is considered mostly for patients with a short life expectancy. In patients with a prolonged life expectancy, these methods carry a high risk of failure with an increased possibility of re-operation. (Wedin and Bauer 2005, Gadde, Tamariz et al. 2015) Nails and plates are load-sharing devices and will break if the fracture does not heal. They are also not as stable as a cemented endoprosthesis and may not provide the same immediate relief from pain.

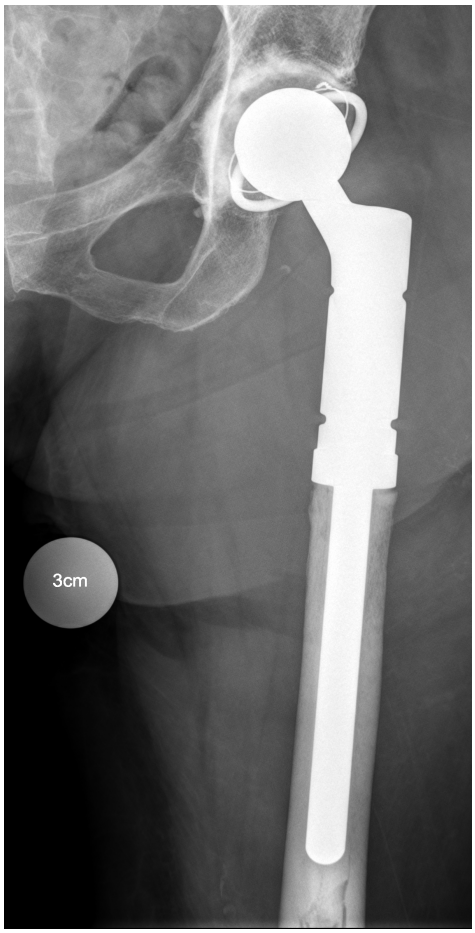


Figure 4. Proximal femoral endoprosthetic reconstruction with cemented stem, modular endoprosthesis and cemented constrained acetabular cup after tumour resection.

In a recent review including several studies on surgical treatments for pathological fractures in the proximal femur concluded that, in the femoral

neck, prosthetic replacement is the operative choice, but the evidence is less clear in intertrochanteric and subtrochanteric fractures. (Issack, Barker et al. 2014) With modular EPRs and intercalary prostheses, lesions in above-mentioned areas can be resected and stabile construction achieved. Problems with EPRs are difficulty in regaining abductor muscle function in the absence of greater trochanteric stability, frequent loss of iliopsoas function, and the risk of hip dislocation or instability. With developments in manufacturing and surgical techniques, these complications have been reduced, and studies have shown modular EPRs to be long-standing with relatively few and easily manageable complications with no implant failures (Fig. 4). (Hattori, Mibe et al. 2011)

The distal femur and below is a rare location for skeletal metastases. Skeletal metastasis involving the foot has been reported to occur in only 0.6% of all skeletal metastases. (Evans, Ramasamy et al. 2014) Due to the rarity of acrometastatic cancer, no standard treatment protocols exist. Any decisions regarding surgical intervention should be made on a case-by-case basis, depending on the patient's prognosis and functional capabilities. (Mavrogenis, Mimidis et al. 2014) All of the above-mentioned techniques could be used, or even amputation. (De Geeter, Reynders et al. 2001)

2.6.2.2 Surgical management of upper extremity pathological fractures

The treatment of humeral fractures differs from femoral fractures. The gleno-humeral joint is not a weight-bearing joint, but has the greatest range of motion of any joint in the body. Because the proximal humerus consists mainly of cancellous bone with low cortical rigidity and lacks a strong cortex, skeletal metastasis widely invading the proximal humerus causes large lytic lesions, making osteosynthesis very difficult and EPR preferred. (Fig.5)(Scotti, Camnasio et al. 2008) Active shoulder function is difficult to achieve after segmental tumour resection of the proximal humerus and EPR. Concerning large tumour lesions, there is a risk of rotator cuff failure, and the presence of axillary nerve damage after segmental surgery. (Piccioli, Maccauro et al. 2010)

To provide better function, modular reverse EPR has been introduced with promising preliminary results. (Streitbuerger, Henrichs et al. 2015) The use of intramedullary nailing or plate fixation has resulted in satisfactory function after surgery, but the rate of re-operation has been reported to be as high as 20%. (Wedin, Hansen et al. 2012) In one study, patients treated with prosthesis or nailing had similar results in regards to function and pain management. (Piccioli, Maccauro et al. 2010) Lesions in the humeral diaphysis can be managed with intramedullary nailing or plate fixation with or without cement. The use of cement has been shown to be accompanied by quicker recovery. (Piccioli, Maccauro et al. 2010, Wedin, Hansen et al. 2012)

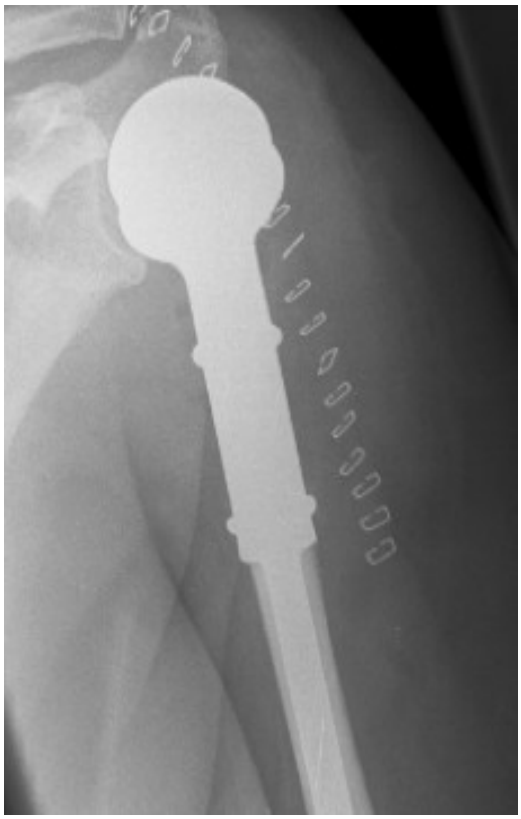


Figure 5. Proximal humeral hemiendoprosthetic reconstruction with a cemented stem.

Lesions in the distal humerus present unique treatment challenges; the choice of reconstruction varies, but EPRs seem to have fewer complications. (Wedin, Hansen et al. 2012) More distal pathological fractures of the forearm bones are an uncommon problem in clinical practice and literature is scarce. (Martin, Field et al. 2002) The choice to operate should be made on a case-by-case basis.

2.6.2.3 Surgical management of pathological pelvic lesions

Resection of pelvic tumours is one of the most technically demanding procedures in orthopaedic oncology. Peri-acetabular metastases have been at the forefront of skeletal metastasis surgery for over 30 years, as Harrington introduced his classification in 1981 with instructions on treating lesions with a deficient medial wall, a deficient roof, and one column, and lesions in which both columns are involved. (Harrington 1981) In Harrington's procedure, reconstruction is performed with total hip arthroplasty regardless of the cause of the damage. A reinforcement ring inserted after curettage of the lesion, supplemented by cement, will normally suffice to restore the acetabulum. If the bony destruction is extensive, threaded pins introduced through the iliac crest in a fan-like manner will augment stability. (Fig.6)(Harrington 1981, Bauer 2005)

Most peri-acetabular fractures result in displacement of the femoral head proximally or medially, depending on the extent and distribution

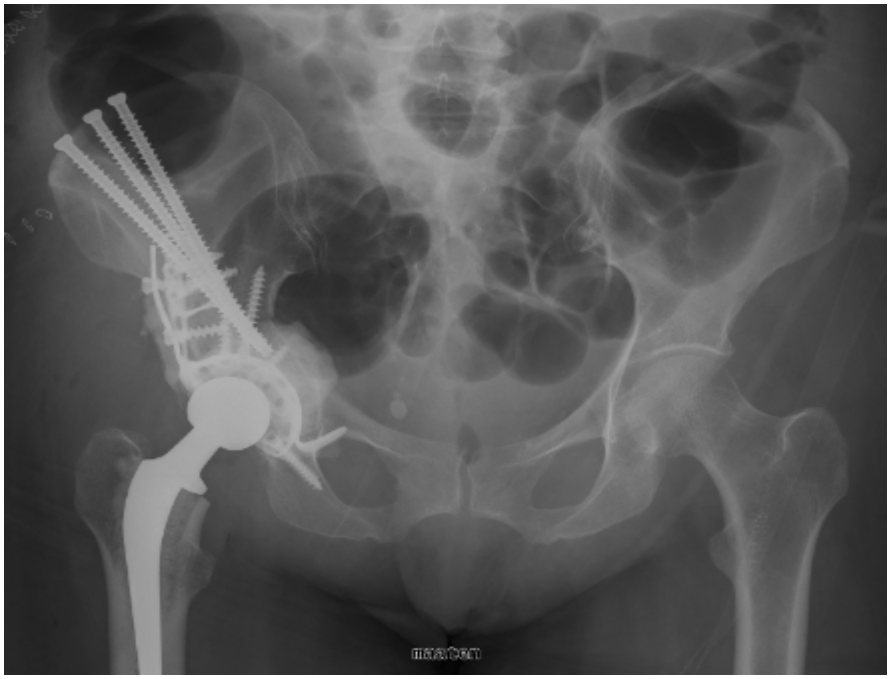


Figure 6. Radiograph showing the reconstruction achieved with three full-threated screws, reinforcement cup and of the cemented acetabular component with cemented femoral stem.

of tumour osteolysis in the ilium. In either instance, conventional total hip arthroplasty is likely to fail if there is insufficient structurally adequate bone around the medial wall and/or inferiorly.(Harrington 1997)

In a recent study, 70 consecutive patients were operated on using the simplified Harrington technique. Metastatic lesions in the peri-acetabular region were treated with curettage of the tumour and reconstruction with a protrusion cage and total hip replacement. Screws were placed through the cage in a retrograde fashion. Although surgery was associated with a considerable complication rate (33% (23/70), it resulted in pain relief in all patients and better ambulation in a majority of them. (Tsagozis, Wedin et al. 2015)

EPR of the peri-acetabular area of the pelvis is one of the most challenging types of limb salvaging surgery, and the prosthesis used has become known as the 'ice cream cone' prosthesis because it looks like an inverted ice cream cone. The prosthesis is inserted into the remnant of the pelvis and often surrounded by antibiotic-laden bone cement. The overall complication rate has been reported to be 37%, with a re-operation rate of 18.5%, but the use of ice cream cone prostheses is more common in primary tumours than skeletal metastases. (Fisher, Patton et al. 2011)

2.6.3 Pre-operative embolization

Some skeletal metastases, such as metastases from RCC and thyroid cancer, are hypervascular, carrying a risk of massive blood loss during operation. (Wilson, Cooke et al. 2010) Also, the extent of surgery is thought to be an important risk factor for intra-operative blood loss. (Robial, Charles et al. 2012) The possible risk of profound bleeding has raised interest in pre-operative embolization, as it has been thought to significantly decrease intra-operative blood loss, making surgery easier and facilitating radical removal. (Chatziioannou, Johnson et al. 2000, Wirbel, Roth et al. 2005, Nair, Gobin et al. 2013, Pazionis, Papanastassiou et al. 2014)

Pre-operative embolization has been performed frequently in spinal RCC metastases and is recommended despite inconsistent outcomes. (Wilson, Cooke et al. 2010, Robial, Charles et al. 2012, Quraishi,

Purushothamdas et al. 2013, Thiex, Harris et al. 2013, Clausen, Dahl et al. 2015) Thus far, few reports have described the benefit of embolization in non-spinal metastatic cases involving more than 10 patients (Barton, Waneck et al. 1996, Sun and Lang 1998, Chatziioannou, Johnson et al. 2000, Wirbel, Roth et al. 2005, Kickuth, Waldherr et al. 2008, Pazionis, Papanastassiou et al. 2014). Some studies support the belief that pre-operative embolization decreases intra-operative blood loss, (Chatziioannou, Johnson et al. 2000, Wirbel, Roth et al. 2005) as other studies suggest that feeding vessels clearly identified during surgery are easily ligated and no embolization is needed. (Baloch, Grimer et al. 2000, Lin, Mirza et al. 2007)

2.7 Complications after surgical treatment

Operative procedures in pathological skeletal metastasis are not without risk, which may explain some of the reluctance to refer patients to orthopaedics. Surgical reconstruction for pathological fractures carries a risk of several complications and reduction in the overall function of the patient due to, for example, the need for hospitalization for weeks instead of remaining at home. (Bauer 2005) Complications can be categorized as mechanical complications (e.g., soft tissue failures, aseptic loosening, non-union, and structural failure, such as prosthetic dislocation) and non-mechanical complications (e.g., infection and recurrence of disease). (Henderson, O'Connor et al. 2014)

In a large study concerning prosthetic complications, mechanical failures accounted for 259 (49%) and non-mechanical causes for 275 (51%) of all 534 failures. These cases included 93 failures (17%) due to tumour progression and 182 failures (34%) due to infection, which was the most common mode of failure for all anatomic sites. (Henderson, Groundland et al. 2011)

Other complications have also been reported: nerve palsies, bleeding, thromboembolic complications, coagulopathies, pressure ulcers, gastrointestinal complications, and death. (Marco, Sheth et al. 2000, Piccioli, Spinelli et al. 2014) In a large systematic review of 45 studies, the proportion of complications reported across the studies was 17%. Peri-operative mortality was reported in 36 studies and found to be 4%. (Wood, Racano et al. 2014)

2.7.1 Mechanical complications

Non-union, nail breakage (Fig. 7), and fracture displacement are possible mechanical complications after any attempt for biological healing, such as intramedullary nailing or plating. A mechanical complication occurs as the pathological fracture fails to heal. Hardware failures, such as implant wear, stem fracture, periprosthetic fracture, and dislocations, are possible mechanical complications after EPR. Even though the exact numbers of non-unions and healing problems in pathological fractures are not available, several studies have shown that EPRs have a lower failure rate and higher implant survival than implants relying on biological healing. (Wedin and Bauer 2005, Harvey, Ahlmann et al. 2012)

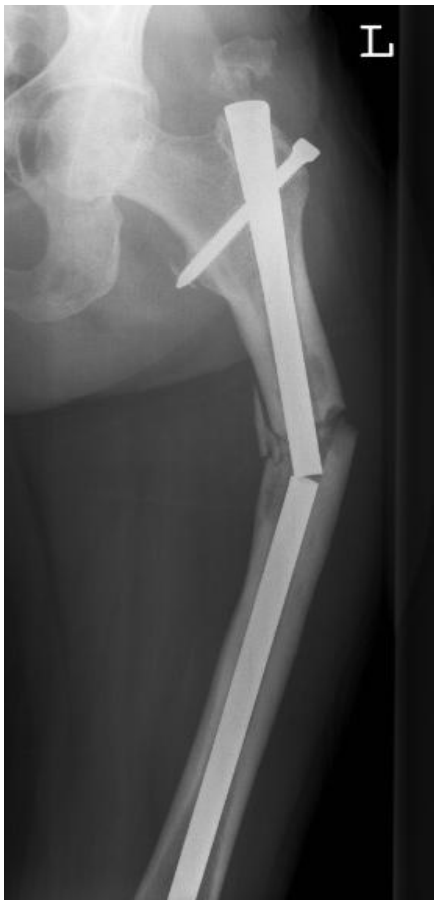


Figure 7. Nail breakage after femoral fracture fixation.

In a study of 286 patients, Steensma et al reported a failure rate that was significantly lower in the prosthetic reconstruction group (3%) than the intramedullary nailing (6%) and open reduction and internal fixation (42%) groups. (Steensma, Boland et al. 2012) In addition, some previous studies showed that intralesional procedures have higher complication and re-operations rates than wide resection, as intralesional resection allows the continuation of tumourous growth. (Wedin, Bauer et al. 2001, Steensma, Boland et al. 2012)

2.7.2 Non-mechanical complications

Infection rates after surgery for skeletal metastases are high compared to rates for conventional arthroplasty or fracture treatment. For example, after intramedullary nailing, the overall infection rate has been reported to be 1.0% (0.7% for humerus, 0.8% for femur, and 1.5% for tibia fractures) (Young, Lie et al. 2013), and according to a study of 48 307 patients with primary total hip arthroplasty, the deep infection rate was 1.3% and systemic sepsis rate 0.3%. (Bohl, Samuel et al. 2015) In a study concerning deep periprosthetic infections after oncological resection, the infection rate was 11%. The rate of infection significantly decreased in the last 5 years of the study period. Several risk factors were identified, including radiation therapy, myeloma, and a tibial or pelvic site. There was no evidence that local recurrence, chemotherapy, gender, or patient age increased the infection risk. (Jeys, Grimer et al. 2005)

Studies, particularly those on metastatic disease, usually cover only a few patients. For example, in Piccioli´s study on humerus metastasis, the infection rate was 5.3% (3/57) in intramedullary nailing and 6.7% (2/30) in EPR. (Piccioli, Maccauro et al. 2010) In contrast, the infection rate was 2.3% (3/130) in Sorensen's study on EPR. (Sorensen, Gregersen et al. 2013) In Hwang´s study about the usage of massive endoprosthesis in RCC, the infection rate was 5.9% (8/135). (Hwang, Nandra et al. 2014)

Already 20 years ago, the risk of intra-operative tumour and fat embolization as measured on transoesophageal echocardiography was recognized to be higher with intramedullary fixation of metastatic lesions versus non-pathological fracture or in non-pathological hip replacement surgery. (Christie, Robinson et al. 1995) Intramedullary fixation of femoral metastases is associated with a high incidence of cardiorespiratory and vascular dysfunction. There have been reports of desaturation in one-third of patients treated with cement to augment femoral nail fixation. (Barwood, Wilson et al. 2000) The passage of normal marrow contents or tumour into the pulmonary circulation is thought to cause various biochemical, hemodynamic, or physical responses that may lead to hypotension, arrhythmia, and O_2 desaturation, or even death, (Choong 2003) which is the most catastrophic complication of the surgical treatment of skeletal

metastases. Premature deaths are generally the result of acute right ventricular failure and cardiogenic shock. (Agnelli and Becattini 2010)

2.7.3 Venous thromboembolic events

Cancer is a well-known risk factor for VTEs deep vein thrombosis (DVT) and pulmonary embolism (PE). The overall risk of a venous thrombosis is estimated to be increased 7-fold in patients with a malignancy vs. persons without malignancy. (Blom, Vanderschoot et al. 2006) In patients with cancer, each of the three components of Virchow's triad (blood composition, vessel wall components, and blood flow) present with abnormalities that predispose to thrombus formation. (Lip, Chin et al. 2002) Patients who are treated with chemotherapy, like antiestrogens in breast cancer treatment, and have metastatic disease have an additional risk of VTE. (Lip, Chin et al. 2002, Blom, Vanderschoot et al. 2006, Onitilo, Doi et al. 2012)

Different models have been developed for predicting chemotherapy-associated VTE. One model, called the Khorana score, includes the following variables: site of cancer, platelet count, haemoglobin, leukocyte count, and body mass index (BMI). (Khorana, Kuderer et al. 2008) Mortality rates are three-times higher in the first 6 months after VTE in patients with cancer than those without. (Levitan, Dowlati et al. 1999) A necropsy study revealed that 10% of patients (648/6197) who died of cancer had PE. (Svendsen and Karwinski 1989) After major surgery, as much as 10-40% of the deaths are related to PE. (Dahl, Caprini et al. 2005)

2.7.4 Re-operations

Re-operations are catastrophic in this group of fragile patients. Treatment of primary disease maybe delayed which can lead disease progression. For example cancer therapy increases the risk for infections and sytopenia. In a study from Weiss et al concerning 301 breast cancer patients, the re-operation rate was 14%. (Weiss, Tullberg et al. 2014) A study by Kelly et al including 257 patients with operated long-bone metastases, the revision rate was approximately 3%. (Kelly,

Lee et al. 2012) In a study from Wedin and Bauer including 142 patients with skeletal metastases, the overall rate of re-operation was 8.3% (9/109) in the prosthetic group and 16.2% (6/37) in the osteosynthetic group. (Wedin and Bauer 2005) In a large review concerning humerus lesions, the re-operation rate was 4.4% (26/585) in the intramedullary nailing group, 9.3% (14/150) in the plate-screw fixation group and 2.5% (2/81) in the EPR group. (Janssen, Teunis et al. 2015)

Reported reasons for failures are poor initial fixation, improper implant selection, and progression of disease within the operative field. (Yazawa, Frassica et al. 1990) There is also a tendency for a higher re-operation rate in hospitals with fewer treated patients, which may be due to improper surgical treatment and inexperience in identifying pathological fractures and the proper surgical option, as the management of pathological fractures is different from standard fracture treatment. Osteosynthesis was used more frequently in units treating few cancer patients with pathological fractures, which may explain part of the higher failure rate. (Wedin, Bauer et al. 2001)

2.8 Prognostic factors and survival

Survival from cancer has increased annually. (Howlader N 2012) Metastases, rather than primary tumours, are responsible for most cancer deaths. (Chambers, Groom et al. 2002) Cancer is usually incurable after it metastasizes to bone. In a study regarding data from two large US health systems, survival after the diagnosis of skeletal metastases in patients with breast cancer was 66% at 1 year and 33% at 3 years; in patients with lung cancer it was 19% and 2.5%, respectively; and in patients with prostate cancer it was 74% and 43%, respectively. (Oster, Lamerato et al. 2013) After surgery, the calculated probability of survival decreased to 51% at 6 months, 39% at one year, and 22% at 3 years, and the median survival time was 7 months. (Sorensen, Gregersen et al. 2013) Of all factors, the primary tumour is considered to have the greatest impact on survival. (Katagiri, Okada et al. 2014)

2.8.1 Breast cancer

Breast cancer is the most common malignancy and the second leading cause of death in women. (Howlader N 2012) In a Swedish study of 649 breast cancer patients with surgically treated skeletal metastases, the median survival was 6 years after diagnosis of breast carcinoma and 2 years after the first recurrence. The median survival from the diagnosis of bone metastases was 22 months for patients with bone as the first site of metastases and 12 months for those with soft tissue or multiple sites of metastases. Post-operative survival was 8 months. (Wedin, Bauer et al. 2001) Possible prognostic factors are oestrogen receptor status, metastasis-free interval, additional sites of metastases (other than bone), and elevated tumour marker levels. (James, Evans et al. 2003) In addition, the absence of pathological fracture and visceral metastases has been predictive of longer survival. (Wegener, Schlemmer et al. 2012) In a study by Weiss et al of 300 operated patients, age over 60 years and haemoglobin levels <110 g/L increased the risk of death after surgery. Patients with impending fractures had a lower death rate. (Weiss, Tullberg et al. 2014) In previous studies, a long disease-free interval was a good prognostic factor in breast cancer, and it is commonly believed that a breast cancer patient with long disease-free survival should be treated more aggressively (Coleman, Smith et al. 1998, Insa, Lluch et al. 1999, James, Evans et al. 2003).

2.8.2 Lung cancer

Worldwide, lung cancer is the most common cancer and the leading cause of cancer-related deaths, accounting for an estimated 1.6 million new cancers (nearly 13% of the total) and 1.4 million deaths (>18% of the total) in the year 2008. (Ferlay, Shin et al. 2010) In Utzschneider´s study of lung cancer patients, 80% had lung/pleura metastases, 69% mediastinal node metastases, and 39% bone metastases. (Utzschneider, Wicherek et al. 2011) In a study by Kuchuk et al, the median survival of patients with skeletal metastases was 6 months versus 10 months in patients without metastases. (Kuchuk, Kuchuk et al. 2015) In a study of lung cancer, cumulative survival rates after bone metastasis with pathological fracture were 60% at 6 months, 32% at 1 year, and 11% at 2

years. The overall median survival time after surgery was only 3 months, and just 13% of the patients were still alive 1 year after surgery. (Weiss and Wedin 2011) Histological subtype, no evidence of appendicular bone metastases, and use of gefitinib independently predicted better survival. (Sugiura, Yamada et al. 2008) Good prognostic factors in studies have been good performance status and no pathological fracture in skeletal metastases. (Utzschneider, Wicherek et al. 2011, Weiss and Wedin 2011)

2.8.3 Prostate cancer

Prostate cancer is the most commonly diagnosed non-skin cancer and the second leading cause of cancer death in men. (Howlader N 2012) In metastatic bone disease, survival has been reported to be 13-18 months. (Scher, Fizazi et al. 2012) Lately there have been a lot of new drugs developed like radium-223, which can prolong survival even more. (Heidenreich, Bastian et al. 2014) The median survival time after the first surgical procedure has been reported to be 0.5 (0 9) years. (Weiss, Forsberg et al. 2012) Age over 70 years, generalized metastases, multiple skeletal metastases, and interval between the diagnosis of metastasis have been significantly associated with decreased survival. Whether the metastasis was osteoblastic or osteolytic did not affect outcome. (Cheville, Tindall et al. 2002, Weiss, Forsberg et al. 2012)

2.8.4 Renal cell carcinoma

The incidence of RCC has been increasing (Engholm, Ferlay et al. 2010). RCC is characterized by the absence of early warning signs, especially because small tumours rarely produce symptoms. Thus, diagnosis can be delayed until the disease has progressed. (Motzer, Bander et al. 1996) Among patients with RCC, the overall 5-year survival has been reported to be 77-92% for locally treated disease, (Ito, Kojima et al. 2015) decreasing to 21% after the first metastasis. (Schlesinger-Raab, Treiber et al. 2008) The lung is the most common site of metastasis, but an estimated 30% of patients will develop skeletal metastases. The overall survival rate after the first operation for skeletal

metastasis is only about 11% at 5 years. (Lin, Mirza et al. 2007) Both primary RCC and metastases from RCC are relatively resistant to adjuvant treatments; therefore, surgery is considered an index option for skeletal metastatic lesions. (Hwang, Nandra et al. 2014) In general, the possibility of nephrectomy, absence of visceral metastases, and solitary skeletal metastases improve overall survival. Regarding the operative procedures, data suggest that resection of a solitary skeletal lesion with a tumour-free margin increases the survival rate, (Baloch, Grimer et al. 2000, Jung, Ghert et al. 2003, Fottner, Szalantzy et al. 2010) but other published data question this. (Durr, Maier et al. 1999, Lin, Mirza et al. 2007, Evenski, Ramasunder et al. 2012) The possible increase in morbidity due to surgery and prolonged post-operative rehabilitation also decreases the tendency towards aggressive surgery, as the benefit may be insignificant. Nonetheless, several studies reported that en bloc resection prevents local progression in addition to the probable benefit of increased survival. (Baloch, Grimer et al. 2000, Les, Nicholas et al. 2001, Evenski, Ramasunder et al. 2012)

2.8.5 Prediction of survival

Various assessment systems have been designed to predict survival periods and select the ideal treatment option. Assessment scoring systems are applicable to spinal metastases, (Bauer and Wedin 1995, Tomita, Kawahara et al. 2001, Tokuhashi, Matsuzaki et al. 2005) and the original Bauer and modified Bauer scoring systems for pathological fracture have had the best correlation with the prediction of survival. (Leithner, Radl et al. 2008, Wibmer, Leithner et al. 2011) Four positive prognostic factors are included in the modified Bauer's scoring system: absence of visceral metastases, solitary skeletal metastasis, not primary lung cancer, and primary tumour (breast, kidney, lymphoma, or myeloma). In a multivariable analysis by Katagiri et al, primary tumour, performance status, visceral and cerebral metastases, previous chemotherapy, and multiple metastases were significant independent prognostic factors. (Katagiri, Okada et al. 2014)

Different models have been developed for use via the Internet using factors reported to affect survival. For example, the PATHFx models are Bayesian Belief Networks comprised of 10 prognostic features,

including age at the time of surgery, sex, indication for surgery (impending or completed pathological fracture), number of bone metastases (solitary or multiple), surgeon's estimate of survival (post-operatively, in months), presence or absence of visceral metastases, presence or absence of lymph node metastasis, pre-operative haemoglobin concentration (g/dL, upon admission to the hospital, prior to transfusion, if applicable), absolute lymphocyte count (K/μL), and the patient's primary oncological diagnosis, classified into one of three groups: group 1, lung, gastric, and hepatocellular carcinoma and melanoma; group 2, sarcomas and other carcinomas; and group 3, breast, prostate, renal cell, and thyroid carcinoma, multiple myeloma, and malignant lymphoma. (Forsberg, Eberhardt et al. 2011) PATHFx is relatively sensitive and specific as classified by 3-month survival in 253 of 287 (88%) patients and 12-month survival in 199 of 287 (69%) patients. (Forsberg, Wedin et al. 2012)

2.9 Economical concepts

Metastatic bone disease and SREs are signs of cancer progression; these patients utilize more health resources than patients who have only cancer. Not only are the inpatient lengths of stay longer through their index and follow-up admissions, but they are also re-admitted more often. In addition, once a patient has developed skeletal metastases and has a SRE, the risk for subsequent events increases with the time between re-admissions for SREs becoming shorter. (Pockett, Castellano et al. 2010) SREs are associated with substantial increases in health resource utilization in many countries. (Body, Pereira et al. 2015) A population-based study of prostate cancer in the US reported that the inflation-adjusted charges associated with hospital visits for patients with bone metastases rose by 92% to $1 512 449 106 and those for SREs rose by 94% to $369 256 799 in 12 years. This overtaking by surgery also had an effect on the trends in hospital charges, as the median charges associated with surgery were higher than those associated with radiation. (Roghmann, Antczak et al. 2015) The economic burden of SREs in patients with lung cancer with skeletal metastases has also been noted. (Delea, Langer et al. 2004) In RCC, surgery due to SREs increased from 3.6% in 1998 to 5.9% in 2010.

The overall inflation-adjusted mean costs associated with hospital visits by patients with RCC and skeletal metastasis increased by 207%. The study demonstrated that the prevalence and mortality of SRE-associated hospitalization in patients with metastatic RCC is decreasing, but associated costs are increasing at a staggering rate. (Antczak, Trinh et al. 2014) Prompt surgical management can be cost-effective, and choosing the right surgical method becomes more important, e.g. modular prostheses are cheaper than custom made prostheses. (Ashford, Hanna et al. 2010)

Treatment of patients with metastatic bone disease is a complex and sensitive area of orthopaedic surgery. This thesis will give insight into surgically treated skeletal metastases, particularly survival, surgical methods, and complications. This thesis emphasizes the role of the multidisciplinary team and the prediction of survival in patient care.

3 AIMS OF THE STUDY

Patients suffering from non-spinal skeletal metastases were the most important reason for this study, as there was a need to highlight the complicated situation in these patients. Some of these patients spend the last days of their lives relying on the expertise of orthopaedic surgeons, and they should be treated with the most concern. On the other hand, in some patients the situation is not as devastating as one might first think. Thus, there is a need for more unique treatment guidelines. The specific aim of each publication is listed below.

I To evaluate the data on 1195 surgically treated non-spinal skeletal metastases to gain a better understanding of the relationship between primary diagnose, location of bone metastases, and history of cancer disease with survival, disease-free interval, and complications after surgery.

II To research the differences in prognostic factors for survival after surgical treatment of non-spinal skeletal metastases in the four most common primary tumours causing bone metastasis: breast, lung, prostate, and kidney. We also wanted to know whether there would be any differences in complication or re-operation rates.

III To evaluate the impact of pre-operative embolization on intra-operative blood loss and operating time, and the effect of marginal resection in non-spinal skeletal metastases in RCC.

IV To identify the incidence of VTE and the impact of PE on survival in this patient cohort.

4 PATIENTS AND METHODS

4.1 Patients and study designs

Patient data for the first and second study are based on the Scandinavian Sarcoma Group (SSG) Skeletal Metastases Registry. Interested physicians and scientists from the Scandinavian countries constituted the SSG in 1979. In 1999, a multicentre prospective SSG Skeletal Metastases Registry was constituted to evaluate treatment results and prognostic factors in patients with surgically treated non-spinal skeletal metastases. There are 11 centres, five of which are responsible for more than 80% of the cases. These centres are Karolinska University Hospital Stockholm, Sweden; Aarhus University Hospital, Aarhus, Denmark; Tampere University Hospital, Tampere, Finland; Sahlsgrenska University Hospital, Gothenburg, Sweden; and Haukeland University Hospital, Bergen, Norway. The indications for surgery were an existing pathological fracture or impending fracture where the degree of bone disruption warranted prophylactic surgical stabilization to prevent a fracture or intractable pain or the loss of ambulatory ability. Contraindications to surgery were suspected survival <4 weeks and poor overall status. In Tampere, approval was obtained from the local ethical committee of Tampere University Hospital.

In the first study, we gathered all of the SSG data on a total of 1195 operated skeletal metastases in 1107 patients. Patients were operated on between June 1999 and October 2009. Chest X-ray, abdominal ultrasound and/or whole-body CT were performed for all patients to determine if the disease had spread. We gathered information on demographic characteristics, primary tumour, performance status, location of skeletal metastases, presence of other metastases, type of surgery, and complications. Following time intervals were recorded diagnosis of primary cancer to diagnosis of metastases, diagnosis of metastases to operation on skeletal metastases, and diagnosis of

primary tumour to operation. The date and cause of death was also recorded. Full information on dates was found on 1024 patients.

In the second study, we addressed the four most common primary cancers inducing skeletal metastasis. Using the SSG data as a framework, we also collected missing information from the centres involved. Data were collected from seven referral centres. The patients were operated on between July 1999 and July 2009. The scope of this study included 672 skeletal metastases in 617 patients with breast (n=307 metastases), lung (n=97 metastases), or prostate cancer (n=146 metastases) or RCC (n=122 metastases). The average age at the first operation was 62 years (range 28-87 years) in breast cancer patients, 64 years (range 34-86 years) in lung cancer, 73 years (range 49-96 years) in prostate cancer, and 65 years (range 39-95 years) in RCC.

To determine potential prognostic factors for survival, the cases were distributed by age (<65 years and ≥65 years), bone location (scapula, humerus, radius, ulna->upper limb, pelvis, femur, tibia, talus->lower limb), number of skeletal metastases (solitary or multiple), presence of organ metastases, presence of pathological fracture and degree of Karnofsky score (<70, no special care needed and ≥70, assistance needed), previous radiotherapy (yes or no), surgical method (plating and nailing, prosthesis, tumour prosthesis, other), surgical strategy (resection with marginal/wide margins or other including stabilization without tumour removal, curettage only, or curettage with cement), and time intervals from diagnosis of primary cancer to diagnosis of metastases, diagnosis of metastases to operation on skeletal metastases, and diagnosis of primary tumour to operation. All of the time intervals were checked at 6 months, 12 months and 2, 5, and 10 years. If wide resection positively impacted survival, we also analysed the impact comparing single and multiple skeletal metastases.

The scope of the third study was RCC patients. Patients were identified from prospectively maintained databases at four institutions acting as referral bone tumour centres (Aarhus, Denmark; Bergen, Norway; Stockholm, Sweden; and Tampere, Finland). All patients were operated on for non-spinal skeletal metastases from a primary RCC and identified between October 1999 and June 2014. Metastatic RCC was confirmed histologically in all cases. A total of 148 operations were performed in 144 patients. The study population comprised 99 (69%) male and 45 (31%) female patients, with a mean age of 67 years (range

40-90 years) at primary reconstruction. Fifty-six of the 148 tumours (38%) were pre-operatively embolized.

Patient demographics, including age at presentation, sex, comorbidities (diabetes and heart disease), American Society of Anaesthesiologist (ASA) physical status classification, smoking, size of metastases, site of metastases (humerus, femur, pelvic, or other), pre-operative investigations (radiographs, CT, MRI, and haemoglobin), number of skeletal metastases, and previous radiotherapy at the site of interest, were recorded. Data on the RCC, including nephrectomy, use of targeted drugs, and presence of organ metastases, were also recorded. Pre-operative embolization was recorded and the decision to refer the patient for angiography and pre-operative embolization was based on tumour size, location, and the availability of angioradiological service. Surgery was always performed within 72 h following pre-operative embolization when it was performed. Feeding arteries (range: 1 to 7 arteries) were accessed with microcatheters and occluded using diverse techniques according to operator and institutional preferences. Detachable platinum coils, liquid embolization materials (acrylic glues), particles (polyvinyl alcohol), gelatine foam powder, or a combination of these methods were used. The majority of tumours were embolized with platinum coils, particles, or a combination of these. The technical success of embolization was evaluated by comparing the pre-embolization and post-embolization angiography images after completing the procedure. The primary outcome of the study was intra-operative estimated blood loss (IBL). Information on IBL was found on 140 patients. Information on number of skeletal metastases was found on 136 patients. The variables used in the analyses included the surgical strategy, pre-operative embolization, tumour size, operation time, patient age, co-morbidities, pre-operative haemoglobin value, surgical method, and tumour localization.

In the fourth study, patients were identified from a prospectively maintained database at Tampere University Hospital. All consecutive patients treated surgically for non-spinal skeletal metastases between 1 April 1999 and 31 July 2014 were included in the study. A total of 343 procedures were performed in 306 patients. Specific data were retrospectively collected from the medical records. Surgical procedures included intramedullary nailing or plating with or without cementing, total arthroplasty, tumour prosthesis, and Harrington's procedure.

Symptomatic DVT was identified by ultrasound. PE was diagnosed by CT or autopsy. Data regarding deaths were verified by death certificates and autopsy reports from Tampere University Hospital. Death dates and diagnoses were verified by Statistics Finland for patients who died outside the hospital. In the year 2004, the national guidelines for post-operative thromboprophylaxis were introduced. After this recommendation, all major orthopaedic patients had post-operative prophylaxis comprising enoxaparin (40 mg) or dalteparin (5000 IU) started 6-12 hours post-operatively and continued on a once daily basis unless a bleeding complication or major bleeding risk was present. No mechanical prophylaxis was used. The following variables were used: gender, age, primary diagnosis, number of skeletal metastases (solitary/multiple), metastatic load and sites (lung and liver), intra-operative bleeding events, operating time, intra-operative oxygen saturation drop during nailing or when cementing the nail or stem (no vs. minor drop 5-15% and major drop >15%), fracture location (humerus, radius, ulna, scapula, pelvis, femur, or tibia), specific surgical method, surgical strategy (marginal vs. intralesional), low molecular weight heparin (LMWH) use (cut-off point: 28 days), and the variables from the Khorana score: site of cancer (2 points for very high-risk site including pancreas and stomach cancer, 1 point for high-risk site including lung, lymphoma, gynaecologic, genitourinary cancers, excluding prostate cancer), platelet count ≥350×10⁹/L, haemoglobin <100 g/L and/or use of erythropoiesis-stimulating agents, leukocyte count >11×10⁹/L, and BMI ≥35 kg/m² (1 point each).

4.2 Statistical analysis

Statistical analyses were performed using SPSS version 20.0 or 21.0. In all four studies, the survival analyses were conducted by the Kaplan-Meier (K-M) method and Cox regression analysis. Overall survival rates and differences in survival with respective variables were calculated using the K-M method and log-rank test, and cumulative intervals were calculated in Microsoft Excel. Cox regression analyses were performed to find significantly independent prognostic factors. The significance level was set at P=0.05. Patients for whom the date of death was missing because the patient was either still alive or lost to follow-up

were censored at the last time they were known to be alive. If the reason for death was not cancer, the case was censored. Survival was calculated as the time from the operation date to the date of death. Data were presented as hazard ratios (HRs) and 95% confidence intervals (CIs). The proportional hazard assumption was taken into account. All of the variables were checked with K-M curves. We plotted the cumulative hazard functions for the covariates and confirmed that lines do not cross each other.

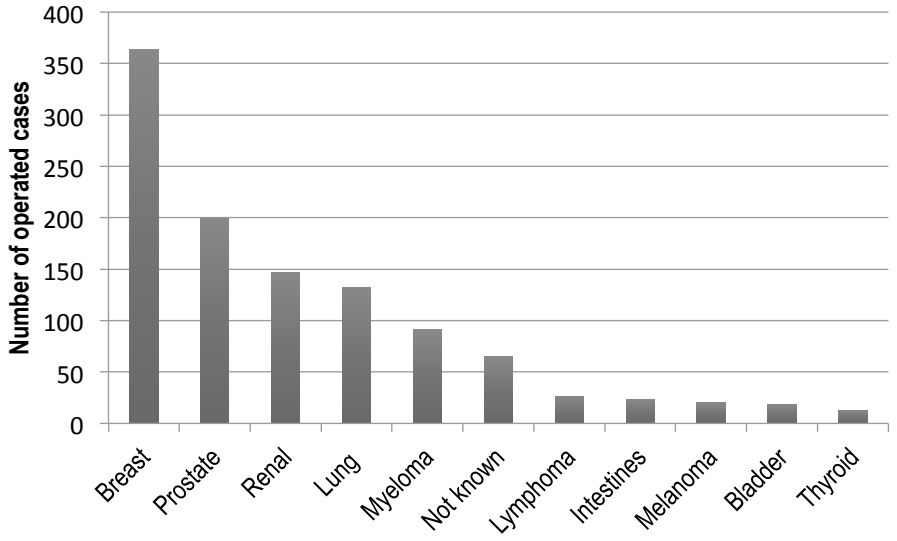
Logarithmic transformation was used because the amount of IBL was not normally distributed. Interactions between variables were also evaluated. In addition, in the third study the Mann-Whitney U test was used to evaluate the significant differences between the groups with or without embolization. In the fourth study, the chi-square test or Fisher's exact test was used in the case of proportions and the t-test in the case of continuous variables for the analysis of risk factors for VTEs. Independent risk factors were evaluated for VTE and PE using multivariable analysis with binary logistic regression.

5 RESULTS

5.1 Insight into surgically treated skeletal metastases (study I)

The SSG Skeletal Metastases Registry comprised a total of 1195 skeletal metastases in 1107 patients with more than 20 different fracture-causing metastatic primary tumours. The most common primary tumour was breast cancer (31%), followed by prostate cancer (17%), renal cancer (12%), lung cancer (11%), and myeloma (8%). These tumours accounted for 78% of the cases (Fig. 8).

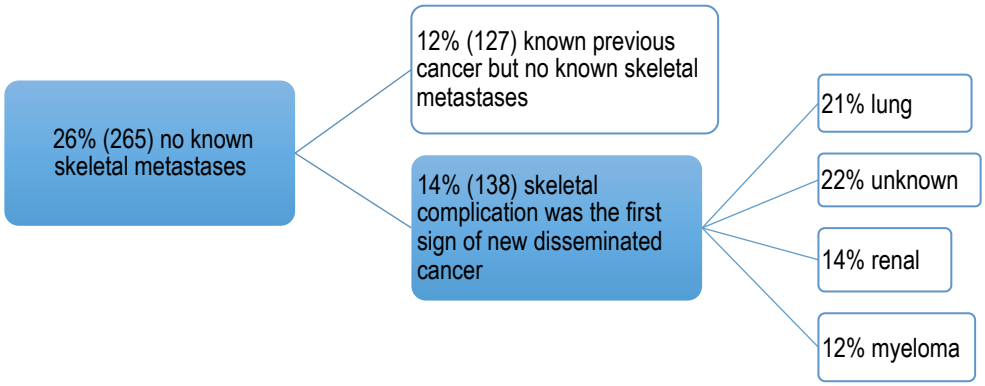
Figure 8. Number of operated cases according to different primary tumours.



Data on diagnostic dates was found in 1024 patients. In 14% (138/1024) of the patients, skeletal complications were the first manifestation of cancer. Among these cases, the most frequent diagnoses were unknown cancer (22%, 30/138), lung cancer (21%, 29/138), renal cancer (14%, 20/138), and myeloma (12%, 17/138) (Fig. 9). No skeletal metastases were detected in 26% (265/1024) of patients 1 week before surgery. In

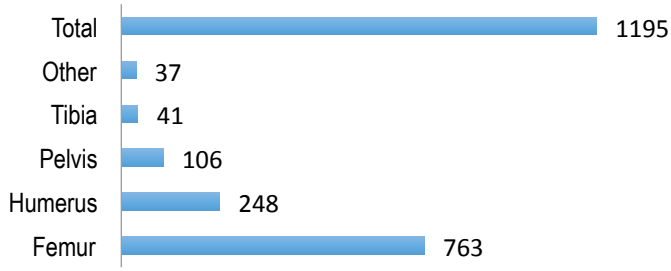
36% (371/1024) of the patients, the primary cancer and metastatic disease were diagnosed at the same time. Among patients with known cancer, the skeletal complication was the first sign of skeletal metastasis in 12% (127/1024) of patients.

Figure 9. Skeletal complication as the first sign of disseminated cancer.



In these patients, the cancer diagnosis was made less than 1 year earlier in 25% (32/127) of patients, and more than 5 years before in 32% (41/127) of patients. The most common affected location was the femur, followed by the humerus, pelvis, and tibia (Fig. 10). Of the treated femoral fractures (763/1195, 64%), 79% were located in the proximal parts of the femur, followed by the diaphysis in 14% and the distal femur in 7% of fractures. In the humerus, the diaphysis was the most common location (58%). Prosthetic reconstruction including tumour prosthesis was performed in 47% (556/1195) of cases and nailing or plating in 46% (554/1195) of cases.

Figure 10. Localization of non-spinal skeletal metastases at the time of operation.



5.2 Indication for surgery (study I)

Complete fracture was the cause for surgery in 74% of cases and impending fracture in 18% of cases (Table 1). Survival was longer in cases in which the indication for surgery was pain or impending fracture. In these patients, the mean age was lower (64 years with impending fracture vs. 67 years with complete fracture) and time from metastases to surgery shorter (12 months vs. 15 months, respectively) compared to patients with complete fractures.

Table 1. Survival, patient age, and time from metastasis diagnosis based on the main indication for surgery included all 1195 operated metastases.

Main indication	Complete fracture	Impending fracture	Pain
Number of cases	886 (74%)	219 (18%)	57 (5%)
Median survival, months (range)	7.5 (6.6-8.4)	11.9 (9.4-14.4)	11.6 (6.4-16.7)
Mean age at operation, years	67	63	63
Mean time from diagnosis to operation, months	15	9	13

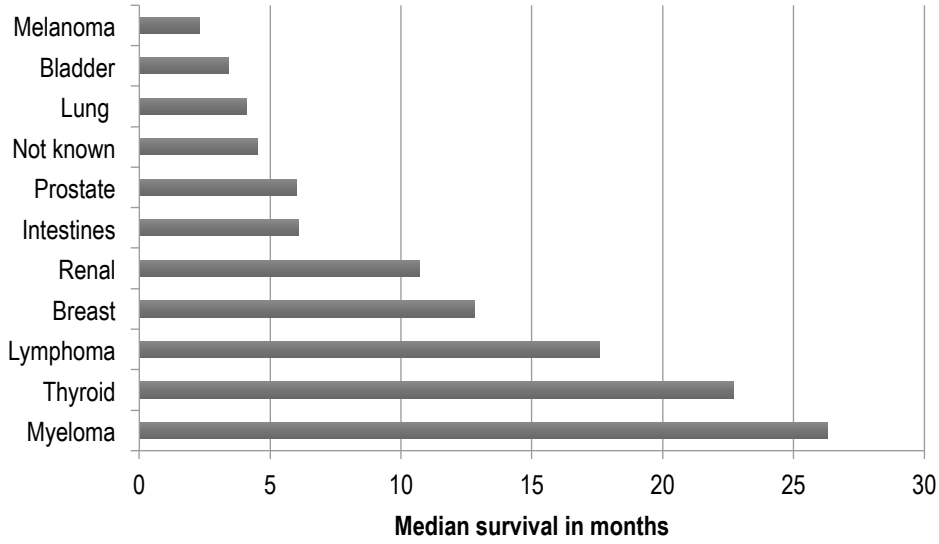
3% of cases did not have adequate data for analysis

5.3 Survival and a prognostic scale (study I)

The overall patient survival rate after surgery for metastases was 58% at 6 months, 41% at 1 year, and 2% after 5 years. The median survival was longest in myeloma patients (26 months), thyroid cancer (23 months), breast cancer (12 months), and kidney cancer (10 months). Melanoma had the worst prognosis of 2.3 months (Fig. 11). The longest survival times, >10 years, were in patients with breast and prostate cancer. Some patients with RCC, myeloma, and lymphoma survived >9.5 years after surgery. In 131 of the 1195 cases (11%), death occurred within 4 weeks after surgery.

To develop a simple prognostic scale for estimating survival, the following prognostic factors were examined: number of skeletal metastases, presence of visceral metastases, age, performance status, presence of pathological fracture, and primary site of the tumour.

Figure 11. Median survival in patients with different primary tumours analysed by the K-M method.



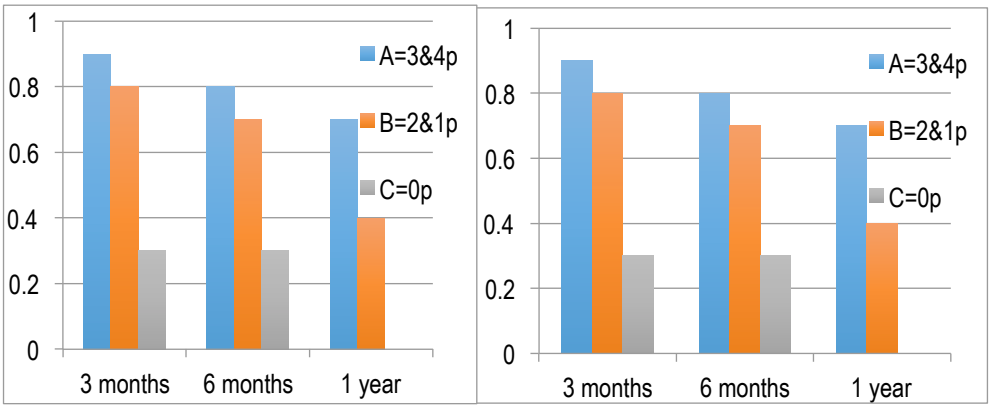
The K-M method and Cox regression analysis were used to identify significant factors. Significant variables had the same corresponding estimated regression coefficients, which were multiplied by 2 and rounded off to the nearest integer so that all variables were given 1 point (Table 2). Primary tumours with survival >12 months were sorted into one group and survival <12 months into another group

Table 2. Significant variables and points for estimation.

Significant variables	Point
Solitary metastasis	1
Karnofsky score >70	1
No organ metastasis	1
Breast, renal, thyroid, myeloma, lymphoma	1

Full data was available on 833 patients. We randomized 20% of patients (n=178) to a "testing set" and performed the analysis with 651 patients called a "training set". Patients were scored from 0 to 4 and divided into five groups according to the prognostic score. The rates of survival for each group were calculated using the K-M method. Survival rates seemed to sort into three lines; thus, three groups were created (A, B, and C). Survival was estimated at 3, 6, and 12 months. The training and testing sets had similar results (Figure 12).

Figure 12. Patient survival in the training and testing groups. (A) Survival was reliable over 6 months for patients with 3 or 4 points. (B) Patients with 1 or 2 points were likely to survive over 3 months. (C) Survival for 3 months was unsure for patients with 0 point.



training set testing set

5.4 Differences in prognostic factors in different primary cancers (study II)

For breast cancer patients, the independent prognostic factors for better survival were age <65 years, Karnofsky score >70, and solitary skeletal metastases. Solitary skeletal metastasis was rare in breast cancer, as 90% of the patients had widely spread disease. A long interval between the diagnosis of primary cancer and the operation for

skeletal metastases did not affect survival. Survival was short in all lung cancer patients, just a few months on average. A Karnofsky score <70 and organ metastases were independent risk factors for decreased survival (Table 3). Prostate cancer patients were typically older and had multiple skeletal metastases. Only a few patients (5%) had solitary metastasis at the time of operation. In addition to the presence of organ metastases, an interval >6 months between the diagnosis of primary disease and surgery for skeletal metastases was a significant negative prognostic factor. In RCC, 45% of the patients had solitary skeletal metastases. Metastasis to the upper extremities and pelvis and a Karnofsky score >70 indicated better survival (Table 3).

Table 3. Prognostic factors in different primary tumours based on the multivariable analysis.

Primary cancer	Prognostic factor	P-value	HR	95%CI	
Breast cancer	Karnofsky score <70	0.001	1.5	1.2	1.9
(n=307)	Multiple skeletal metastases	0	2.3	1.4	3.8
	Age >65 years	0.01	1.4	1.1	1.8
Lung cancer	Karnofsky score < 70	0.013	1.7	1.1	2.6
(n=97)	Presence of organ metastases	0.002	2	1.3	3.2
Prostate cancer	Presence of organ metastases	0.005	1.9	1.2	3
(n=146)	Time from primary diagnosis to operation < 6 months	0.007	2.1	1.2	3.6
Renal cancer	Karnofsky score < 70	0	3	1.9	4.6
(n=122)	Pelvis	0.026	0.4	0.2	0.9
	Upper limb	0.053	0.6	0.4	1
	Surgical strategy other than wide resection	0.039	1.8	1	3.3

5.5 Marginal resection in renal cell carcinoma (study II & III)

Marginal resection of solitary skeletal metastasis resulted in enhanced survival in all primary tumour groups. The difference was 20 months on average and significant. Because solitary skeletal metastases were so rare, the statistical justification was lost in all other primary tumours except RCC. RCC patients undergoing marginal resection of a solitary metastasis had 4-fold increased survival compared to patients with a solitary metastasis undergoing intralesional surgery. (Fig.13, Table 4) Age, tumour size, tumour location, surgical method, and pre-operative embolization did not have any effect on survival. In the Cox model, solitary metastasis ($p=0.013$), marginal resection ($p<0.001$), haemoglobin >100 g/L ($p<0.001$), and nephrectomy ($p<0.001$) were independently associated with improved survival rates. There was no significant interaction between these variables.

Figure 13. K-M survival curves for intralesional and marginal resection including 140 RCC patients with 144 operated metastases.

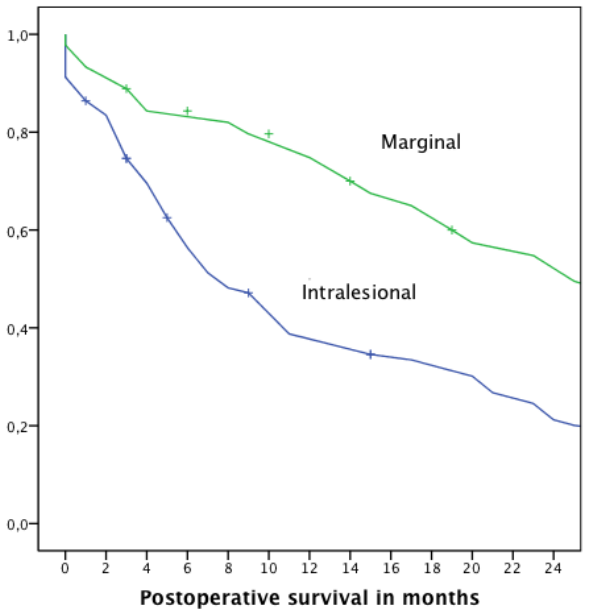


Table 4. Comparison of surgical strategies and survival in RCC patients.

	n	Survival, months	95%CI		P-value
Multiple skeletal metastases	58				0.004
intralesional resection	46	6	4.2	7.5	
marginal resection	12	14	6.7	21	
Solitary skeletal metastasis	78				
intralesional resection	49	11	6.8	15	0.017
marginal resection	29	29	12	46	

5.6 Complications and re-operations (study I &II)

Complications were reported in 13% (154/1195) of cases. The following mechanical complications were reported: 37 prosthetic complications, 9 nail breakages, 8 fractures, and 4 hematomas. The following non-mechanical complications were reported: 19 deep infections, 22 wound infections, 13 nerve complications, 10 systemic complications (disease progression, PE, liver failure, aspiration pneumonia, DVT, embolism, fat embolism, and fibrosis). In all fatal PE complications (n=4 cases), the main reason for surgery was impending fracture.

A comparison of the features of cases with complications, such as age, sex, metastatic load, primary tumour type, localization, Karnofsky score, surgical method, and nationality, revealed no specific risk factors. In the plating and nailing group (including plating, reconstruction, and intramedullary nailing), the total number of complications was 61 out of 554 (11%) (Table 5). The reported complications were wound infections, deep infections, nail breakage, fractures next to implant, nerve injuries, non-union, and technical errors/immediate failures. In the prosthetic replacement group (including hemiprothesis, total joint replacement, EPR, and acetabular reconstruction), the total number of complications was 72 out of 479 (15%). In addition to systemic complications, there were wound

infections, deep infections, nerve injuries, immediate fails/technical errors, and prosthetic complications, including dislocations and hematomas. The complication rate in EPRs was 13%.

Table 5. Survival and complications associated with surgical methods.

Surgical method	n	Survival, months	95%CI	Complications	%
Plate and nail	554	7.4	(6.1-8.6)	61	11
Prosthesis	479	8.1	(6.6-9.5)	72	15
Tumour prosthesis	77	15	(13-18)	10	13

In the second study, we could not find differences in complication rates between different primary tumours, but pre-operative RT was associated with a higher complication rate. The complication rates in patients not receiving pre-operative RT were 5%, 12%, 10%, and 8% in lung, prostate, breast, and kidney cancer, respectively, whereas the corresponding complication rates in patients receiving pre-operative RT were 15%, 15%, 15%, and 35%, respectively. The same effect was seen when different surgical methods were studied; for example, after plating and nailing, the patients receiving pre-operative RT had complications more frequently (18%, 14/78) than patients who did not receive pre-operative RT (9%, 20/234). This was also seen with prosthetic complications (11%, 9/82 vs. 4%, 6/172, respectively) and wound and deep infections (9%, 7/82 vs. 4%, 7/172, respectively).

The overall re-operation rate was 5.9%; the rate of re-operation was 6.1% in the plating and nailing group and 4% in the prosthetic replacement group. The re-operation rate was the same for complete pathological fracture (6%, 53/867) and impending pathological fracture (6%; 16/267). Common reasons for re-operation were non-union (n=14), local tumour progression (n=7), and fracture (n=9). Four impending fractures and one pre-operatively radiated fracture were re-operated because of local tumour progression. The number of re-operations was similar for different primary tumours. The re-operation rates in patients with breast, lung, and prostate cancer and RCC were 6%

(19/306), 2% (2/97), 6% (9/136), and 7% (9/122), respectively. The reasons for re-operation did not differ between different primary tumours. All local recurrences were re-operated on in patients in which the primary indication for surgery was an impending fracture, and none of these patients received pre-operative RT. The complication and re-operation rates were low after marginal resection. (Table 6)

Table 6. Complication and re-operation rates after intralesional and marginal resection.

Complications

Number of skeletal metastases	Surgical strategy	
	Intralesional	Marginal
solitary n=115 (17%)	12/86 (14%)	4/29 (14%)
multiple n=556 (83%)	13/542 (2%)	1/14 (7%)

Re-operations

Number of skeletal metastases	Surgical strategy	
	Intralesional	Marginal
solitary n=115	11/86 (13%)	2/29 (7%)
multiple n=556	14/542 (3%)	0/14 (0)

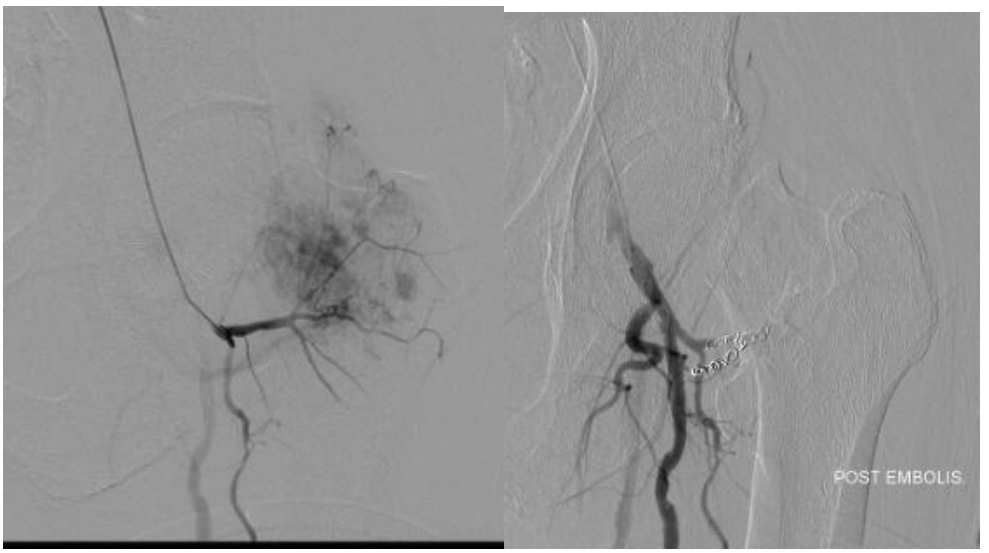
5.7 The role of preoperative embolization (study III)

A total of 140 RCC patients had information on IBL: 86 without pre-operative embolization and 54 with pre-operative embolization. Adequate post-embolization results were obtained in 46 cases (82%).

The IBL was significantly greater in the pelvic region than other sites (i.e., humerus, femur, others). Pelvic localization ($p<0.001$) and large tumour size ($p<0.001$) were identified as significant factors affecting IBL. No interactions were found between variables. Age, liver metastases, overall metastatic load, solitary skeletal metastases, pre-operative haemoglobin value, use of tourniquet, and the surgical time,

method, and strategy, as well as pre-operative embolization (including adequate cases), did not have any effect on the IBL.

Figure 14. Adequate embolization result in the proximal femur region.

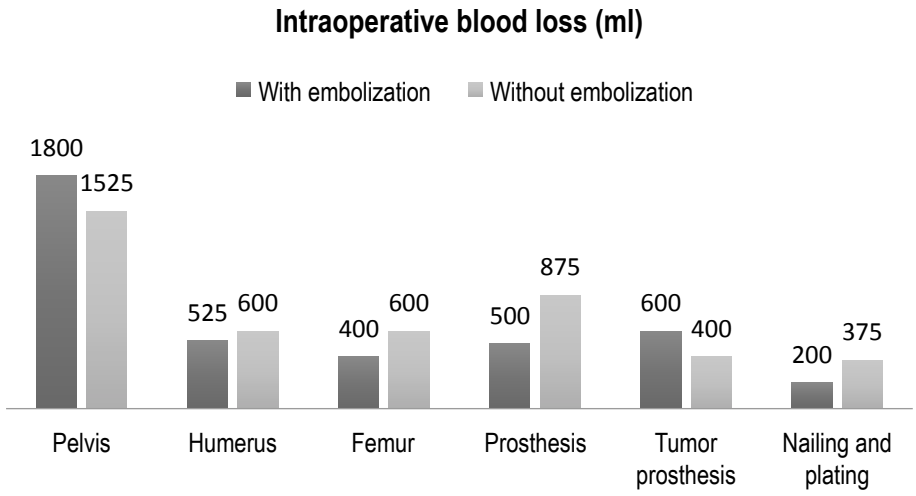


There were no significant differences between the groups with or without pre-operative embolization (Table 7 and Fig. 14). In addition, pre-operative embolization did not have a positive effect on the operating time. No procedure-related complications occurred during or after embolization, and it did not predispose patients to complications.

Table 7. Number of metastatic lesions treated with or without embolization at each site and in different surgical methods, median IBL and statistical significance from Mann-Whitney U-test.

With embolization	n	Median IBL	Without embolization	n	Median IBL	p-value
Femur	29	400	Femur	47	600	0.5
Pelvis	9	1800	Pelvis	6	1525	0.6
Humerus	14	525	Humerus	23	600	0.8
Other	2		Other	10		
Total	54		Total	86		
				n		
Prosthesis	22	500	Prosthesis	20	875	0.2
Tumor prosthesis	17	600	Tumor prosthesis	17	400	0.2
Nailing and plating	9	200	Nailing and plating	26	375	0.2
Other	6		Other	24		
Total	54		Total	86		

Figure 15. Median IBL (ml) among the different subgroups, with and without pre-operative embolization.



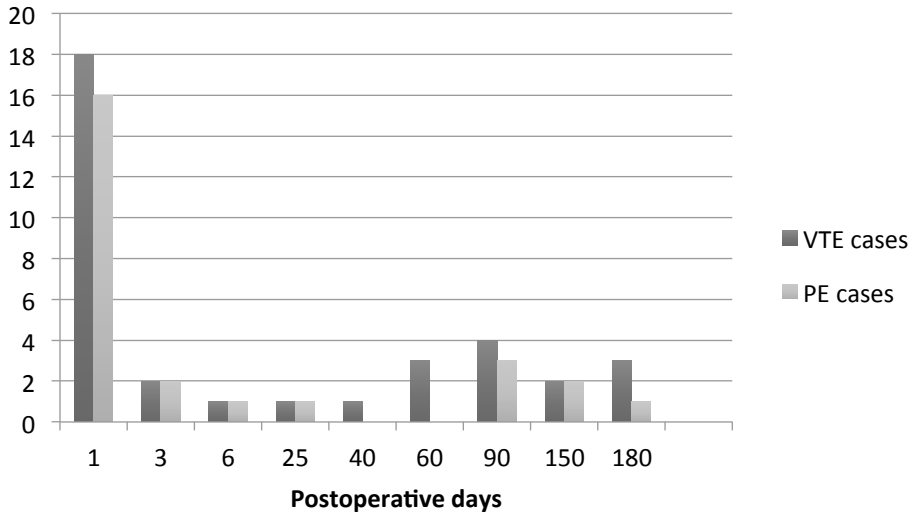
5.8 Postoperative VTE (study IV)

A total of 343 procedures were performed in 306 patients, including 171 females (55.9%) and 135 males (44%). The study population comprised several different primary tumours. Breast cancer, myeloma, and RCC were the most common primary cancers. Pathological fracture was present in 92% of cases (n=317). VTE was identified in 35 patients (11%), 26 of which had PE (8.5%). The mean time from operation to symptoms was 62 (range 0 180) days. DVT occurred in 11 patients (3.6%). The mean time from operation to symptoms was 82 (range 0 180) days. In the 3-month post-operative period, the VTE rate was 10%. The rate of fatal PE was 38.5% (10/26) (Fig. 16).

Age, BMI >30 kg/m^2, anaemia (Hb <100), presence of a pathological fracture, pelvic location, femoral location, multiple skeletal metastases, IBL, or post-operative LMWH prophylaxis did not affect the occurrence of VTE. Leukocytosis ($p<0.01$), intramedullary nailing ($p=0.03$), pulmonary metastases ($p=0.02$), lung cancer ($p=0.04$), and decreased intra-operative saturation ($p<0.002$) were significant factors in the univariate analysis. In the multivariable analysis, decreased intra-operative saturation ($p=0.002$) pulmonary metastases ($p=0.04$), and

intramedullary nailing (p=0.02) were significant independent factors. Of the 35 VTE patients, 30 (85.7%) used LMWH post-operatively at a prophylactic dose. The Khorana score did not predict VTE in this patient cohort.

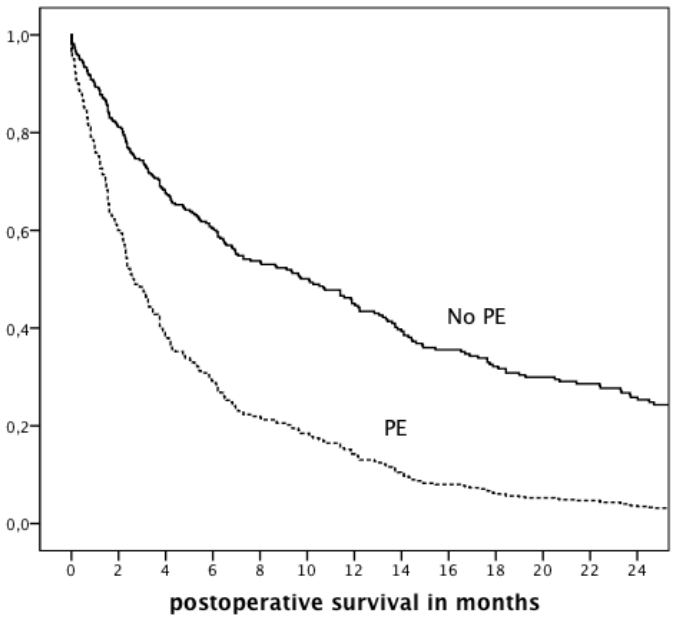
Figure 16. The number of post-operative VTE and PE cases.



5.9 Intra-operative decrease in saturation and survival (study IV)

Half of the patients with PE presented with a major decrease in oxygen saturation (13/26) during surgery compared to 3.2% (9/280) of the patients without PE. Six patients died within 24 hours post-operatively; five had decreased oxygen saturation and four had PE. Survival markedly declined in patients suffering from PE (p<0.001; Fig. 5). Overall survival was 42.9% at 1 year and 23.9% at 2 years, declining to only 16.1% at 3 years. Lung cancer (RR=2.3, p<0.001), intramedullary nailing (RR=1.5, p<0.003), multiple skeletal metastases (RR=1.3, p<0.016), anaemia (RR=2.7, p<0.001), leukocytosis (RR=1.5, p<0.006), PE (RR=2.1, p<0.004), and pulmonary metastases (RR=1.5, p<0.013) were independently associated with decreased survival. There were no interactions between variables.

Figure 17. Curve showing the adverse effect of pulmonary embolism on survival in the Cox regression analysis.



6 DISCUSSION

This is the first thesis having the main focus on surgical treatment of skeletal metastases in Finland. This thesis with the articles involved hopefully raises knowledge on the topic of skeletal metastases among medical staff treating these patients. The large SSG metastasis registry database is an international and multicentric and provides excellent opportunity to investigate the association between pathologic fractures and patient survival. More personalized survival data is needed to improve the understanding of prognostic factors for patients with skeletal metastasis. As the possible survival time is taken into account the long survivors could be treated more aggressively and short survivors with minimal surgery leading to more humane treatment and also to more cost-effective use of health care resources. According to previous studies, skeletal metastasis at the time of cancer diagnosis is rare; 4.8% of RCC patients have skeletal metastasis at the initial diagnosis, 2.5% of prostate carcinoma patients, and 7.3% of breast carcinoma patients (Salonia, Gallina et al. 2006, Schlesinger-Raab, Treiber et al. 2008, Sathiakumar, Delzell et al. 2012). In our series, 36% of the patients treated surgically had diagnosis of cancer and metastatic bone disease at the same time. (I)

6.1 Survival after surgery, is there any point to operate?

In our study, the overall survival of cancer patients with skeletal metastases after operating on pathological fracture ranged from a few months to several years depending on the primary tumour. The mean survival was >1 year in breast cancer patients, compared to <6 months post-operative survival in lung cancer patients. Though almost all pathological fractures herald end-stage disease, in this study 58% of patients survived >6 months and 41% >1 year. Moreover, some of the patients even survived 9 years post-operatively in study I. In our

studies, we showed that primary tumour, number of skeletal metastases, load of organ metastases, and performance status were independent and significant factors affecting post-operative survival. To avoid burdensome overtreatment in patients with limited remaining lifetime, we created a simple and robust scale for distinguishing patients who are likely to die within 3 months and those who are likely to survive over a year. This scoring system is easy to use in everyday practise, even in the emergency room. New modern internet-based scoring systems have been developed since introduction our scoring system, and some have boosting (machine learning) algorithms. These new studies also take into account the comorbidity status and BMI. (Forsberg, Eberhardt et al. 2011, Janssen, Teunis et al. 2015) In study IV, we also took into account anaemia and leukocytosis, variables that are risk factors for poor survival. High BMI is a significant factor among cancer patients in general, but patients suffering from disseminated cancer with skeletal metastases are almost never overweight. Other significant variables associated with decreased survival in that study were pulmonary metastases and intramedullary nailing. The data indicate that our scale has similar results to other scoring systems, as they stress the importance of assessing the primary site and metastatic load.

6.2 Marginal resection, useful or not?

Marginal resection of solitary skeletal metastases significantly increased survival in all primary cancer groups, though the numbers of patients in the groups, with the exception of RCC, were so small that statistical conclusions could not be drawn. In RCC, survival was significantly increased in the marginal resection group (4-fold) compared to the intralesional surgery group (study II). The subject of aggressive resection of skeletal metastases in cancer patients has raised controversies in the literature. In some studies, wide resection has been shown to be a positive prognostic factor for improved survival, (Baloch, Grimer et al. 2000, Fottner, Szalantzy et al. 2010) but other published results have questioned this. (Durr, Maier et al. 1999, Lin, Mirza et al. 2007, Evenski, Ramasunder et al. 2012) Several studies have reported

that en bloc resection prevents local progression, (Baloch, Grimer et al. 2000, Les, Nicholas et al. 2001, Evenski, Ramasunder et al. 2012) but the possible increase in morbidity due to surgery and prolonged post-operative rehabilitation also diminished the tendency towards aggressive surgery, as the benefit may be insignificant. In our study, the complication and re-operation rates were not higher in the marginal resection group compared to the intralesional group. These results are in concordance with previous studies. (Wedin, Bauer et al. 2001, Steensma, Boland et al. 2012) In addition to the increased patient survival, our study confirmed that marginal resection increases reconstruction survival, as it prevents local progression of the disease. Our study indicates that marginal resection should be the golden standard in treating RCC patients, at least for those with solitary metastasis.

6.3 Impending fracture, stabilize or not?

Surgery for impending fractures is controversial. Surgical treatment of impending fractures is thought to be less complicated and easier to perform than surgery for complete pathological fractures. Surgery for non-displaced fractures is easier as well, but it is not an acceptable indication for surgery, at least not in traumatology. Eighteen percent of cases in the SSG database were operated on because of impending fracture (study I). We observed a great difference in indications between different countries; for example, in the US the rates are reversed with impending fractures accounting for 56%, even up to 90%, of cases. (Lin, Mirza et al. 2007, Shallop, Starks et al. 2015) In many reports, survival after surgery is usually better in the impending fracture group compared to the complete fracture group (Mavrogenis, Pala et al. 2012, Arvinius, Parra et al. 2014). That was also the case in our study; survival was better in the impending fracture group compared to the complete fracture group.

Notably, among these patients, the time between diagnosis of metastasis and surgery was shorter in the impending fracture group, indicating that the patients were operated on earlier in the course of the disease. In addition, the median age of patients operated on for

impending fracture was lower, indicating that these patients are younger, in better overall health, and have a longer life expectancy overall. The risk of complications was also lower in the group of patients operated on for impending fractures, but there was still a risk of major complications. In study IV, all fatal PEs occurred when treating impending fractures. Impending fractures are usually treated with intramedullary nailing, which was shown to be an additional significant risk factor for VTE and decreased survival. The risk for VTE and fatal PE, especially in nailing procedures for impending fractures, is high; therefore, a prophylactic nailing procedure should be carefully considered. Overall, pathological fracture is infrequent among patients with skeletal metastases. SREs are frequent, but pathological fracture is rare and the risk of a fracture is difficult to evaluate. Prophylactic procedures should be performed to prevent fracture by RT, bisphosphonates, or other medications, and surgery should be performed mainly for existing fractures. Indications for prophylactic treatments do exist, but they should be discussed with care. Solitary, massively destructive lesions from RCC and patients with infernal pain resistance to conservative treatment, for example, should be considered for prophylactic treatment.

6.4 Too fragile patients, too risky operations?

Although the data included patients with severe disease and severe complications, the complication rate was not that high. We found a complication rate of 13% among all operations, which is similar to the rates given in the literature. (Wood, Racano et al. 2014) No special risk factors were detected in cases that developed complications, including age, sex, metastatic load, primary tumour type, Karnofsky score, surgical method, bone localization, or treatment centre. More complications occurred in the prosthetic replacement group compared to the plating and nailing groups, but there were fewer re-operations. Cases with complications more often had previous RT, especially in the prosthetic replacement group. In contrast, the rate of non-union did not differ between patients who had previous RT and patients who did not have previous RT, indicating an overall poor rate of union of

pathological fractures. Previous RT apparently results in an increased risk of the number of post-operative complications, which should be kept in mind when operating on these patients. The overall re-operation rate in study II was 5.6%, which can be considered low. This may be due to our study being multinational, as all Scandinavian countries share the same methods and the treating centres were referral centres.

Additionally it has been indicated that e.g. VEGF-targeted therapies affect on wound healing, but it seems like surgery in patients receiving therapies would be safe when an appropriate interval of time is allowed between surgical procedures and treatment. This highlights the importance of cooperation with orthopaedic surgeons and oncologists.

6.5 No effect of pre-operative embolization?

We could not find significant effects of pre-operative embolization of skeletal non-spinal metastases on IBL, irrespective of whether adequate embolization results were available among the 148 cases (56 underwent pre-operative embolization) in study III. This was unexpected. In contrast, several studies advocated pre-operative embolization of bone metastases from RCC as an effective procedure for minimizing intra-operative bleeding. (Olerud, Jonsson et al. 1993, Barton, Waneck et al. 1996, Chatziioannou, Johnson et al. 2000, Pazionis, Papanastassiou et al. 2014). In our study, tourniquet use did not have an effect on the IBL, and the tumours did not differ in size or location between the embolized and non-embolized groups.

Embolization has been said to be needed, especially for vascular metastases and if the tumour is directly exposed as in proximal femoral replacement.(Issack, Barker et al. 2014) In the literature, studies that have shown any effect of embolization on reducing IBL have several limitations, including small numbers of patients, heterogeneous patient groups, and statistical methods sensitive to selection bias. (Sun and Lang 1998, Wirbel, Roth et al. 2005, Issack, Barker et al. 2014) In our study, there was a significant correlation between tumour size and IBL, irrespective of whether embolization was performed. We found that pelvic location was a significant predictor of excessive blood loss and

was probably associated with tumour size. Thus, this select group of patients with pelvic metastasis may benefit from pre-operative embolization.

6.6 True risk for thromboembolic events

Symptomatic VTE was identified in 11% of the patients, and PE was identified in 8.5% of the patients. In the 3-month post-operative period the rate of VTE was 10%. The fatal PE rate was 38.5% (10/26). We observed multiple VTEs, whereas other studies evaluating post-operative complications the number of reported VTE complications was low or not studied at all. (Henderson, Groundland et al. 2011) (Weiss, Tullberg et al. 2014) (Sorensen, Gregersen et al. 2013) (Camnasio, Scotti et al. 2008) The lack of reports of VTE can be explained several ways. First, symptoms may develop after discharge and patients may be treated in a different ward or hospital. In a study by Bjornara et al, 70% of the patients who underwent emergency and elective hip surgeries and developed symptomatic DVT or PE did so after discharge. (Bjornara, Gudmundsen et al. 2006) Second, patients suffering from disseminated cancer may die because of VTE but the cause of death is recorded as cancer. In our study, symptomatic PE significantly enhanced premature death and overall post-operative survival. The mean survival after PE was only 2 months, compared to 10 months in patients who did not experience PE. PE has been suggested to be one of the leading medical emergencies in clinical practice, (Laack and Goyal 2004) with significant mortality. (Godzik, McAndrew et al. 2014) Despite high PE-associated mortality, it has not been the focus of survival studies among patients with surgically treated skeletal metastases. In orthopaedic surgery, the use of anticoagulants has become a standard treatment in the 21st century. The use of anticoagulants among cancer surgery patients is controversial because of bleeding complications. The high risk of bleeding complications may be due to reduced blood cell count, chemotherapy and other drug interactions, renal impairment, and hepatic involvement with metastases or large dissection areas. (Lee and Carrier 2014) Treatment and prophylaxis for VTE in cancer patients have received more

attention in recent years due to the development of direct oral anticoagulants (DOACs) that target either thrombin or activated factor Xa. It is anticipated that VTE prevention and treatment will become more practical; however, the evidence of DOAC use in cancer patients is still limited. (Verso and Agnelli 2012) The only official surgical indications for DOACs are major hip and knee replacement surgery, and only a small number of cancer patients have been treated with these new drugs; therefore, the safety issues are of concern. (Lee and Carrier 2014) In our study, we had no bleeding complications among treated patients, but one of our patients died of intracerebral haemorrhage after LMWH was changed to DOAC in a health care centre.

In conclusion, we noted a striking number of symptomatic VTE events despite 79% of patients receiving post-operative thromboprophylaxis. Intramedullary nailing, pulmonary metastases, and decreased intra-operative saturation were risk factors for VTE. Interestingly, lung cancer had the most frequent decreases in intra-operative saturation and more PE cases compared to other primary cancers. As the main indication for surgery among these patients is QoL for the remaining time, any additional complication should be prevented if possible. Whether the survival of these patients could be improved by implementing a careful haematological approach that takes into account cancer-specific coagulation disorders is an important question. We need further collaboration between haematologists and oncological orthopedic surgeons to provide new insight into the diagnosis and treatment of VTE patients suffering from this devastating disease. In the future, we hope to prevent the excessively premature deaths caused by thromboembolic events.

6.7 Limitations

We acknowledge various limitations of our studies. Even though the database is quality-controlled, it is retrospective and has its limitations. The exact indications for surgical treatment varied during the study period and there could be patient and treatment selection biases. There may have been bias in selecting the types of surgical procedures,

patients for pre-operative embolization, and different embolization methods. In addition, there may be selection bias due to different medical treatments, which varied considerably, making the number of patients in different treatment categories too small for meaningful statistical analyses. Study data on thromboembolic events were gathered from a single centre. Data from Statistics Finland on deaths are updated 1 year later, thereby underestimating the true rate of VTE occurrence. The VTE study was observational and lacked a control group, which may raise concerns. However, this study group is a highly specific cohort and a control group is very difficult to compose.

Patients with a lower extremity pathological fracture jeopardizing mobility and independence cannot be left without surgery if they are likely to have more than 4 weeks to survive, as it would be unethical. Patients with skeletal metastases without a fracture are not a relevant comparison group because these patients would hardly be operated on. Also, as all of the patients had disseminated cancer and surgery there is no clinical need to distinguish or separate surgery and cancer.

Our studies also have strengths. As a multicentre and international cohort, it was large with long follow-up times. We also had the largest published series of cases with the same RCC histology. The patient information system is united; consequently, all of the reported VTEs were captured and registered. Statistics Finland is the only Finnish public authority that gathers data regarding deaths, which facilitated the comprehensive accrual of patients who died of PE after discharge.

6.8 Future

By collecting more information on patients who have been operated on because of skeletal metastases, we can proceed towards more personalized treatment strategies. Even though a cost-benefit analysis was not the subject of this study, it has been reported that the costs of surgical treatment of metastatic skeletal disease are increasing. We should find a customized treatment approach for all patients, regardless of their place of residence. Further research is warranted to define the patient groups that may benefit from embolization procedures. In addition, with the expansion of the application of

interventional radiology, the use of embolization for palliative pain control requires further investigation.

Whether the survival of the patients suffering from fractures secondary to skeletal metastases could be improved by implementing a careful hematological approach that takes into account cancer-specific coagulation disorders is an important question. We need further collaboration between hematologists and oncological orthopaedic surgeons to provide new insights into the pathophysiology, risk scoring, diagnosis, and treatment of VTE in patients suffering from this devastating disease. In the future, we hope to prevent the excessively premature deaths caused by thromboembolic events. There is also need for collaboration between oncologists and orthopaedic surgeons to find patients who benefit of surgical treatment of non spinal skeletal metastases and to choose the right time for surgery.

7 SUMMARY AND CONCLUSIONS

On the basis of the present clinical observational studies, the following ten conclusions can be drawn concerning patients operated on for non-spinal skeletal metastases:

1. With information on primary cancer, number of skeletal metastases, load of organ metastases, and performance status, post-operative survival can be roughly divided into groups of patients surviving less or more than 6 months.

2. Some of the patients can survive a substantially long period of time, even years.

3. Prophylactic fixation of impending pathological fracture with intramedullary nailing should not be encouraged because of the potential risk of severe, even fatal, complications.

4. Skeletal metastases from RCC should be treated with marginal resection, especially solitary metastases.

5. Large tumour size and pelvic location are risk factors for IBL.

6. More research is needed on the use of pre-operative embolization.

7. VTE is an under-diagnosed complication after surgery.

8. Intra-operative saturation drop and pulmonary metastases are risk factors for PE.

9. PE is a major risk factor for early post-operative death.

10. Well designed treatment plan requires collaboration between hematologists, oncologists, radiologists and orthopaedic surgeons.

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9 REFERENCES

(1994). "Impact of follow-up testing on survival and health-related quality of life in breast cancer patients. A multicenter randomized controlled trial. The GIVIO Investigators." JAMA **271**(20): 1587-1592.

Adiga, G. U., J. P. Dutcher, M. Larkin, S. Garl and J. Koo (2004). "Characterization of bone metastases in patients with renal cell cancer." BJU Int **93**(9): 1237-1240.

Agarwal, M. G. and P. Nayak (2015). "Management of skeletal metastases: An orthopaedic surgeon's guide." Indian J Orthop **49**(1): 83-100.

Agnelli, G. and C. Becattini (2010). "Acute pulmonary embolism." N Engl J Med **363**(3): 266-274.

Aktipis, C. A. and R. M. Nesse (2013). "Evolutionary foundations for cancer biology." Evol Appl **6**(1): 144-159.

Anez-Bustillos, L., L. C. Derikx, N. Verdonschot, N. Calderon, D. Zurakowski, B. D. Snyder, A. Nazarian and E. Tanck (2014). "Finite element analysis and CT-based structural rigidity analysis to assess failure load in bones with simulated lytic defects." Bone **58**: 160-167.

Antczak, C., V. Q. Trinh, A. Sood, P. Ravi, F. Roghmann, V. Trudeau, S. L. Chang, P. I. Karakiewicz, A. S. Kibel, N. Krishna, P. L. Nguyen, F. Saad, J. D. Sammon, S. Sukumar, K. C. Zorn, M. Sun and Q. D. Trinh (2014). "The health care burden of skeletal related events in patients with renal cell carcinoma and bone metastasis." J Urol **191**(6): 1678-1684.

Arvinius, C., J. L. Parra, L. S. Mateo, R. G. Maroto, A. F. Borrego and L. L. Stern (2014). "Benefits of early intramedullary nailing in femoral metastases." Int Orthop **38**(1): 129-132.

Ashford, R. U., S. A. Hanna, D. H. Park, R. C. Pollock, J. A. Skinner, T. W. Briggs and S. R. Cannon (2010). "Proximal femoral replacements for metastatic bone disease: financial implications for sarcoma units." Int Orthop **34**(5): 709-713.

Baloch, K. G., R. J. Grimer, S. R. Carter and R. M. Tillman (2000). "Radical surgery for the solitary bony metastasis from renal-cell carcinoma." J Bone Joint Surg Br **82**(1): 62-67.

Barnadas, A., L. Manso, C. de la Piedra, C. Meseguer, C. Crespo, P. Gomez, L. Calvo, P. Martinez, M. Ruiz-Borrego, A. Perello, A. Anton, M. Codes, M. Margeli, A. Murias, J. Salvador, M. A. Segui, A. de Juan, J. Gavila, M. Luque, D. Perez, P. Zamora, A. Arizcuma, J. I. Chacon, L. Heras, M. Martin-Fernandez, I. Mahillo-Fernandez and I. Tusquets (2014). "Bone turnover markers as predictive indicators of outcome in patients with breast cancer and bone metastases treated with bisphosphonates: results from a 2-year multicentre observational study (ZOMAR study)." Bone **68**: 32-40.

Barton, P. P., R. E. Waneck, F. J. Karnel, P. Ritschl, J. Kramer and G. L. Lechner (1996). "Embolization of bone metastases." J Vasc Interv Radiol **7**(1): 81-88.

Barwood, S. A., J. L. Wilson, R. R. Molnar and P. F. Choong (2000). "The incidence of acute cardiorespiratory and vascular dysfunction following intramedullary nail fixation of femoral metastasis." Acta Orthop Scand **71**(2): 147-152.

Bauer, H. C. (2005). "Controversies in the surgical management of skeletal metastases." J Bone Joint Surg Br **87**(5): 608-617.

Bauer, H. C. and R. Wedin (1995). "Survival after surgery for spinal and extremity metastases. Prognostication in 241 patients." Acta Orthop Scand **66**(2): 143-146.

BH Hansen, J. K., Minna Laitinen et al (2009). " The Scandinavian Sarcoma Group Skeletal Metastasis Registry. Functional outcome and pain after surgery for bone metastases in the pelvis and extremities." Acta Orthop **334**(80): 85-90.

Bickels, J., S. Dadia and Z. Lidar (2009). "Surgical management of metastatic bone disease." J Bone Joint Surg Am **91**(6): 1503-1516.

Bjarnason, N. H., M. Hitz, N. R. Jorgensen and P. Vestergaard (2008). "Adverse bone effects during pharmacological breast cancer therapy." Acta Oncol **47**(4): 747-754.

Bjornara, B. T., T. E. Gudmundsen and O. E. Dahl (2006). "Frequency and timing of clinical venous thromboembolism after major joint surgery." J Bone Joint Surg Br **88**(3): 386-391.

Blom, J. W., J. P. Vanderschoot, M. J. Oostindier, S. Osanto, F. J. van der Meer and F. R. Rosendaal (2006). "Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: results of a record linkage study." J Thromb Haemost **4**(3): 529-535.

Body, J. J., J. Pereira, H. Sleeboom, N. Maniadakis, E. Terpos, Y. P. Acklin, J. Finek, O. Gunther, G. Hechmati, T. Mossman, L. Costa, W. Rogowski, H. Nahi and R. von Moos (2015). "Health resource utilization associated with skeletal-related events: results from a retrospective European study." Eur J Health Econ.

Bohl, D. D., A. M. Samuel, B. A. Basques, C. J. Della Valle, B. R. Levine and J. N. Grauer (2015). "How Much Do Adverse Event Rates Differ Between Primary and Revision Total Joint Arthroplasty?" J Arthroplasty.

Botsa, E., S. Mylona, I. Koutsogiannis, A. Koundouraki and L. Thanos (2014). "CT image guided thermal ablation techniques for palliation of painful bone metastases." Ann Palliat Med **3**(2): 47-53.

Bremner, R. A. and A. M. Jelliffe (1958). "The management of pathological fracture of the major long bones from metastatic cancer." J Bone Joint Surg Br **40-B**(4): 652-659.

Briganti, A., N. Suardi, A. Gallina, F. Abdollah, G. Novara, V. Ficarra and F. Montorsi (2014). "Predicting the risk of bone metastasis in prostate cancer." Cancer Treat Rev **40**(1): 3-11.

Brown, J. E., R. J. Cook, P. Major, A. Lipton, F. Saad, M. Smith, K. A. Lee, M. Zheng, Y. J. Hei and R. E. Coleman (2005). "Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer, and other solid tumors." J Natl Cancer Inst **97**(1): 59-69.

Bussard, K. M., C. V. Gay and A. M. Mastro (2008). "The bone microenvironment in metastasis; what is special about bone?" Cancer Metastasis Rev **27**(1): 41-55.

Camnasio, F., C. Scotti, G. M. Peretti, F. Fontana and G. Fraschini (2008). "Prosthetic joint replacement for long bone metastases: analysis of 154 cases." Arch Orthop Trauma Surg **128**(8): 787-793.

Casiraghi, M., P. Maisonneuve, D. Brambilla, F. Petrella, P. Solli, J. Guarize, F. De Marinis and L. Spaggiari (2015). "The role of extended pulmonary metastasectomy." J Thorac Oncol **10**(6): 924-929.

Chambers, A. F., A. C. Groom and I. C. MacDonald (2002). "Dissemination and growth of cancer cells in metastatic sites." Nat Rev Cancer **2**(8): 563-572.

Charalampoudis, P., D. Mantas, G. C. Sotiropoulos, D. Dimitroulis, G. Kouraklis and C. Markopoulos (2015). "Surgery for liver metastases from breast cancer." Future Oncol **11**(10): 1519-1530.

Chatziioannou, A. N., M. E. Johnson, S. G. Pneumaticos, D. D. Lawrence and C. H. Carrasco (2000). "Preoperative embolization of bone metastases from renal cell carcinoma." Eur Radiol **10**(4): 593-596.

Cheung, F. H. (2014). "The practicing orthopedic surgeon's guide to managing long bone metastases." Orthop Clin North Am **45**(1): 109-119.

Cheville, J. C., D. Tindall, C. Boelter, R. Jenkins, C. M. Lohse, V. S. Pankratz, T. J. Sebo, B. Davis and M. L. Blute (2002). "Metastatic prostate carcinoma to bone: clinical and pathologic features associated with cancer-specific survival." Cancer **95**(5): 1028-1036.

Chiras, J., C. Adem, J. N. Vallee, L. Spelle, E. Cormier and M. Rose (2004). "Selective intra-arterial chemoembolization of pelvic and spine bone metastases." Eur Radiol **14**(10): 1774-1780.

Choong, P. F. (2003). "Cardiopulmonary complications of intramedullary fixation of long bone metastases." Clin Orthop Relat Res(415 Suppl): S245-253.

Chow, E., K. Harris, G. Fan, M. Tsao and W. M. Sze (2007). "Palliative radiotherapy trials for bone metastases: a systematic review." J Clin Oncol **25**(11): 1423-1436.

Chow, E., Y. M. van der Linden, D. Roos, W. F. Hartsell, P. Hoskin, J. S. Wu, M. D. Brundage, A. Nabid, C. J. Tissing-Tan, B. Oei, S. Babington, W. F. Demas, C. F. Wilson, R. M. Meyer, B. E. Chen and R. K. Wong (2014). "Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial." Lancet Oncol **15**(2): 164-171.

Chow, E., L. Zeng, N. Salvo, K. Dennis, M. Tsao and S. Lutz (2012). "Update on the systematic review of palliative radiotherapy trials for bone metastases." Clin Oncol (R Coll Radiol) **24**(2): 112-124.

Christie, J., C. M. Robinson, A. C. Pell, J. McBirnie and R. Burnett (1995). "Transcardiac echocardiography during invasive intramedullary procedures." J Bone Joint Surg Br **77**(3): 450-455.

Clausen, C., B. Dahl, S. C. Frevert, L. V. Hansen, M. B. Nielsen and L. Lonn (2015). "Preoperative embolization in surgical treatment of spinal metastases: single-blind, randomized controlled clinical trial of efficacy in decreasing intraoperative blood loss." J Vasc Interv Radiol **26**(3): 402-412 e401.

Clement-Demange, L. and P. Clezardin (2015). "Emerging therapies in bone metastasis." Curr Opin Pharmacol **22**: 79-86.

Coleman, R., L. Costa, F. Saad, R. Cook, P. Hadji, E. Terpos, P. Garnero, J. Brown, J. J. Body, M. Smith, K. A. Lee, P. Major, M. Dimopoulos and A. Lipton (2011). "Consensus on the utility of bone markers in the malignant bone disease setting." Crit Rev Oncol Hematol **80**(3): 411-432.

Coleman, R. E., P. Smith and R. D. Rubens (1998). "Clinical course and prognostic factors following bone recurrence from breast cancer." Br J Cancer **77**(2): 336-340.

Colleoni, M., A. O'Neill, A. Goldhirsch, R. D. Gelber, M. Bonetti, B. Thurlimann, K. N. Price, M. Castiglione-Gertsch, A. S. Coates, J. Lindtner, J. Collins, H. J. Senn, F. Cavalli, J. Forbes, A. Gudgeon, E. Simoncini, H. Cortes-Funes, A. Veronesi, M. Fey and C. M. Rudenstam (2000). "Identifying breast cancer patients at high risk for bone metastases." J Clin Oncol **18**(23): 3925-3935.

Colman, M. W., J. M. Kirkwood, T. Schott, M. A. Goodman and R. L. McGough, 3rd (2014). "Does metastasectomy improve survival in skeletal melanoma?" Melanoma Res **24**(4): 354-359.

Costelloe, C. M., E. M. Rohren, J. E. Madewell, T. Hamaoka, R. L. Theriault, T. K. Yu, V. O. Lewis, J. Ma, R. J. Stafford, A. M. Tari, G. N. Hortobagyi and N. T. Ueno (2009). "Imaging bone metastases in breast cancer: techniques and recommendations for diagnosis." Lancet Oncol **10**(6): 606-614.

Dahl, O. E., J. A. Caprini, C. W. Colwell, Jr., S. P. Frostick, S. Haas, R. D. Hull, S. Laporte and P. D. Stein (2005). "Fatal vascular outcomes following major orthopedic surgery." Thromb Haemost **93**(5): 860-866.

Damron, T. A., A. Nazarian, V. Entezari, C. Brown, W. Grant, N. Calderon, D. Zurakowski, R. M. Terek, M. E. Anderson, E. Y. Cheng, A. J. Aboulafia, M. C. Gebhardt and B. D. Snyder (2015). "CT-based Structural Rigidity Analysis Is More Accurate Than Mirels Scoring for Fracture Prediction in Metastatic Femoral Lesions." Clin Orthop Relat Res.

Damron, T. A., A. Nazarian, V. Entezari, C. Brown, W. Grant, N. Calderon, D. Zurakowski, R. M. Terek, M. E. Anderson, E. Y. Cheng, A. J. Aboulafia, M. C. Gebhardt and B. D. Snyder (2016). "CT-based Structural Rigidity Analysis Is More Accurate Than Mirels Scoring for Fracture Prediction in Metastatic Femoral Lesions." Clin Orthop Relat Res **474**(3): 643-651.

De Geeter, K., P. Reynders, I. Samson and P. L. Broos (2001). "Metastatic fractures of the tibia." Acta Orthop Belg **67**(1): 54-59.

Decroisette, C., I. Monnet, H. Berard, G. Quere, H. Le Caer, S. Bota, C. Audigier-Valette, L. Geriniere, J. M. Vernejoux, C. Chouaid and T. Groupe Francais de

Pneumo-Cancerologie (2011). "Epidemiology and treatment costs of bone metastases from lung cancer: a French prospective, observational, multicenter study (GFPC 0601)." J Thorac Oncol **6**(3): 576-582.

Delea, T., C. Langer, J. McKiernan, M. Liss, J. Edelsberg, J. Brandman, J. Sung, M. Raut and G. Oster (2004). "The cost of treatment of skeletal-related events in patients with bone metastases from lung cancer." Oncology **67**(5-6): 390-396.

Diel, I. J., J. J. Body, A. T. Stopeck, S. Vadhan-Raj, A. Spencer, G. Steger, R. von Moos, F. Goldwasser, A. Feng and A. Braun (2015). "The role of denosumab in the prevention of hypercalcaemia of malignancy in cancer patients with metastatic bone disease." Eur J Cancer.

Diel, I. J., J. J. Body, A. T. Stopeck, S. Vadhan-Raj, A. Spencer, G. Steger, R. von Moos, F. Goldwasser, A. Feng and A. Braun (2015). "The role of denosumab in the prevention of hypercalcaemia of malignancy in cancer patients with metastatic bone disease." Eur J Cancer **51**(11): 1467-1475.

Donskov, F., M. D. Michaelson, I. Puzanov, M. P. Davis, G. A. Bjarnason, R. J. Motzer, D. Goldstein, X. Lin, D. P. Cohen, R. Wiltshire and B. I. Rini (2015). "Sunitinib-associated hypertension and neutropenia as efficacy biomarkers in metastatic renal cell carcinoma patients." Br J Cancer **113**(11): 1571-1580.

Duong le, T., G. A. Wesolowski, P. Leung, R. Oballa and M. Pickarski (2014). "Efficacy of a cathepsin K inhibitor in a preclinical model for prevention and treatment of breast cancer bone metastasis." Mol Cancer Ther **13**(12): 2898-2909.

Durr, H. R., M. Maier, M. Pfahler, A. Baur and H. J. Refior (1999). "Surgical treatment of osseous metastases in patients with renal cell carcinoma." Clin Orthop Relat Res(367): 283-290.

Eastley, N., M. Newey and R. U. Ashford (2012). "Skeletal metastases - the role of the orthopaedic and spinal surgeon." Surg Oncol **21**(3): 216-222.

Edwards, S. A., H. G. Pandit and H. J. Clarke (2001). "The treatment of impending and existing pathological femoral fractures using the long gamma nail." Injury **32**(4): 299-306.

Elice, F. and F. Rodeghiero (2012). "Side effects of anti-angiogenic drugs." Thromb Res **129 Suppl 1**: S50-53.

Engholm, G., J. Ferlay, N. Christensen, F. Bray, M. L. Gjerstorff, A. Klint, J. E. Kotlum, E. Olafsdottir, E. Pukkala and H. H. Storm (2010). "NORDCAN--a Nordic

tool for cancer information, planning, quality control and research." Acta Oncol **49**(5): 725-736.

Enneking, W. F., S. S. Spanier and M. A. Goodman (1980). "Current concepts review. The surgical staging of musculoskeletal sarcoma." J Bone Joint Surg Am **62**(6): 1027-1030.

Evans, A. R., J. Bottros, W. Grant, B. Y. Chen and T. A. Damron (2008). "Mirels' rating for humerus lesions is both reproducible and valid." Clin Orthop Relat Res **466**(6): 1279-1284.

Evans, S., A. Ramasamy, L. Jeys and R. Grimer (2014). "Delayed diagnosis in metastatic lesions of the foot." Ann R Coll Surg Engl **96**(7): 536-538.

Evenski, A., S. Ramasunder, W. Fox, V. Mounasamy and H. T. Temple (2012). "Treatment and survival of osseous renal cell carcinoma metastases." J Surg Oncol **106**(7): 850-855.

Fairchild, A., E. Barnes, S. Ghosh, E. Ben-Josef, D. Roos, W. Hartsell, T. Holt, J. Wu, N. Janjan and E. Chow (2009). "International patterns of practice in palliative radiotherapy for painful bone metastases: evidence-based practice?" Int J Radiat Oncol Biol Phys **75**(5): 1501-1510.

Falkmer, U., J. Jarhult, P. Wersall and E. Cavallin-Stahl (2003). "A systematic overview of radiation therapy effects in skeletal metastases." Acta Oncol **42**(5-6): 620-633.

Fallon, M., P. J. Hoskin, L. A. Colvin, S. M. Fleetwood-Walker, D. Adamson, A. Byrne, G. D. Murray and B. J. Laird (2016). "Randomized Double-Blind Trial of Pregabalin Versus Placebo in Conjunction With Palliative Radiotherapy for Cancer-Induced Bone Pain." J Clin Oncol **34**(6): 550-556.

Ferlay, J., H. R. Shin, F. Bray, D. Forman, C. Mathers and D. M. Parkin (2010). "Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008." Int J Cancer **127**(12): 2893-2917.

Fisher, N. E., J. T. Patton, R. J. Grimer, D. Porter, L. Jeys, R. M. Tillman, A. Abudu and S. R. Carter (2011). "Ice-cream cone reconstruction of the pelvis: a new type of pelvic replacement: early results." J Bone Joint Surg Br **93**(5): 684-688.

Forauer, A. R., E. Kent, W. Cwikiel, P. Esper and B. Redman (2007). "Selective palliative transcatheter embolization of bony metastases from renal cell carcinoma." Acta Oncol **46**(7): 1012-1018.

Ford, J. A., R. Jones, A. Elders, C. Mulatero, P. Royle, P. Sharma, F. Stewart, R. Todd and G. Mowatt (2013). "Denosumab for treatment of bone metastases secondary to solid tumours: systematic review and network meta-analysis." Eur J Cancer **49**(2): 416-430.

Foro Arnalot, P., A. V. Fontanals, J. C. Galceran, F. Lynd, X. S. Latiesas, N. R. de Dios, A. R. Castillejo, M. L. Bassols, J. L. Galan, I. M. Conejo and M. A. Lopez (2008). "Randomized clinical trial with two palliative radiotherapy regimens in painful bone metastases: 30 Gy in 10 fractions compared with 8 Gy in single fraction." Radiother Oncol **89**(2): 150-155.

Forsberg, J. A., J. Eberhardt, P. J. Boland, R. Wedin and J. H. Healey (2011). "Estimating survival in patients with operable skeletal metastases: an application of a bayesian belief network." PLoS One **6**(5): e19956.

Forsberg, J. A., R. Wedin, H. C. Bauer, B. H. Hansen, M. Laitinen, C. S. Trovik, J. O. Keller, P. J. Boland and J. H. Healey (2012). "External validation of the Bayesian Estimated Tools for Survival (BETS) models in patients with surgically treated skeletal metastases." BMC Cancer **12**: 493.

Fottner, A., M. Szalantzy, L. Wirthmann, M. Stahler, A. Baur-Melnyk, V. Jansson and H. R. Durr (2010). "Bone metastases from renal cell carcinoma: patient survival after surgical treatment." BMC Musculoskelet Disord **11**: 145.

Gadde, R., L. Tamariz, M. Hanna, E. Avisar, A. Livingstone, D. Franceschi and D. Yakoub (2015). "Metastatic gastric cancer (MGC) patients: Can we improve survival by metastasectomy? A systematic review and meta-analysis." J Surg Oncol **112**(1): 38-45.

Goblirsch, M. J., P. P. Zwolak and D. R. Clohisy (2006). "Biology of bone cancer pain." Clin Cancer Res **12**(20 Pt 2): 6231s-6235s.

Godzik, J., C. M. McAndrew, S. Morshed, U. Kandemir and M. P. Kelly (2014). "Multiple lower-extremity and pelvic fractures increase pulmonary embolus risk." Orthopedics **37**(6): e517-524.

Hansen, B. H., J. Keller, M. Laitinen, P. Berg, S. Skjeldal, C. Trovik, J. Nilsson, A. Walloe, A. Kalen and R. Wedin (2004). "The Scandinavian Sarcoma Group Skeletal Metastasis Register. Survival after surgery for bone metastases in the pelvis and extremities." Acta Orthop Scand Suppl **75**(311): 11-15.

Harada, H., H. Katagiri, M. Kamata, Y. Yoshioka, H. Asakura, T. Hashimoto, K. Furutani, M. Takahashi, H. Sakahara and T. Nishimura (2010). "Radiological response and clinical outcome in patients with femoral bone metastases after radiotherapy." J Radiat Res **51**(2): 131-136.

Harrington, K. D. (1981). "The management of acetabular insufficiency secondary to metastatic malignant disease." J Bone Joint Surg Am **63**(4): 653-664.

Harrington, K. D. (1997). "Orthopedic surgical management of skeletal complications of malignancy." Cancer **80**(8 Suppl): 1614-1627.

Harris, K., E. Chow, L. Zhang, G. Velikova, A. Bezjak, J. Wu, M. Barton, O. Sezer, R. Eek, J. Shafiq, A. Yee, M. Clemons, M. Brundage, P. Hoskin, Y. van der Linden, C. D. Johnson, A. Bottomley and E. Q. o. L. Group (2009). "Patients' and health care professionals' evaluation of health-related quality of life issues in bone metastases." Eur J Cancer **45**(14): 2510-2518.

Hartsell, W. F., C. B. Scott, D. W. Bruner, C. W. Scarantino, R. A. Ivker, M. Roach, 3rd, J. H. Suh, W. F. Demas, B. Movsas, I. A. Petersen, A. A. Konski, C. S. Cleeland, N. A. Janjan and M. DeSilvio (2005). "Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases." J Natl Cancer Inst **97**(11): 798-804.

Harvey, N., E. R. Ahlmann, D. C. Allison, L. Wang and L. R. Menendez (2012). "Endoprostheses last longer than intramedullary devices in proximal femur metastases." Clin Orthop Relat Res **470**(3): 684-691.

Hattori, H., J. Mibe and K. Yamamoto (2011). "Modular megaprosthesis in metastatic bone disease of the femur." Orthopedics **34**(12): e871-876.

Heidenreich, A., P. J. Bastian, J. Bellmunt, M. Bolla, S. Joniau, T. van der Kwast, M. Mason, V. Matveev, T. Wiegel, F. Zattoni, N. Mottet and U. European Association of (2014). "EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer." Eur Urol **65**(2): 467-479.

Heindel, W., R. Gubitz, V. Vieth, M. Weckesser, O. Schober and M. Schafers (2014). "The diagnostic imaging of bone metastases." Dtsch Arztebl Int **111**(44): 741-747.

Henderson, E. R., J. S. Groundland, E. Pala, J. A. Dennis, R. Wooten, D. Cheong, R. Windhager, R. I. Kotz, M. Mercuri, P. T. Funovics, F. J. Hornicek, H. T. Temple, P. Ruggieri and G. D. Letson (2011). "Failure mode classification for tumor endoprostheses: retrospective review of five institutions and a literature review." J Bone Joint Surg Am **93**(5): 418-429.

Henderson, E. R., M. I. O'Connor, P. Ruggieri, R. Windhager, P. T. Funovics, C. L. Gibbons, W. Guo, F. J. Hornicek, H. T. Temple and G. D. Letson (2014). "Classification of failure of limb salvage after reconstructive surgery for bone tumours : a modified system Including biological and expandable reconstructions." Bone Joint J **96-B**(11): 1436-1440.

Hipp, J. A., D. S. Springfield and W. C. Hayes (1995). "Predicting pathologic fracture risk in the management of metastatic bone defects." Clin Orthop Relat Res(312): 120-135.

Hofbauer, L. C., T. D. Rachner, R. E. Coleman and F. Jakob (2014). "Endocrine aspects of bone metastases." Lancet Diabetes Endocrinol **2**(6): 500-512.

Howlader N, N. A., Krapcho M, Neyman N, Aminou R, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA (2012). SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations), National Cancer Institute. Bethesda, MD.

Hwang, N., R. Nandra, R. J. Grimer, S. R. Carter, R. M. Tillman, A. Abudu and L. M. Jeys (2014). "Massive endoprosthetic replacement for bone metastases resulting from renal cell carcinoma: factors influencing patient survival." Eur J Surg Oncol **40**(4): 429-434.

Insa, A., A. Lluch, F. Prosper, I. Marugan, A. Martinez-Agullo and J. Garcia-Conde (1999). "Prognostic factors predicting survival from first recurrence in patients with metastatic breast cancer: analysis of 439 patients." Breast Cancer Res Treat **56**(1): 67-78.

Issack, P. S., J. Barker, M. Baker, S. Y. Kotwal and J. M. Lane (2014). "Surgical management of metastatic disease of the proximal part of the femur." J Bone Joint Surg Am **96**(24): 2091-2098.

Ito, N., S. Kojima, S. Teramukai, Y. Mikami, O. Ogawa and T. Kamba (2015). "Outcomes of curative nephrectomy against renal cell carcinoma based on a central pathological review of 914 specimens from the era of cytokine treatment." Int J Clin Oncol.

James, J. J., A. J. Evans, S. E. Pinder, E. Gutteridge, K. L. Cheung, S. Chan and J. F. Robertson (2003). "Bone metastases from breast carcinoma: histopathological - radiological correlations and prognostic features." Br J Cancer **89**(4): 660-665.

Janssen, S. J., T. Teunis, F. J. Hornicek, J. A. Bramer and J. H. Schwab (2015). "Outcome of operative treatment of metastatic fractures of the humerus: a systematic review of twenty three clinical studies." Int Orthop **39**(4): 735-746.

Jeys, L. M., R. J. Grimer, S. R. Carter and R. M. Tillman (2005). "Periprosthetic infection in patients treated for an orthopaedic oncological condition." J Bone Joint Surg Am **87**(4): 842-849.

Jick, S., L. Li, V. M. Gastanaga and A. Liede (2015). "Prevalence of hypercalcemia of malignancy among cancer patients in the UK: analysis of the Clinical Practice Research Datalink database." Cancer Epidemiol **39**(6): 901-907.

Joerger, M. and J. Huober (2012). "Diagnostic and prognostic use of bone turnover markers." Recent Results Cancer Res **192**: 197-223.

Johnstone, C. and S. T. Lutz (2014). "External beam radiotherapy and bone metastases." Ann Palliat Med **3**(2): 114-122.

Jung, K. and M. Lein (2014). "Bone turnover markers in serum and urine as diagnostic, prognostic and monitoring biomarkers of bone metastasis." Biochim Biophys Acta **1846**(2): 425-438.

Jung, S. T., M. A. Ghert, J. M. Harrelson and S. P. Scully (2003). "Treatment of osseous metastases in patients with renal cell carcinoma." Clin Orthop Relat Res(409): 223-231.

Kamiya, N., H. Suzuki, T. Endo, M. Yano, M. Naoi, D. Nishimi, K. Kawamura, T. Imamoto and T. Ichikawa (2012). "Clinical usefulness of bone markers in prostate cancer with bone metastasis." Int J Urol **19**(11): 968-979.

Katagiri, H., R. Okada, T. Takagi, M. Takahashi, H. Murata, H. Harada, T. Nishimura, H. Asakura and H. Ogawa (2014). "New prognostic factors and scoring system for patients with skeletal metastasis." Cancer Med **3**(5): 1359-1367.

Kato, S., H. Murakami, A. Takeuchi, S. Demura, K. Yoshioka, N. Kawahara, K. Tomita and H. Tsuchiya (2013). "Fifteen-year survivor of renal cell carcinoma after metastasectomies for multiple bone metastases." Orthopedics **36**(11): e1454-1457.

Kelly, M., M. Lee, P. Clarkson and P. J. O'Brien (2012). "Metastatic disease of the long bones: a review of the health care burden in a major trauma centre." Can J Surg **55**(2): 95-98.

Keyak, J. H., T. S. Kaneko, H. B. Skinner and B. H. Hoang (2007). "The effect of simulated metastatic lytic lesions on proximal femoral strength." Clin Orthop Relat Res **459**: 139-145.

Khorana, A. A., N. M. Kuderer, E. Culakova, G. H. Lyman and C. W. Francis (2008). "Development and validation of a predictive model for chemotherapy-associated thrombosis." Blood **111**(10): 4902-4907.

Kickuth, R., C. Waldherr, H. Hoppe, H. M. Bonel, K. Ludwig, M. Beck and J. Triller (2008). "Interventional management of hypervascular osseous metastasis: role of

embolotherapy before orthopedic tumor resection and bone stabilization." AJR Am J Roentgenol **191**(6): W240-247.

Krzeszinski, J. Y. and Y. Wan (2015). "New therapeutic targets for cancer bone metastasis." Trends Pharmacol Sci.

Kuchuk, M., I. Kuchuk, E. Sabri, B. Hutton, M. Clemons and P. Wheatley-Price (2015). "The incidence and clinical impact of bone metastases in non-small cell lung cancer." Lung Cancer **89**(2): 197-202.

Laack, T. A. and D. G. Goyal (2004). "Pulmonary embolism: an unsuspected killer." Emerg Med Clin North Am **22**(4): 961-983.

Lee, A. Y. and M. Carrier (2014). "Treatment of cancer-associated thrombosis: perspectives on the use of novel oral anticoagulants." Thromb Res **133 Suppl 2**: S167-171.

Leithner, A., R. Radl, G. Gruber, M. Hochegger, K. Leithner, H. Welkerling, P. Rehak and R. Windhager (2008). "Predictive value of seven preoperative prognostic scoring systems for spinal metastases." Eur Spine J **17**(11): 1488-1495.

Les, K. A., R. W. Nicholas, B. Rougraff, D. Wurtz, N. J. Vogelzang, M. A. Simon and T. D. Peabody (2001). "Local progression after operative treatment of metastatic kidney cancer." Clin Orthop Relat Res(390): 206-211.

Levitan, N., A. Dowlati, S. C. Remick, H. I. Tahsildar, L. D. Sivinski, R. Beyth and A. A. Rimm (1999). "Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data." Medicine (Baltimore) **78**(5): 285-291.

Lin, P. P., A. N. Mirza, V. O. Lewis, C. P. Cannon, S. M. Tu, N. M. Tannir and A. W. Yasko (2007). "Patient survival after surgery for osseous metastases from renal cell carcinoma." J Bone Joint Surg Am **89**(8): 1794-1801.

Lip, G. Y., B. S. Chin and A. D. Blann (2002). "Cancer and the prothrombotic state." Lancet Oncol **3**(1): 27-34.

Lipton, A., K. Fizazi, A. T. Stopeck, D. H. Henry, J. E. Brown, D. A. Yardley, G. E. Richardson, S. Siena, P. Maroto, M. Clemens, B. Bilynskyy, V. Charu, P. Beuzeboc, M. Rader, M. Viniegra, F. Saad, C. Ke, A. Braun and S. Jun (2012). "Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials." Eur J Cancer **48**(16): 3082-3092.

Liu, J., W. Huang, R. Zhou, S. Jia, W. Tang, Y. Luo and J. Zhang (2015). "Bisphosphonates in the Treatment of Patients With Metastatic Breast, Lung, and Prostate Cancer: A Meta-Analysis." Medicine (Baltimore) **94**(46): e2014.

Lutz, S., L. Berk, E. Chang, E. Chow, C. Hahn, P. Hoskin, D. Howell, A. Konski, L. Kachnic, S. Lo, A. Sahgal, L. Silverman, C. von Gunten, E. Mendel, A. Vassil, D. W. Bruner, W. Hartsell and O. American Society for Radiation (2011). "Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline." Int J Radiat Oncol Biol Phys **79**(4): 965-976.

Marco, R. A., D. S. Sheth, P. J. Boland, J. S. Wunder, J. A. Siegel and J. H. Healey (2000). "Functional and oncological outcome of acetabular reconstruction for the treatment of metastatic disease." J Bone Joint Surg Am **82**(5): 642-651.

Mark, R. J., J. Poen, L. M. Tran, Y. S. Fu, M. T. Selch and R. G. Parker (1994). "Postirradiation sarcomas. A single-institution study and review of the literature." Cancer **73**(10): 2653-2662.

Martin, W. N., J. Field and M. Kulkarni (2002). "Intramedullary nailing of pathological forearm fractures." Injury **33**(6): 530-532.

Mavrogenis, A. F., A. Angelini, C. Vottis, E. Pala, T. Calabro, P. J. Papagelopoulos and P. Ruggieri (2015). "Modern Palliative Treatments for Metastatic Bone Disease: Awareness of Merits, Demerits and Guidance." Clin J Pain.

Mavrogenis, A. F., G. Mimidis, Z. T. Kokkalis, E. S. Karampi, I. Karampela, P. J. Papagelopoulos and A. Armaganidis (2014). "Acrometastases." Eur J Orthop Surg Traumatol **24**(3): 279-283.

Mavrogenis, A. F., E. Pala, C. Romagnoli, M. Romantini, T. Calabro and P. Ruggieri (2012). "Survival analysis of patients with femoral metastases." J Surg Oncol **105**(2): 135-141.

Mercadante, S. (1997). "Malignant bone pain: pathophysiology and treatment." Pain **69**(1-2): 1-18.

Mirels, H. (1989). "Metastatic disease in long bones. A proposed scoring system for diagnosing impending pathologic fractures." Clin Orthop Relat Res(249): 256-264.

Motzer, R. J., N. H. Bander and D. M. Nanus (1996). "Renal-cell carcinoma." N Engl J Med **335**(12): 865-875.

Mundy, G. R. (1997). "Mechanisms of bone metastasis." Cancer **80**(8 Suppl): 1546-1556.

Nagata, Y., Y. Nakano, M. Abe, M. Takahashi and S. Kohno (1989). "Osseous metastases from hepatocellular carcinoma: embolization for pain control." Cardiovasc Intervent Radiol **12**(3): 149-153.

Nair, S., Y. P. Gobin, L. Z. Leng, J. D. Marcus, M. Bilsky, I. Laufer and A. Patsalides (2013). "Preoperative embolization of hypervascular thoracic, lumbar, and sacral spinal column tumors: technique and outcomes from a single center." Interv Neuroradiol **19**(3): 377-385.

Napoli, A., M. Anzidei, B. C. Marincola, G. Brachetti, V. Noce, F. Boni, L. Bertaccini, R. Passariello and C. Catalano (2013). "MR imaging-guided focused ultrasound for treatment of bone metastasis." Radiographics **33**(6): 1555-1568.

Nathan, S. S., J. H. Healey, D. Mellano, B. Hoang, I. Lewis, C. D. Morris, E. A. Athanasian and P. J. Boland (2005). "Survival in patients operated on for pathologic fracture: implications for end-of-life orthopedic care." J Clin Oncol **23**(25): 6072-6082.

Nazarian, A., V. Entezari, D. Zurakowski, N. Calderon, J. A. Hipp, J. C. Villa-Camacho, P. P. Lin, F. H. Cheung, A. J. Aboulafia, R. Turcotte, M. E. Anderson, M. C. Gebhardt, E. Y. Cheng, R. M. Terek, M. Yaszemski, T. A. Damron and B. D. Snyder (2015). "Treatment Planning and Fracture Prediction in Patients with Skeletal Metastasis with CT-Based Rigidity Analysis." Clin Cancer Res **21**(11): 2514-2519.

Nilsson, S., P. Strang, A. K. Aksnes, L. Franzen, P. Olivier, A. Pecking, J. Staffurth, S. Vasanthan, C. Andersson and O. S. Bruland (2012). "A randomized, dose-response, multicenter phase II study of radium-223 chloride for the palliation of painful bone metastases in patients with castration-resistant prostate cancer." Eur J Cancer **48**(5): 678-686.

Nishihara, M., Y. C. Arai, Y. Yamamoto, K. Nishida, M. Arakawa, T. Ushida and M. Ikeuchi (2013). "Combinations of low-dose antidepressants and low-dose pregabalin as useful adjuvants to opioids for intractable, painful bone metastases." Pain Physician **16**(5): E547-552.

O'Donnell, P. W., A. M. Griffin, W. C. Eward, A. Sternheim, C. N. Catton, P. W. Chung, B. O'Sullivan, P. C. Ferguson and J. S. Wunder (2014). "The effect of the setting of a positive surgical margin in soft tissue sarcoma." Cancer **120**(18): 2866-2875.

Olerud, C., H. Jonsson, Jr., A. M. Lofberg, L. E. Lorelius and L. Sjostrom (1993). "Embolization of spinal metastases reduces peroperative blood loss. 21 patients operated on for renal cell carcinoma." Acta Orthop Scand **64**(1): 9-12.

Onitilo, A. A., S. A. Doi, J. M. Engel, I. Glurich, J. Johnson and R. Berg (2012). "Clustering of venous thrombosis events at the start of tamoxifen therapy in breast cancer: a population-based experience." Thromb Res **130**(1): 27-31.

Oster, G., L. Lamerato, A. G. Glass, K. E. Richert-Boe, A. Lopez, K. Chung, A. Richhariya, T. Dodge, G. G. Wolff, A. Balakumaran and J. Edelsberg (2013). "Natural history of skeletal-related events in patients with breast, lung, or prostate cancer and metastases to bone: a 15-year study in two large US health systems." Support Care Cancer **21**(12): 3279-3286.

Ottewell, P. D., L. O'Donnell and I. Holen (2015). "Molecular alterations that drive breast cancer metastasis to bone." Bonekey Rep **4**: 643.

Otto, S., C. Schreyer, S. Hafner, G. Mast, M. Ehrenfeld, S. Sturzenbaum and C. Pautke (2012). "Bisphosphonate-related osteonecrosis of the jaws - characteristics, risk factors, clinical features, localization and impact on oncological treatment." J Craniomaxillofac Surg **40**(4): 303-309.

Oudard, S., B. Beuselinck, J. Decoene and P. Albers (2011). "Sunitinib for the treatment of metastatic renal cell carcinoma." Cancer Treat Rev **37**(3): 178-184.

Paice, J. A. and B. Ferrell (2011). "The management of cancer pain." CA Cancer J Clin **61**(3): 157-182.

Pazionis, T. J., I. D. Papanastassiou, M. Maybody and J. H. Healey (2014). "Embolization of hypervascular bone metastases reduces intraoperative blood loss: a case-control study." Clin Orthop Relat Res **472**(10): 3179-3187.

Peddi, P., M. A. Lopez-Olivo, G. F. Pratt and M. E. Suarez-Almazor (2013). "Denosumab in patients with cancer and skeletal metastases: a systematic review and meta-analysis." Cancer Treat Rev **39**(1): 97-104.

Petre, E. N., C. T. Sofocleous and S. B. Solomon (2015). "Ablative and catheter-directed therapies for colorectal liver and lung metastases." Hematol Oncol Clin North Am **29**(1): 117-133.

Piccioli, A., G. Maccauro, B. Rossi, L. Scaramuzzo, F. Frenos and R. Capanna (2010). "Surgical treatment of pathologic fractures of humerus." Injury **41**(11): 1112-1116.

Piccioli, A., M. S. Spinelli and G. Maccauro (2014). "Impending fracture: A difficult diagnosis." Injury **45 Suppl 6**: S138-141.

Pockett, R. D., D. Castellano, P. McEwan, A. Oglesby, B. L. Barber and K. Chung (2010). "The hospital burden of disease associated with bone metastases and skeletal-

related events in patients with breast cancer, lung cancer, or prostate cancer in Spain." Eur J Cancer Care (Engl) **19**(6): 755-760.

Quraishi, N. A., S. Purushothamdas, S. R. Manoharan, G. Arealis, R. Lenthall and M. P. Grevitt (2013). "Outcome of embolised vascular metastatic renal cell tumours causing spinal cord compression." Eur Spine J **22 Suppl 1**: S27-32.

Reid, I. R. (2011). "Bisphosphonates in the treatment of osteoporosis: a review of their contribution and controversies." Skeletal Radiol **40**(9): 1191-1196.

Robial, N., Y. P. Charles, I. Bogorin, J. Godet, R. Beaujeux, F. Boujan and J. P. Steib (2012). "Is preoperative embolization a prerequisite for spinal metastases surgical management?" Orthop Traumatol Surg Res **98**(5): 536-542.

Roghmann, F., C. Antczak, R. R. McKay, T. Choueiri, J. C. Hu, A. S. Kibel, S. P. Kim, K. J. Kowalczyk, M. Menon, P. L. Nguyen, F. Saad, J. D. Sammon, M. Schmid, S. Sukumar, M. Sun, J. Noldus and Q. D. Trinh (2015). "The burden of skeletal-related events in patients with prostate cancer and bone metastasis." Urol Oncol **33**(1): 17 e19-18.

Roodman, G. D. (2001). "Biology of osteoclast activation in cancer." J Clin Oncol **19**(15): 3562-3571.

Rossfeld, K. K. and W. E. Carson, 3rd (2015). "Surgical management of ovarian carcinoma metastatic to the breast and axilla: A role for metastasectomy?" J Surg Oncol **112**(6): 581-584.

Rossi, G., A. F. Mavrogenis, E. Rimondi, L. Braccaioli, T. Calabro and P. Ruggieri (2011). "Selective embolization with N-butyl cyanoacrylate for metastatic bone disease." J Vasc Interv Radiol **22**(4): 462-470.

Rusz, O. and Z. Kahan (2013). "Bone homeostasis and breast cancer: implications for complex therapy and the maintenance of bone integrity." Pathol Oncol Res **19**(1): 1-10.

Saad, F., A. Lipton, R. Cook, Y. M. Chen, M. Smith and R. Coleman (2007). "Pathologic fractures correlate with reduced survival in patients with malignant bone disease." Cancer **110**(8): 1860-1867.

Salonia, A., A. Gallina, T. C. Camerota, M. Picchio, M. Freschi, L. F. DaPozzo, G. Guazzoni, F. Fazio, P. Rigatti and F. Montorsi (2006). "Bone metastases are infrequent in patients with newly diagnosed prostate cancer: analysis of their clinical and pathologic features." Urology **68**(2): 362-366.

Santini, D., G. Procopio, C. Porta, T. Ibrahim, S. Barni, C. Mazzara, A. Fontana, A. Berruti, R. Berardi, B. Vincenzi, C. Ortega, D. Ottaviani, G. Carteni, G. Lanzetta, V. Virzi, M. Santoni, N. Silvestris, M. A. Satolli, E. Collova, A. Russo, G. Badalamenti, S. L. Fedeli, F. M. Tanca, V. Adamo, E. Maiello, R. Sabbatini, A. Felici, S. Cinieri, G. Tonini and S. Bracarda (2013). "Natural history of malignant bone disease in renal cancer: final results of an Italian bone metastasis survey." PLoS One **8**(12): e83026.

Sathiakumar, N., E. Delzell, M. A. Morrisey, C. Falkson, M. Yong, V. Chia, J. Blackburn, T. Arora, I. Brill and M. L. Kilgore (2012). "Mortality following bone metastasis and skeletal-related events among women with breast cancer: a population-based analysis of U.S. Medicare beneficiaries, 1999-2006." Breast Cancer Res Treat **131**(1): 231-238.

Scher, H. I., K. Fizazi, F. Saad, M. E. Taplin, C. N. Sternberg, K. Miller, R. de Wit, P. Mulders, K. N. Chi, N. D. Shore, A. J. Armstrong, T. W. Flaig, A. Flechon, P. Mainwaring, M. Fleming, J. D. Hainsworth, M. Hirmand, B. Selby, L. Seely, J. S. de Bono and A. Investigators (2012). "Increased survival with enzalutamide in prostate cancer after chemotherapy." N Engl J Med **367**(13): 1187-1197.

Schlesinger-Raab, A., U. Treiber, D. Zaak, D. Holzel and J. Engel (2008). "Metastatic renal cell carcinoma: results of a population-based study with 25 years follow-up." Eur J Cancer **44**(16): 2485-2495.

Scotti, C., F. Camnasio, G. M. Peretti, F. Fontana and G. Fraschini (2008). "Modular prostheses in the treatment of proximal humerus metastases: review of 40 cases." J Orthop Traumatol **9**(1): 5-10.

Shallop, B., A. Starks, S. Greenbaum, D. S. Geller, A. Lee, J. Ready, G. Merli, M. Maltenfort and J. A. Abraham (2015). "Thromboembolism After Intramedullary Nailing for Metastatic Bone Lesions." J Bone Joint Surg Am **97**(18): 1503-1511.

Shane, E., D. Burr, B. Abrahamsen, R. A. Adler, T. D. Brown, A. M. Cheung, F. Cosman, J. R. Curtis, R. Dell, D. W. Dempster, P. R. Ebeling, T. A. Einhorn, H. K. Genant, P. Geusens, K. Klaushofer, J. M. Lane, F. McKiernan, R. McKinney, A. Ng, J. Nieves, R. O'Keefe, S. Papapoulos, T. S. Howe, M. C. van der Meulen, R. S. Weinstein and M. P. Whyte (2014). "Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research." J Bone Miner Res **29**(1): 1-23.

Smith, M. R., R. E. Coleman, L. Klotz, K. Pittman, P. Milecki, S. Ng, K. N. Chi, A. Balakumaran, R. Wei, H. Wang, A. Braun and K. Fizazi (2015). "Denosumab for the prevention of skeletal complications in metastatic castration-resistant prostate cancer: comparison of skeletal-related events and symptomatic skeletal events." Ann Oncol **26**(2): 368-374.

Sorensen, M. S., K. G. Gregersen, T. Grum-Schwensen, D. Hovgaard and M. M. Petersen (2013). "Patient and implant survival following joint replacement because of metastatic bone disease." Acta Orthop **84**(3): 301-306.

Steensma, M., P. J. Boland, C. D. Morris, E. Athanasian and J. H. Healey (2012). "Endoprosthetic treatment is more durable for pathologic proximal femur fractures." Clin Orthop Relat Res **470**(3): 920-926.

Streitbuerger, A., M. Henrichs, G. Gosheger, H. Ahrens, M. Nottrott, W. Guder, R. Dieckmann and J. Hardes (2015). "Improvement of the shoulder function after large segment resection of the proximal humerus with the use of an inverse tumour prosthesis." Int Orthop **39**(2): 355-361.

Sugiura, H., K. Yamada, T. Sugiura, T. Hida and T. Mitsudomi (2008). "Predictors of survival in patients with bone metastasis of lung cancer." Clin Orthop Relat Res **466**(3): 729-736.

Sun, L. M., C. L. Lin, M. C. Lin, J. A. Liang and C. H. Kao (2015). "Radiotherapy- and chemotherapy-induced myelodysplasia syndrome: a nationwide population-based nested case-control study." Medicine (Baltimore) **94**(17): e737.

Sun, S. and E. V. Lang (1998). "Bone metastases from renal cell carcinoma: preoperative embolization." J Vasc Interv Radiol **9**(2): 263-269.

Svendsen, E. and B. Karwinski (1989). "Prevalence of pulmonary embolism at necropsy in patients with cancer." J Clin Pathol **42**(8): 805-809.

Theriault, R. L. and R. L. Theriault (2012). "Biology of bone metastases." Cancer Control **19**(2): 92-101.

Thiex, R., M. B. Harris, C. Sides, C. M. Bono and K. U. Frerichs (2013). "The role of preoperative transarterial embolization in spinal tumors. A large single-center experience." Spine J **13**(2): 141-149.

Thobe, M. N., R. J. Clark, R. O. Bainer, S. M. Prasad and C. W. Rinker-Schaeffer (2011). "From prostate to bone: key players in prostate cancer bone metastasis." Cancers (Basel) **3**(1): 478-493.

Tokuhashi, Y., H. Matsuzaki, H. Oda, M. Oshima and J. Ryu (2005). "A revised scoring system for preoperative evaluation of metastatic spine tumor prognosis." Spine (Phila Pa 1976) **30**(19): 2186-2191.

Tomita, K., N. Kawahara, T. Kobayashi, A. Yoshida, H. Murakami and T. Akamaru (2001). "Surgical strategy for spinal metastases." Spine (Phila Pa 1976) **26**(3): 298-306.

Tsagozis, P., R. Wedin, O. Brosjo and H. Bauer (2015). "Reconstruction of metastatic acetabular defects using a modified Harrington procedure." Acta Orthop: 1-5.

Twombly, R. (2005). "Cancer surpasses heart disease as leading cause of death for all but the very elderly." J Natl Cancer Inst **97**(5): 330-331.

Utzschneider, S., E. Wicherek, P. Weber, G. Schmidt, V. Jansson and H. R. Durr (2011). "Surgical treatment of bone metastases in patients with lung cancer." Int Orthop **35**(5): 731-736.

Vakaet, L. A. and T. Boterberg (2004). "Pain control by ionizing radiation of bone metastasis." Int J Dev Biol **48**(5-6): 599-606.

van den Hout, W. B., Y. M. van der Linden, E. Steenland, R. G. Wiggenraad, J. Kievit, H. de Haes and J. W. Leer (2003). "Single- versus multiple-fraction radiotherapy in patients with painful bone metastases: cost-utility analysis based on a randomized trial." J Natl Cancer Inst **95**(3): 222-229.

Van der Linden, Y. M., P. D. Dijkstra, H. M. Kroon, J. J. Lok, E. M. Noordijk, J. W. Leer and C. A. Marijnen (2004). "Comparative analysis of risk factors for pathological fracture with femoral metastases." J Bone Joint Surg Br **86**(4): 566-573.

van der Linden, Y. M., J. J. Lok, E. Steenland, H. Martijn, H. van Houwelingen, C. A. Marijnen, J. W. Leer and G. Dutch Bone Metastasis Study (2004). "Single fraction radiotherapy is efficacious: a further analysis of the Dutch Bone Metastasis Study controlling for the influence of retreatment." Int J Radiat Oncol Biol Phys **59**(2): 528-537.

van der Linden, Y. M., E. Steenland, H. C. van Houwelingen, W. J. Post, B. Oei, C. A. Marijnen, J. W. Leer and G. Dutch Bone Metastasis Study (2006). "Patients with a favourable prognosis are equally palliated with single and multiple fraction radiotherapy: results on survival in the Dutch Bone Metastasis Study." Radiother Oncol **78**(3): 245-253.

Verso, M. and G. Agnelli (2012). "New and old anticoagulants in cancer." Thromb Res **129 Suppl 1**: S101-105.

Waalkes, S. S., Andres; Kuczyk ,Marcus (2012). "Current Treatment Options for Disseminated Renal Cell Carcinoma." European Urology Supplements **11**: 73-78.

Wang, N., K. J. Reeves, H. K. Brown, A. C. Fowles, F. E. Docherty, P. D. Ottewell, P. I. Croucher, I. Holen and C. L. Eaton (2015). "The frequency of osteolytic bone metastasis is determined by conditions of the soil, not the number of seeds; evidence from in vivo models of breast and prostate cancer." J Exp Clin Cancer Res **34**(1): 124.

Wedin, R. and H. C. Bauer (2005). "Surgical treatment of skeletal metastatic lesions of the proximal femur: endoprosthesis or reconstruction nail?" J Bone Joint Surg Br **87**(12): 1653-1657.

Wedin, R., H. C. Bauer and L. E. Rutqvist (2001). "Surgical treatment for skeletal breast cancer metastases: a population-based study of 641 patients." Cancer **92**(2): 257-262.

Wedin, R., B. H. Hansen, M. Laitinen, C. Trovik, O. Zaikova, P. Bergh, A. Kalen, G. Schwarz-Lausten, F. Vult von Steyern, A. Walloe, J. Keller and R. J. Weiss (2012). "Complications and survival after surgical treatment of 214 metastatic lesions of the humerus." J Shoulder Elbow Surg **21**(8): 1049-1055.

Wegener, B., M. Schlemmer, J. Stemmler, V. Jansson, H. R. Durr and M. F. Pietschmann (2012). "Analysis of orthopedic surgery of bone metastases in breast cancer patients." BMC Musculoskelet Disord **13**: 232.

Weiss, R. J., J. A. Forsberg and R. Wedin (2012). "Surgery of skeletal metastases in 306 patients with prostate cancer." Acta Orthop **83**(1): 74-79.

Weiss, R. J., E. Tullberg, J. A. Forsberg, H. C. Bauer and R. Wedin (2014). "Skeletal metastases in 301 breast cancer patients: patient survival and complications after surgery." Breast **23**(3): 286-290.

Weiss, R. J. and R. Wedin (2011). "Surgery for skeletal metastases in lung cancer." Acta Orthop **82**(1): 96-101.

Wibmer, C., A. Leithner, G. Hofmann, H. Clar, M. Kapitan, A. Berghold and R. Windhager (2011). "Survival analysis of 254 patients after manifestation of spinal metastases: evaluation of seven preoperative scoring systems." Spine (Phila Pa 1976) **36**(23): 1977-1986.

Willeumier, J., M. Fiocco, R. Nout, S. Dijkstra, W. Aston, R. Pollock, H. Hartgrink, J. Bovee and M. van de Sande (2015). "High-grade soft tissue sarcomas of the extremities: surgical margins influence only local recurrence not overall survival." Int Orthop **39**(5): 935-941.

Wilson, M. A., D. L. Cooke, B. Ghodke and S. K. Mirza (2010). "Retrospective analysis of preoperative embolization of spinal tumors." AJNR Am J Neuroradiol **31**(4): 656-660.

Wirbel, R. J., R. Roth, M. Schulte, B. Kramann and W. Mutschler (2005). "Preoperative embolization in spinal and pelvic metastases." J Orthop Sci **10**(3): 253-257.

Wong, E., P. Hoskin, G. Bedard, M. Poon, L. Zeng, H. Lam, H. Vulpe, M. Tsao, N. Pulenzas and E. Chow (2014). "Re-irradiation for painful bone metastases - a systematic review." Radiother Oncol **110**(1): 61-70.

Wong, M. H., M. R. Stockler and N. Pavlakis (2012). "Bisphosphonates and other bone agents for breast cancer." Cochrane Database Syst Rev **2**: CD003474.

Wood, T. J., A. Racano, H. Yeung, F. Farrokhyar, M. Ghert and B. M. Deheshi (2014). "Surgical management of bone metastases: quality of evidence and systematic review." Ann Surg Oncol **21**(13): 4081-4089.

Woodward, E., S. Jagdev, L. McParland, K. Clark, W. Gregory, A. Newsham, S. Rogerson, K. Hayward, P. Selby and J. Brown (2011). "Skeletal complications and survival in renal cancer patients with bone metastases." Bone **48**(1): 160-166.

Yazawa, Y., F. J. Frassica, E. Y. Chao, D. J. Pritchard, F. H. Sim and T. C. Shives (1990). "Metastatic bone disease. A study of the surgical treatment of 166 pathologic humeral and femoral fractures." Clin Orthop Relat Res(251): 213-219.

Young, S., S. A. Lie, G. Hallan, L. G. Zirkle, L. B. Engesaeter and L. I. Havelin (2013). "Risk factors for infection after 46,113 intramedullary nail operations in low- and middle-income countries." World J Surg **37**(2): 349-355.

Zheng, Y., H. Zhou, C. Fong-Yee, J. R. Modzelewski, M. J. Seibel and C. R. Dunstan (2008). "Bone resorption increases tumour growth in a mouse model of osteosclerotic breast cancer metastasis." Clin Exp Metastasis **25**(5): 559-567.

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Review

Insight opinion to surgically treated metastatic bone disease: Scandinavian Sarcoma Group Skeletal Metastasis Registry report of 1195 operated skeletal metastasis

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ABSTRACT

The number of cancer patients living with metastatic disease is growing. The increased survival has led to an increase in the number of cancer-induced complications, such as pathologic fractures due to bone metastases. Surgery is most commonly needed for mechanical complications, such as fractures and intractable pain. We determined survival, disease free interval and complications in surgically treated bone metastasis. Data were collected from the Scandinavian Skeletal Metastasis Registry for patients with extremity skeletal metastases surgically treated at eight major Scandinavian referral centres between 1999 and 2009 covering a total of 1195 skeletal metastases in 1107 patients. Primary breast, prostate, renal, lung, and myeloma tumors make up 78% of the tumors. Number of complications is tolerable and is affected by methods of surgery as well as preoperative radiation therapy. Overall 1-year patient survival was 36%; however, mean survival was influenced by the primary tumor type and the presence of additional visceral metastases. Patients with impending fracture had more systemic complications than those with complete fracture. Although surgery is usually only a palliative treatment, patients can survive for years after surgery. We developed a simple, useful and reliable scoring system to predict survival among these patients. This scoring system gives good aid in predicting the prognosis when selecting the surgical method. While it is important to avoid unnecessary operations, operating when necessary can provide benefit.

Contents

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Introduction

The burden of cancer is increasing in welfare states. In the Nordic countries, the prevalence of cancer has grown steadily over recent years to about 100 cases per 100,000 persons annually. The cancer mortality rate has remained almost the same over the last 10 years, with an increase of only 2% (58 130 in 1999 vs. 59 440 in 2008) while the incidence of cancer has increased 18% (110 629 in 1999 vs. 130 455 in 2008) [1]. Although the treatment of different primary cancers has become very specialized and effective, the disease will eventually disseminate in some patients. Metastasis results from the spread of tumour cells from their site of origin to other organs. The organ distribution of metastases depends on the type and location of the primary tumour and the route of dissemination of metastatic cells; for example, breast and prostate cancer often metastasize to bone [2]. As treatment options for patients with metastases have improved, the number of patients living with disease is growing, which has led to an increase in cancer-induced complications, such as skeletal-related events like pain, pathologic fractures, hypercalcaemia, anaemia, and paraparesis [3].

Destruction of bone by metastatic disease reduces its load-bearing capabilities and results initially in microfractures. Microfractures can cause pain and eventually lead to a complete fracture of the bone. Some bone metastases are painless, but most bone lesions develop symptoms such as load-related pain or pain at rest [4]. Surgery is most commonly needed for mechanical complications, such as impending or existing fracture, or intractable pain [5]. The main advantages of surgery are immediate pain relief, restored function with possible full weight-bearing, and unlimited range of motion, which can help the patient with activities of daily living.

Bone metastasis indicates that the malignant process is incurable. Survival with metastasized cancer has increased and continues to increase especially in some patients, and therefore data about long-term survivors is needed. In oncologic orthopaedics, the choice of surgical treatment varies between prophylactic intramedullary nailing to massive resection prosthesis. The method of choice depends on the site of metastasis and patient survival. The value and predictability of survival in patients with pathologic fractures in the extremities has increased with the number of case studies reported.

The purpose of this study was to evaluate 1195 surgically treated bone metastases to better understand the relationship between primary diagnosis, location of bone metastases and history of cancer disease with survival, disease free interval and complications after surgery and making a simple prognostic scale for survival after operation of skeletal metastases.

Patients and methods

Study design

The Scandinavian Sarcoma Group (SSG) was constituted in 1979. The SSG Skeletal Metastases Registry was started in 1999 to improve treatment of patients with bone metastases. It is a multicenter prospective registry of surgically treated non-spinal skeletal metastases in patients treated at one of eight major Scandinavian referral centres. It is the world's largest registry of surgically treated skeletal metastases; a total of 1195 skeletal metastases in 1107 patients. Patients were operated on between June 1999 and October 2009. In 88 cases, the patient had more than one surgically treated metastasis. We gathered information on the demographic characteristics, the primary tumour, the site of metastasis, the presence of other metastases, the type of surgery, and complications. The date and cause of death were also recorded.

Patients for whom the date of death was missing either because the patient was still alive or lost to follow-up were censored at the last time they were known to be alive. If the reason for death was not cancer, the case was censored. Survival was calculated as the time from the operation date to the date of death. Statistical analyses were performed using SPSS 20.0. Survival rates were calculated using the Kaplan–Meier method and log-rank test and cumulative intervals were calculated in Microsoft Excel. Cox regression analyses were used to assess significance of different variables affecting survival.

The purpose of this article is to (1) describe main indications for surgery of skeletal non-spinal metastases (2) describe and analyse complications after surgery (3) evaluate disease free interval and (4) develop a simple prognostic scale.

Patients

A total of 1195 consecutive cases with operatively treated non-spinal skeletal metastases were included in the study. Indications for surgery were an existing fracture or impending fracture where the degree of bone disruption warranted prophylactic surgical stabilization to prevent fracture or intractable pain and loss of ambulatory ability. Contraindications to surgery were suspected survival less than 4 weeks and poor overall status to undergo procedure.

There were a total of 1195 skeletal metastases in 1107 patients. The overall patient survival rate after operation of metastases was 58% at 6 months, 41% at 1 year, and 2% after 5 years. The median survival was longest in myeloma patients (26.3 months), thyroid cancer (22.7 months), breast cancer (12 months), and kidney cancer (10 months). Melanoma had the worst prognosis 2.3 months (Table 1).

The most common primary tumour was breast cancer (31%), followed by prostate cancer (17%), kidney cancer (12%), lung cancer (11%), and myeloma (8%). These tumours made up 78% of the cases. The following primary tumours had a greater than 1% incidence: lymphoma, intestine, melanoma, bladder, various sarcomas as one group, and thyroid cancer. Fewer than 10 cases had the following primary tumours: uterus 9, tongue 4, larynx 5, oesophagus 3, liver 5, pancreas 4, vulva 2, ventricle 1, penis 1, ovary 2, and cervix 2. In 65 of 1195 cases (5.4%), the primary tumour was not identified. There were over 20 different fracture-causing metastatic primary tumours.

The most common bone affected was the femur, followed by the humerus, pelvis, and tibia (Table 2). Of the treated femoral fractures (764/1195, 64%), 79% were located in the proximal parts of the femur, followed by the diaphysis in 14%, and the distal femur in 7%. In the humerus, the diaphysis was the main site (58%). Fractures of the

Table 1
Primary site, sex, mean age at the operation, most common location of skeletal metastases, and survival in months with cumulative intervals.

Primary tumor	*n*	%	% Male	Age	Location %		Survival	95CL
Breast	364	30.5	3	62	Fem 70	Prox 30	12.8	10.6–15.0
Prostate	199	16.7	100	73	Fem 72	Prox 36	6	4.5–7.6
Kidney	147	12.3	66	66	Fem 51	Sub troc 17	10.7	6.7–14.8
Lung	132	11	45	65	Fem 68	Prox 23	4.1	3.0–5.3
Myeloma	91	7.6	45	68	Fem 52	Prox 25	26.3	13.5–39.2
Lymphoma	26	2.2	54	68	Fem 69	Prox 31	17.6	5.9–29.3
Intestines	23	1.9	48	70	Fem 39	Prox 30	6.1	0.0–15.7
Melanoma	20	1.7	60	62	Hum 50	Diaph 25	2.3	0.0–4.7
Bladder	18	1.5	89	68	Fem 61	Prox 33	3.4	0.0–6.9
Sarcomas	18	1.5	28	52	Fem 67	Prox 22	11	5.8–7.7
Thyroid	13	1.1	31	73	Fem 54	Diaph 23	22.7	0.0–45.3
Not known	65	5.4	59	68	Fem 71	Prox 29	4.5	2.8–6.3

ulna, scapula, and radius were rarely treated surgically, with an incidence of less than 1%. Solitary locations requiring surgery were found in the talus (breast cancer) and hand (lung cancer). In all cancers other than melanoma, the femur was the most common site of surgical treatment. In cases of melanoma, the humerus was the most common location.

The majority of patients had multiple bone metastases at the time of surgery (breast cancer 84.9%, prostate cancer 81.4%). The greatest number of solitary cases occurred in patients with renal cancer 57/147 (38.8%). Organ metastases were most frequent in lung cancer (62/132, 47%), followed by kidney cancer (61/147, 41.5%) and breast cancer (133/364, 36.5%). The longest survival times, over 10 years, were for patients with breast and prostate cancer. Some patients with renal cancer, myeloma, and lymphoma survived over 9.5 years after surgery. In 131/1195 cases (11%), death occurred within 4 weeks after surgery.

Results

Main indication for surgery

Complete fracture was the major reason for surgery in 74.2% of the cases and impending fracture in 18.3% of cases (Table 3). Survival was longer in cases undergoing surgery was pain or impending fracture. In these patients, mean age was lower (63.8 years with impending fracture vs. 67.7 years with complete fracture) and time from metastases to surgery was shorter (11.7 months vs. 15.4 months, respectively) compared to patients with complete fractures. Operations for impending fracture were performed mostly in cases with renal cancer (39/147, 26.5%), lung cancer (30/132, 22.7%), and cancer metastases of unknown primary tumour (16/65, 24.6%). The most common location for impending fracture was the proximal femur (49/219, 21%). The second most common location for impending fracture treatment was the subtrochanteric femur (36/219, 16.4%).

Table 2
Localization of skeletal metastases at operation.

Localization	*n*	%	Femur	*n*	%	Humerus	*nr*	%
Femur	763	64	Proximal	308	40	Proximal	73	29
Humerus	248	21	Inter trochanteric	100	13	Diaphysis	143	58
Pelvis	106	9	Subtrochanteric	179	26	Distal	20	8
Tibia	41	3	Diaphysis	104	14	Missing	12	5
Ulna	7	1	Distal	54	7			
Scapula	8	1	Combination	4	0.5			
Radius	7	1	Missing	14	2			
Other	15	1						
Total	1195	100	Total	763	100	Total	248	100

Table 3
Main indication for operation, median survival time (months), mean age at the operation, and mean time from diagnosis of metastases to operation (months).

Main indication	*n*	%	Survival	95% CI	Age	Time to op.
Complete fracture	886	74.2	7.5	6.6–8.4	67	14.8
Impending fracture	219	18.3	11.9	9.4–14.4	63	9
Pain	57	4.8	11.6	6.4–16.7	63	12.8
Other	23	1.9				
Missing	10	0.8				
	1195	100				

Surgical methods and complications

Endoprosthetic reconstruction including tumour prosthesis was performed in 46.6% (556/1195) of cases and nailing or plating procedures in 46.4% (554/1195) of cases (Table 4). Complications were reported in 12.9% (154/1195) of all cases. There were reported 18 systemic complications including lung embolism, liver failure, aspiration pneumonia, deep vein thrombosis, lower extremity embolism, thrombosis, fat embolism, and fibrosis. The percentage of systemic complications was 4 (9/219) in impending pathologic fractures and 1 (9/886) in pathological fractures. In all fatal embolism complications (4 cases), the main reason for surgery was impending fracture. A comparison of features of cases with complications with whole data, for example age, sex, metastatic load, primary tumour, localization, Karnofsky score, surgical method and nationality revealed no specific risk factors (Table 5).

In plate and nailing procedure group (including plating, reconstruction and intramedullary nailing) total complication percentage was 11 (61/554) (Table 4). The reported complications were six systemic complications, five wound infections, four deep infections, seven nail brakes, 13 fractures next to implant, and nine nerve injuries, nine non-unions and eight technical errors/immediate fails. In the whole plating and nailing group, 19.3% was preoperatively radiated, whereas in the complication group with the same operative choice 24.9% had been previously radiated. In prosthetic replacement group (including hemiprothesis, total joint replacement, prosthesis and acetabular reconstruction) total complication percentage was 15 (72/479). There were reported nine systemic complications, 12 wound infections, ten deep infections, two nerve injuries, seven immediate fails/technical errors, 35 prosthetic complications including two dislocations and two haematomas. There were more cases that had been previously radiated in cases having complication 36% in respect to whole prosthetic replacement group 26%. There were not more infections in cases having preoperative radiation but number of prosthetic complications was higher (12.8% 16/125 vs. 5.9% 19/332). Complication percentage in tumour prosthesis was 13.

Re-operation percentage was 5.9. In plating and nailing procedure group there were 6.1% reoperations and 4% in prosthetic replacement group. The re-operation rate was same in complete fractures 6.1% (53/867) and in impending fracture 6.0% (16/267). Common reasons for re-operation were non-union ($n = 14$), local

Table 4
Surgical methods, median survival in months with cumulative intervals and complications.

Operation method	*n*	%	Mean age	Survival	95CL	Complications	%
Plate and nail	554	46.4	67	7.4	(6121–8598)	61	11
Prothesis	479	40.1	65	8.1	(6557–9542)	72	15
Tumor prothesis	77	6.4	63	15.3	(12,605–18,015)	10	13
Other	85	87.1	65	12.2	(4163–20,281)		
Total							

Table 5
Distribution of prognostic factors, multivariate analysis and score for each factor.

Prognostic factors	*n*	B	SE	*p*-Value	HR	95CL		Score
Number of skeletal metastases		0.428	0.116	0	1534	1223	1924	1
Single	146							
Multiple	505							
Presence of organ metastases		0.576	0.091	0	1779	1488	2127	1
Absent	384							
Present	267							
Primary tumour		0.59	0.091	0	1804	1.51	2154	1
Breast, kidney, thyroid, myeloma, lymfoma	360							
Other	291							
Karnofsky score		0.408	0.089	0	1504	1262	1792	1
>70	338							
<70	313							
Impending fracture	156	0.15	0.106	0.156	1162	0.944	1429	
Pathological fracture	495							

progression ($n = 7$) and fracture ($n = 9$). Four impending fractures and one preoperatively radiated fracture were re-operated because of local progression. Preoperative radiation caused non-union slightly more often than non-radiated fractures (4.0% 5/125 vs. 2.8 9/14 respectively).

Disease-free interval

Information about the dates of diagnoses (primary tumor and metastases) was available for 1024 of 1107 patients. Among cases with skeletal complications, 74.1% (759/1024) occurred in patients with previously diagnosed bone metastasis (Fig. 1). In this study, we considered disease as known disease if it had been diagnosed at least 1 week before surgery. No known skeletal complication was detected in 25.9% (265/1024) of patients 1 week before surgery. Among patients with known cancer, the skeletal complication was the first sign of bone metastasis in 12.4% (127/1024). In these patients, the cancer diagnosis was made less than 1 year earlier in 25.2% (32/127), and more than 5 years before in 32.3% (41/127). In 36.2% (371/1024) of patients, diagnosis of the primary cancer and the metastatic disease were made at the same time.

In 13.5% (138/1024) of patients, skeletal complications were the first sign of cancer. Among these cases, the most common diagnoses were unknown cancer (21.7%, 30/138), lung cancer (21%, 29/138, 21%), renal cancer (14.5%, 20/138) and myeloma 12.3%, (17/138).

Simple prognostic scale

To develop a simple prognostic scale, to estimate life expectancy remaining, we examined following prognostic factors; number of skeletal metastases, presence of visceral metastases, age, performance status, presence of pathological fracture and primary site of the tumour. Each variable was categorised in two different groups scoring 0 or 1 (Table 6). Variable primary tumour were categorised in two groups by median survival time. Primary tumours with survival time over 12 months to one group and survival time lower than 12 months to one group. There was full data on 833 patients. We randomised 20% of patients (178) to a "testing set" and made the analysis with 651 patients called as "training set". All other

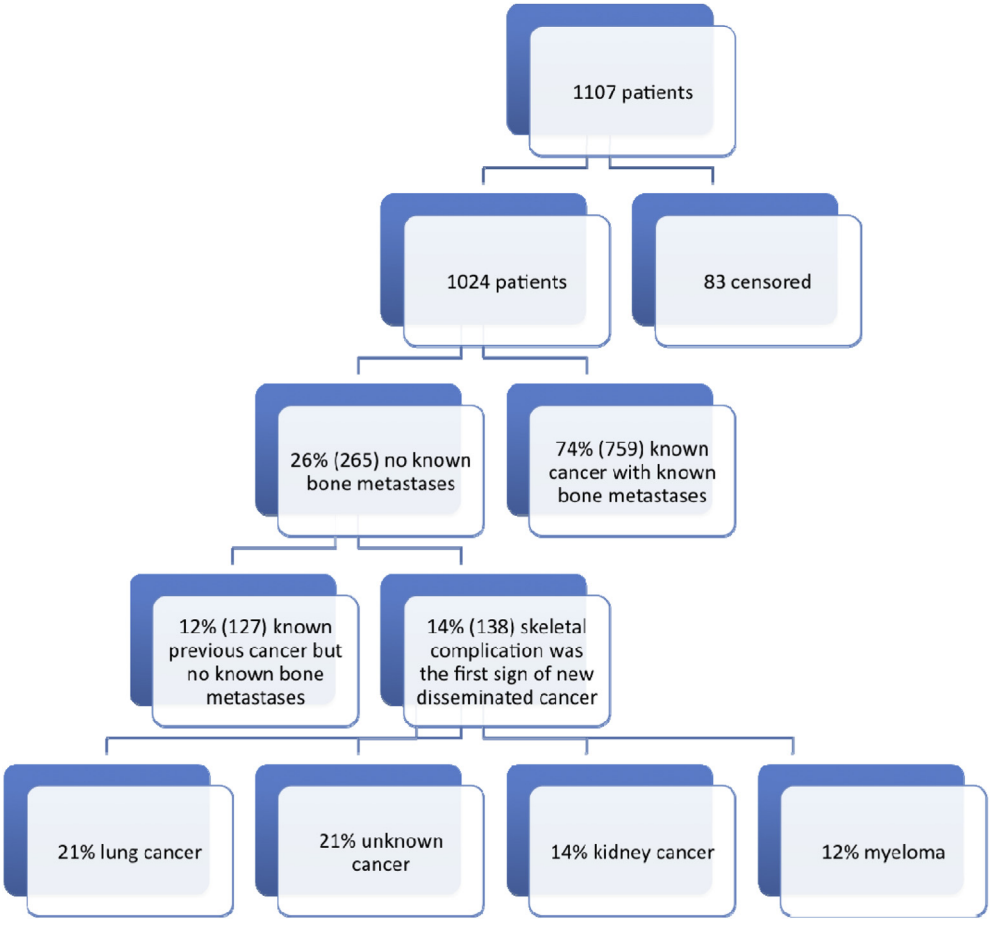

Figure 1. Flow chart describing the patients' status of disease when having a pathologic bone fracture.

Table 6
Survival rates at 3, 6 and 12 months in groups A, B and C.

	Time (months)	Training set		Testing set	
		Survival rate	95CL	Survival rate	95CL
A	3	0.932	0.89–0.97	0.909	0.74–1.08
	6	0.881	0.75–0.87	0.818	0.59–1.05
	12	0.671	0.58–0.72	0.727	0.46–0.99
B	3	0.737	0.69–0.78	0.817	0.76–0.88
	6	0.549	0.5–0.6	0.658	0.58–0.73
	12	0.356	0.31–0.4	0.449	0.37–0.53
C	3	0.286	0.17–0.4	0.273	0.01–0.54
	6	0.143	0.05–0.24	0.273	0.01–0.54
	12	0.104	0.02–0.18	0	0 0

variables except patients' age (under 65 and 65 and higher) were really all of the significant prognostic factors by Kaplain-Meier and log-rank test. Training set and testing set were tested equal by demographics concerning researched variables. All of the significant factors were included in Cox regression analysis. Presence of pathological fracture was not significant factor in Cox regression analysis, so it was dropped out from prognostic scale. The results of the multivariate analyses can be seen in Table 6. The corresponding estimated regression coefficients were quite same, so as those were multiplied by two and rounded off to the nearest integer all the significant variables (1. single bone metastases, 2. absence of organ metastases, 3. primary tumour in location in breast, kidney, thyroid, myeloma or lymphoma and 4. Karnofsky score more than 70) got one point. The prognostic score was calculated by adding all the scores for individual factors. Patients were scored from 0 to 4, and divided into five groups according to the prognostic score. The rates of survival for each group were calculated using the Kaplan–Meier method. As seen in Fig. 2 survival rates seem to go in three lines. Three groups were made patients having 4 or 3 points as Group A, two to one points as group B and zero point group C. All the Kaplain–Meier survival rates were tested significant by log rank analysis. After giving the points and making groups, the testing sets survival rates were checked and they seem to correlate with survival rates in training group. Patient's in-group A survives quite reliable over six months and two thirds of patients will survive over 12 months. Patients in group B are likely to survive over three months and half of patients will survive over six months. Patients' survival even for three months is unsure in-group C.

Discussion

Survival data and knowledge of the primary tumour causing pathologic fractures are highly relevant to physicians who are confronted with the difficult problem of managing pathologic fractures. Palliative surgery is needed for patients with metastatic bone lesions that cause severe pain with no response to other treatment options. Based on these data comprising over 1100 patients, skeletal metastases complicate a wide range of malignancies and malignant tumours can metastasize in many different bones [6,7]. Primary tumours in breast, prostate, renal, lung, and myeloma make up 78% of the cases, but over 20 different primary tumours led to fractures requiring surgery. Metastatic tumours were found in various locations, even in the talus. The femur, humerus, and pelvis were the most common locations, regardless of the site of the primary tumour.

Bone in pathologic fractures differs greatly from normal bone as a result of tumour growth and increased osteoclast activation due to tumour cell factors [13,14]. Pathologic fractures require a long time to heal and often never completely heal [8,9]. Several articles have been published on surgical management of metastatic bone disease [5,9–11] and the factors affecting patient survival [11–15]. Questions remain, however, about which patients benefit from surgery and which kind of surgery is reasonable. Because surgery is always palliative in some way among these patients with limited life expectancy, unnecessary reoperations due to complications resulting from hardware failure are particularly unwarranted. This should be kept in mind in surgical osteosynthesis, like intramedullary nailing; a patient's survival should not exceed the durability of the nail. For patients with a short life expectancy, the surgeon must avoid hastening death through overly aggressive treatment.

In our study, overall survival of cancer patients with bone metastases after pathologic fracture ranged from a few months to several years among different primary tumours. Mean survival in breast cancer patients was more than 1 year compared to lung cancer patients with less than 6 months of survival after pathologic fractures. Even though almost all pathologic fractures herald the end-stage of disease, in this study 58% of patients survived beyond 6 months and 41% beyond 1 year. According to previous studies, bone metastasis at the time of cancer diagnosis is rare; 4.76% of patients have bone metastasis present at the initial diagnosis of kidney carcinoma, 2.5% in prostate carcinoma, and 0.5% in breast carcinoma [16–18]. In our series, 14% of patients did not have a

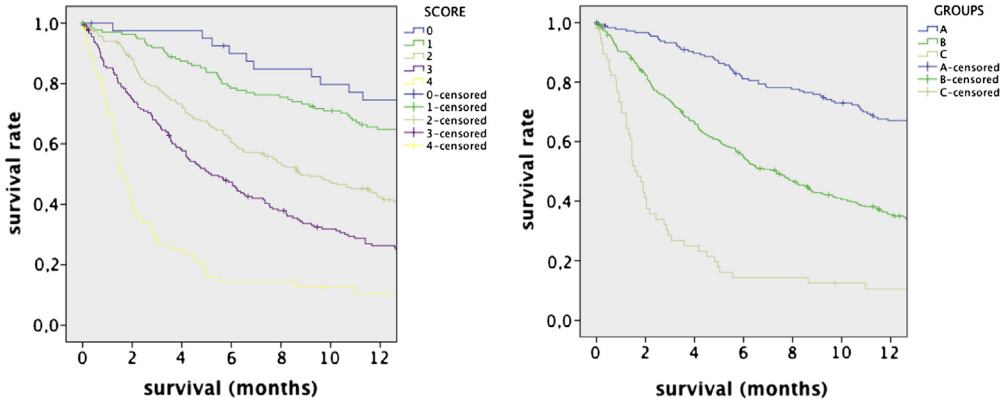

Figure 2. Kaplain–Meier survival curves for different scores and groups.

Table 7 SSG survival scoring

		points	sum	groups	estimated survival
Number of skeletal of skeletal metastases	single	1			
	multiple	0	4	A	more than 6-12 months
Presence of organ metastases	absent	1	3		
	present	0	2	B	3-6 months
Breast cancer, kidney cancer, thyroid cancer,	yes	1	1		
myeloma, lymfoma	no	0	0	C	less than 3 months
Karnofsky score	>=70	1			
	<70	0			

previously diagnosed cancer prior to pathologic fracture. Among these patients, lung cancer was the most common detected primary tumour (21%) accompanied with kidney cancer (14%) and myeloma (14%).

Surgery for impending fractures raises controversies. Indications differ from unbearable pain that is resistant to conservative treatment, to prevention of a pathologic fracture [10,11,19–21]. Surgical treatment of impending fractures is thought to be less complicated and easier to perform than that for complete fractures [10,20], as is operating on non-displaced fractures, but it is not an acceptable indication for surgery, at least not in traumatology. Factors inherent to cancer may worsen the incidence and severity of fat embolism when treating long bone metastases [22]. In impending fractures, the intramedullary canal pressure is even higher than in complete fractures. The incidence of different pulmonary and cardiovascular complications in the treatment of pathologic fractures ranges from 0% to 25% [10,22–27]. In our study, the number of systemic complications was 4-fold in impending pathologic fractures and all fatal embolisms occurred when treating impending pathologic fractures. In many reports, survival after surgery is usually better in the group of impending fractures versus complete fractures [3,11,15]. Also in the present study, survival was better in the group of impending fractures versus complete fractures. It is noteworthy, however, that the time between metastasis diagnosis to surgery was shorter in the group of impending fractures, the patients were operated on earlier in the disease course, and the median age of the patients was lower, indicating that these patients are younger, in better overall health, and have a longer expectant life span. Every physician should calculate and estimate, what is the price of a lethal complication one is willing to take and therefore careful consideration should be taken before operating for impending fractures.

Although these data include patients with severe disease and severe complications, the complication rate was not high. We found a complication rate of 12.9% for all operations, which is considered low compared to previous reports of rates as high as 20% [20,28]. The low complication rate in our study may be due to the fact that although this is a multinational study, all Scandinavian countries share the same surgical methods and the surgical procedures are centralized to oncologic orthopaedics in many of the referred centres. No special risk factors could be detected in the cases that developed complications, e.g., age, sex, metastatic load, primary tumour type, Karnofsky score, surgical method, bone localization, or nationality. There were more complications in prosthetic replacement group compared to plating and nailing procedures, but there were fewer re-operations. Cases having a complication were more often radiated in respect to all cases, especially in prosthetic replacement group. There was no difference in complications due to infections, but complications in endoprosthetis group were more common if metastases were radiated previously. On the contrary the rate on non-union did not differ between preoperatively radiated fractures compared to fractures that were not radiated in advance. Preoperative radiation apparently gives elevated risk in the number of postoperative complications, which should be kept in mind when operating preoperatively radiated pathologic fractures.

To avoid burdensome overtreatment in patients with a very limited remaining lifetime and on the other hand to treat long survivor with adequate surgical choice, a simple instrument distinguishing patients who are likely to die within 3 months from those who most probably live for more than one year would was one of our goals. This information can be used to avoid unnecessary overtreatment for carefully selected patients. There are many ways to develop prognostic scoring systems. Most of them, however, are complicated and have an overwhelming number of variables [13,29–31]. In our study we discovered four significant prognostic factors affecting survival. Radiation preoperatively was not a significant factor as it was in Katagiri's study on 350 patients with skeletal metastases, nor was presence of pathological fracture as in Bauer's score [13,31]. Our scoring system uses the same variables as identified in Karnofsky score, but multiplies the factors which have the most important positive effect in survival. Our SSG scoring system offers a useful tool for this process of estimating survival and it is simple and easy to use and can easily be adopted to everyday work.

In conclusion we can say that the results of this study confirm signs of good and poor survivors among patients with pathologic bone fracture. We have also developed a simple, useful and reliable tool to predict survival among these patients.

Conflict of interest statement

None declared.

References

[1] Engholm G, Ferlay J, Christensen N, Bray F, Gjerstorff ML, Klint A, et al. Nordcan-a nordic tool for cancer information, planning, quality control and research. Acta Oncol 2010;49:725–36.
[2] Chambers AF, Groom AC, MacDonald IC. Dissemination and growth of cancer cells in metastatic sites. Nat Rev Cancer 2002;2:563–72.
[3] Hansen BH, Keller J, Laitinen M, Berg P, Skjeldal S, Trovik C, et al. The Scandinavian Sarcoma Group Skeletal Metastasis Registry. Functional outcome and pain after surgery for bone metastases in the pelvis and extremities. Acta Orthop 2009;334:85–90.
[4] Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res 2006;12:6243s–9s.
[5] Bickels J, Dadia S, Lidar Z. Surgical management of metastatic bone disease. J Bone Jt Surg Am 2009;91:1503–16.
[6] Taube T, Elomaa I, Blomqvist C, Beneton MNC, Kanis JA. Histomorphometric evidence for osteoclast-mediated bone resorption in metastatic breast cancer. Bone 1994;15:161–6.
[7] Roodman GJ. Biology of osteoclast activation in cancer. J Clin Oncol 2001;19:3562–71.
[8] Gainor BJ, Buchert P. Fracture healing in metastatic bone disease. Clin Orthop 1983;178:297.

[9] Jacofsky DJ, Haidukewych GJ. Management of pathologic fractures of the proximal femur: state of the art. J Orthop Trauma 2004;18:459–69.
[10] van Doorn R, Stapert JW. Treatment of impending and actual pathological femoral fractures with the long gamma nail in the Netherlands. Eur J Surg 2000;166:247–54.
[11] Ward WG, Holsenbeck S, Dorey FJ, Spang J, Howe D. Metastatic disease of the femur: surgical treatment. Clin Orthop Relat Res 2003;415S:230–44.
[12] Nathan SS, Healey JH, Mellano D, et al. Survival in patients operated on for pathologic fracture: implications for end-of-life orthopedic care. J Clin Oncol 2005;23(25):6072–82.
[13] Katagiri H, Takahashi M, Wakai K, Sugiura H, Kataoka T, Nakanishi K. Prognostic factors and a scoring system for patients with skeletal metastasis. J Bone Jt Surg Br 2005;87:698–703.
[14] Saad F, Lipton A, Cook R, Chen YM, Smith M, Coleman R. Pathologic fractures correlate with reduced survival in patients with malignant bone disease. Cancer 2007;110:1860–7.
[15] Hansen BH, Keller J, Laitinen M, et al. The Scandinavian Sarcoma Group Skeletal Metastasis Register. Survival after surgery for bone metastases in the pelvis and extremities. Acta Orthop Scand Suppl 2004;75(311):11–5.
[16] Schlesinger-Raab A, Treiber U, Zaak D, Holzel D, Engel J. Metastatic renal cell carcinoma: results of a population-based study with 25 years follow-up. Eur J Cancer 2008;44:2485–95.
[17] Jensen AO, Jacobsen JB, Norgaard M, Yong M, Fryzek JP, Sorensen HT. Incidence of bone metastases and skeletal-related events in breast cancer patients: a population-based cohort study in Denmark. BMC Cancer 2011;11:29.
[18] Salonia A, Gallina A, Camerota TC, et al. Bone metastases are infrequent in patients with newly diagnosed prostate cancer: analysis of their clinical and pathologic features. Urology 2006;68(2):362–6.
[19] Weber KL, Lewis VO, Randall RL, Lee AK, Springfield D. An approach to the management of the patient with metastatic bone disease. Instr Course Lect 2004;53:663–76.
[20] Reich CD. Advances in the treatment of bone metastases. Clin J Oncol Nurs 2003;7(6):641–6.
[21] Johnson SK, Knobf MT. Surgical interventions for cancer patients with impending or actual pathologic fractures. Orthop Nurs 2008;27(3):160–71.
[22] Barwood SA, Wilson JL, Molnar RR, Choong PF. The incidence of acute cardiorespiratory and vascular dysfunction following intramedullary nail fixation of femoral metastasis. Acta Orthop Scand 2000;71(2):147–52.
[23] Wedin R, Bauer HC. Surgical treatment of skeletal metastatic lesions of the proximal femur: endoprosthesis or reconstruction nail? J Bone Jt Surg Br 2005;87(12):1653–7.
[24] Assal M, Zanone X, Peter RE. Osteosynthesis of metastatic lesions of the proximal femur with a solid femoral nail and interlocking spiral blade inserted without reaming. J Orthop Trauma 2000;14(6):394–7.
[25] Cole AS, Hill GA, Theologis TN, Gibbons CL, Willett K. Femoral nailing for metastatic disease of the femur: a comparison of reamed and unreamed femoral nailing. Injury 2000;31(1):25–31.
[26] Giannoudis PV, Bastawrous SS, Bunola JA, Macdonald DA, Smith RM. Unreamed intramedullary nailing for pathological femoral fractures. Good results in 30 cases. Acta Orthop Scand 1999;70(1):29–32.
[27] Peter RE, Schopfer A, Le Coultre B, Hoffmeyer P. Fat embolism and death during prophylactic osteosynthesis of a metastatic femur using an unreamed femoral nail. J Orthop Trauma 1997;11(3):233–4.
[28] Weiss RJ, Wedin R. Surgery for skeletal metastases in lung cancer. Acta Orthop 2011;82(1):96–101.
[29] Tokuhashi Y, Matsuzaki H, Toriyama S, Kawano H, Ohsaka S. Scoring system for the preoperative evaluation of metastatic spine tumor prognosis. Spine 1990;15:1110–3.
[30] Tomita K, Kawahara N, Kobayashi T, et al. Surgical strategy for spinal metastases. Spine 2001;26:298–306.
[31] Bauer HCF, Wedin R. Survival after surgery for spinal and extremity metastases. Acta Orthop Scand 1995;66:143–6.

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Prognostic Role of En-Bloc Resection and Late Onset of Bone Metastasis in Patients With Bone-Seeking Carcinomas of the Kidney, Breast, Lung, and Prostate: SSG Study on 672 Operated Skeletal Metastases

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Background and Objectives: In metastatic disease, decisions regarding potential surgery require reliable data about the patient's survival. In this study, we evaluated different prognostic factors and their impact in four common primary tumors causing bone metastases.
Methods: Data were acquired from the Scandinavian Sarcoma Group (SSG) metastasis registry. The patients underwent surgery between July 1999 and July 2009. This study included breast, prostate, lung, and kidney cancer cases, with a total of 672 operated non-spinal metastases. Differences in prognostic factors were evaluated using the Kaplan-Meier method with long-rank test. Cox regression multivariate analysis was performed to identify statistically independent prognostic factors.
Results: Significant factors affecting survival were the presence of organ metastases, overall heath status, and disease load. In kidney cancer, en bloc resection of solitary metastases was associated with a significant fourfold longer survival compared to intralesional surgery. Preoperative radiotherapy was associated with higher complication and reoperation rates.
Conclusions: This data summary is important tool for clinicians to evaluate survival and choose treatment options for patients suffering from metastatic bone disease.
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KEY WORDS: **bone metastases; surgical treatment; prognostic factors**

INTRODUCTION

Survival from cancer has increased annually [1]. Improvements in oncologic management have also increased the survival of patients with metastatic disease. Once a diagnosis of skeletal metastasis is made, the disease is considered mostly incurable; although survival can still be measured even in years [2–4]. Skeletal metastases can dramatically decrease the quality of life due to skeletal related events (SREs) like pain, hypocalcaemia, anemia, neurological deficiencies including paraparesis and pathologic fractures [5,6]. Radiotherapy (RT) plays an important role in the treatment of bone metastases. Its effectiveness in pain control has been demonstrated in many studies [7,8]. Its role in preventing pathologic fractures, as well as the improvement of survival seems to be less significant in the primary tumors selected in this study: breast, lung, kidney, and prostate [9,10]. SREs requiring surgery are infrequent and depend on the primary tumor. In a study based on a large breast cancer patient population, 7% of the patients had bone metastases and among them, SREs occurred in 46% with only 1% requiring bone surgery [11]. In lung cancer patients with metastatic bone disease (554 patients), 25% had SREs and 9% of these patients needed surgery [12]. The indication for surgery varies from pain to an existing pathologic fracture and seems to differ between nations. In studies in the USA, up to 71% of the patients have been treated due to impending fracture compared with only 18% in the Nordic countries [13–17]. Even though surgery for an existing or impending fracture is demanded in only a minority of SREs, it is sometimes necessary for the patients to remain independent. Immediate relief of pain and improvement of the functional status is particularly important for patients with a short life expectancy [5]. Decisions regarding potential surgery for metastatic disease require reliable data about the patient's survival and quality of life [18]. This is why several studies have been conducted on prognostic factors affecting survival.

The aim of this study was to analyze a prospectively collected for metastasis registry patients with surgically treated bone metastases in four most common bone-seeking primary cancers: breast, lung, kidney and prostate. The goal was to document the survival of this cohort of patients, determine clinicopathological factors affecting survival and analyze surgical complications and reoperation rates.

Conflict of interest: none.

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MATERIALS AND METHODS

The Scandinavian Sarcoma Group (SSG) was constituted in 1979. In 1999, a multi-center prospective SSG skeletal metastases registry was established to evaluate treatment results and prognostic factors in patients with surgically treated non-spinal skeletal metastases. Data for this study were based on this SSG skeletal metastases registry and comprised information on surgically treated skeletal metastases in the extremities and pelvis from referral centers in Nordic countries. The patients underwent surgery between July 1999 and July 2009. The indications for surgery were an existing fracture or impending fracture where the degree of bone disruption warranted prophylactic surgical stabilization to prevent a fracture, intractable pain, or the loss of ambulatory ability. The registry consists of information on over 1100 patients. In the scope of this study were 617 patients with breast, lung, prostate and kidney cancer. To determine if the disease had spread, X-rays, ultrasound and/or computed tomography images were obtained from all patients. The average age at the first operation was 62 years (range 28–87) in breast cancer patients, 64 years (range 34–86) in lung cancer patient, 73 years (range 49–96) in prostate cancer patients, and 65 years (range 39–95) in kidney cancer patients. The study included a total of 672 skeletal metastases in breast (n = 307), in lung (n = 97), in prostate (n = 146), and in kidney (n = 122) cancers.

To determine possible prognostic factors for survival, the cases were distributed by age (<65 or ≥65), bone localization (upper limb: scapula, humerus, radius, ulna; and lower limb: pelvis, femur, tibia, talus), number of skeletal metastases (solitary and multiple), presence of organ metastases, presence of pathological fracture and degree of Karnofsky score (<70 or ≥70), preoperative radiation (yes or no), operation method (plating and nailing, prosthesis, tumor prosthesis, other), operation strategy (en bloc resection or other, including: stabilization without tumor removal, curettage only, and curettage with cement), and time intervals (from diagnosis of primary cancer to diagnosis of metastases, diagnosis of metastases to operation of skeletal metastases, diagnosis of primary tumor to operation). All the time intervals were checked at 6 months, 12 months and 2, 5, and 10 years. If en-bloc resection had a positive impact on survival, we also analyzed the impact comparing single and multiple skeletal metastases.

The Kaplain–Meier method with log-rank test was used for univariate analysis of calculated calculated overall survival rates and differences in survival with respective variables. The statistical significance level was set at a *P*-value of 0.05. Survival was calculated as the time from the operation to the date of death. The patients for whom the date of death was missing either because the patient was still alive or lost to follow-up were censored at the last time they were known to be alive. If the reason for death was not cancer, the case was censored. Cox regression multivariate analysis was performed to find statistically independent prognostic factors. Our data are presented as hazard ratios (HR) and 95% confidence intervals (95% CI). Statistical analyses were performed using IBM SSPS Statistics 20.0.

Information about preoperative RT was found on 650 cases (96.7%). The total dose and number of fractions were not registered. About 27.7% of the cases received RT. The distribution of RT in different primary tumors were 32.2% (99/307), 28.1% (41/146), 20.6% (20/97), and 7% (20/146) in breast, prostate, lung, and kidney cancers, respectively. Metastases in pelvic area were radiated most often (49.1% 27/55). Details of the research variables can be seen in Tables I–VIII.

RESULTS

The median survival time after the operation was 8.9 months; it was 12.9 months in breast cancer, 3.6 months in lung cancer, 6.1 months in prostate cancer, and 12.1 months in renal cancer. The presence of organ metastases was a significant prognostic factor by univariate analysis in all cancers examined. For breast cancer patients, the independent prognostic factors for better survival were: age under 65, Karnofsky score greater than 70, and solitary skeletal metastases (Table II). Solitary bone metastases in breast cancer were rare since 90% of the patients had widely spread disease. However, the patients with solitary bone metastases had statistically enhanced survival, almost 3 years compared with 1 year in patients with multiple bone disease. In the univariate analysis, the presence of organ metastases, presence of pathological fracture, and a long time (over 6 months) between the diagnosis of metastases and the operation also worsened survival. A long time interval between the diagnosis of primary cancer and the operation for skeletal metastases did not affect the survival (Table I).

Survival was short in all lung cancer patients, on the average just a few months. Karnofsky score less than 70 and organ metastases were independent risk factors in multivariate analysis (Table IV).

In prostate cancer, the patients were typically older and had multiple bone metastases. Only a few (5%) had solitary metastases at the time of

TABLE I. Possible Prognostic Factors, Median Survival by Kaplan–Meier With Cumulative Intervals and *P*-Values After Operation of 307 Skeletal Metastases in Breast Cancer

Factor	n	Survival	95% CL	*P*-value
Age (yrs)				**0.003**
<65	177	15.441	12.629–18.254	
≥65	130	9.133	6.061–12.206	
Karnofsky score				**0.001**
≥70	151	17.248	14.089–20.373	
<70	156	9.791	5.975–13.607	
Number of lesions				**0**
One	32	34.957	21.068–48.846	
Multiple	275	11.86	9.676–14.045	
Organ metastases				**0.027**
Absent	173	16.066	11.830–20.301	
Present	134	10.809	8.057–13.561	
Localization				0.931
Lower limb	223	11.86	9.288–14.433	
Pelvis	28	15.441	9.098–21.785	
Upper limb	56	15.441	10.176–20.707	
Pathological fracture				
Yes	227	11.302	8.580–14.023	**0.015**
No	80	16.821	11.122–22.521	
Radiation preop.				
No	199	11.926	8.973–14.879	0.517
Yes	99	14.916	10.635–19.197	
Missing	9			
Operation strategy				
En bloc	12	16.821	3.214–30.429	0.1
other	295	12.583	10.145–15.020	
Time intervals primary diagnosis → metastases				
≤2 years	113	11.86	8.021–15.699	0.942
>2 years	166	13.207	9.450–16.965	
Missing	28			
Metastasis diagnosis → operation				
≤6 months	128	15.047	9.813–20.281	**0.048**
>6 months	159	11.302	8.528–14.066	
Missing	20			
Primary diagnosis → operation				
≤6 months	25	11.63	8.252–15.008	0.837
>6 months	247	12.616	9.865–15.367	
≤2 years	68	11.86	8.760–14.960	0.923
>2 years	204	13.273	9.881–16.665	
≤5 years	131	12.616	10.709–14.524	0.491
>5 years	141	11.86	6.898–16.823	
≤10 years	201	11.893	9.671–1.116	0.276
>10 years	71	16.559	10.934–22.183	
Missing	35			

Statistically significant results are bolded.

TABLE II. Prognostic Factor by Multivariate Analysis *P*-Value, Hazard Rate and Cumulative Intervals

Prognostic factor	Sig.	HR	95% CL	
Karnofsky score under 70	0.001	1.506	1.171	1.936
Multiple skeletal metastases	0	2.331	1.449	3.751
Age over 65	0.01	1.398	1.083	1.804

TABLE IV. Prognostic Factor by Multivariate Analysis *P*-Value, Hazard Rate and Cumulative Intervals

Prognostic factor	Sig.	HR	95% CL	
Karnofsky score under 70	0.013	1.715	1.119	2.628
Presence of organ metastases	0.002	2.049	1.299	3.233

operation and it did not affect survival (Table V). In addition to presence of organ metastases, a significant negative prognostic factor by multivariate analysis was greater than 6 months between the diagnosis of primary disease and the operation of skeletal metastases (Table VI). In the univariate analysis, preoperative RT was also a prognostic factor (Table V).

In kidney cancer, 45% of the patients had solitary bone metastases, which differed from all the other primary cancers (Table VII). The location of the metastasis in the upper arm and especially in the pelvis and a Karnofsky score greater than 70 indicated better survival (Tables VII and VIII). In the univariate analysis, solitary skeletal metastases, the absence of organ metastases, no preoperative RT, a time interval longer than 2 years between the diagnosis of primary cancer, and the operation and between the diagnosis of metastases to the operation also indicated better survival.

En bloc resection of solitary bone metastasis resulted in enhanced survival in all primary tumor groups. The increase was 20 months on average and statistically significant (Fig. 1). Since solitary bone

TABLE III. Possible Prognostic Factors, Median Survival by Kaplan–Meier With Cumulative Intervals and *P*-Values After Operation of 97 Skeletal Metastases in Lung Cancer

Factor	n	Median survival	95% CL	*P*-value
Age (yrs)				
<65	51	4.337	2.857–5.815	0.439
>65	46	2.661	1.474–3.849	
Karnofsky score				**0.05**
≥70	49	5.421	3.785–7.057	
<70	48	2.136	1.355–2.916	
Number of lesions				
One	21	4.14	2.556–5.724	0.319
Multiple	76	3.45	1.625–5.274	
Organ metastases				
Absent	40	5.092	3.324–6.861	**0.006**
Present	57	2.858	1.365–4.351	
Localization				
Lower limb	69	4.172	2.846–5.499	0.984
Pelvis	5	2.103	2.032–2.173	
Upper limb	23	2.136	0.644–3.627	
Pathological fracture				
Yes	67	3.055	1.361–4.749	0.379
No	30	5.552	3.300–7.805	
Radiation				
No	75	3.45	2.118–4.782	0.601
Yes	20	5.388	0.857–9.920	
Missing	1			
Operation strategy				
En bloc	3	5.782	3.153–8.411	0.996
Other	94	3.45	2.010–4.889	
Time intervals primary diagnosis → metastases				
≤2 years	89	3.811	2.422–5.200	0.141
>2 years	5	6.209	0–15.662	
Missing	3			
Metastasis diagnosis → operation				
≤6 months	85	3.811	2.219–5.493	0.868
>6 months	11	3.614	0.509–6.719	
Missing	1			
Primary diagnosis → operation				
≤6 months	68	4.172	2.993–5.352	0.238
>6 months	29	2.136	1.113–3.158	
≤2 years	90	3.614	2.264–4.964	0.76
>2 years	7	6.209	0–17.507	
≤5 years	95	5.749	5.771–12.693	0.412
>5 years	2	8.871	17.582–43.855	

Statistically significant results are bolded.

TABLE V. Possible Prognostic Factors, Median Survival by Kaplan–Meier With Cumulative Intervals and *P*-Values After Operation of 146 Skeletal Metastases in Prostate Cancer

Factor	n	Median survival	95% CL	*P*-value
Age (yrs)				
<65	26	4.14	2.539–5.740	0.321
>65	120	7.359	5.254–9.465	
Karnofsky score				
≥70	74	8.378	5.098–11.658	0.374
<70	72	5.487	3.401–7.572	
Number of lesions				
One	8	10.776	10.534–11.019	0.505
Multiple	138	6.045	4.162–7.928	
Organ metastases				
Absent	117	8.378	5.749–11.007	**0.006**
Present	29	3.515	1.733–5.298	
Localization				
Lower limb	114	6.144	3.892–8.396	0.944
Pelvis	13	8.805	1.745–15.865	
Upper limb	19	4.205	0.842–7.569	
Pathological fracture				
Yes	130	6.209	4.115–8.173	0.344
No	16	4.337	0.000–11.549	
Preop radiation				
No	98	6.144	4.250–8.038	**0.033**
Yes	41	8.641	3.351–13.931	
Missing	7			
Operation strategy				
En bloc	1	15.31	0	0.682
Other	145	6.144	4.079–8.209	
Time intervals primary diagnosis → metastases				
≤2 years				
> 2 years	98	6.045	3.853–8.237	0.539
Missing	41	6.045	4.094–7.996	
Metastasis diagnosis → operation	7			
≤6 months				
>6 months	56	8.805	5.367–12.242	0.96
Missing	83	5.749	4.088–7.411	
Primary diagnosis → operation	7			
≤6 months				
>6 months	24	14.029	5.134–22.924	**0.011**
≤2 years	112	5.979	4.663–7.296	
>2 years	62	5.191	3.361–7.021	0.706
≤5 years	74	8.378	5.739–11.017	
>5 years	97	5.749	4.690–6.809	0.575
Missing	39	8.871	4.870–12.871	
	10			

TABLE VI. Prognostic Factor by Multivariate Analysis *P*-Value, Hazard Rate and Cumulative Intervals

Prognostic factor	Sig.	HR	95% CL	
Presence of organ metastases	0.005	1.911	1.216	3.002
Time from primary dg to operation over 6 months	0.007	2.107	1.227	3.617

TABLE VIII. Prognostic Factor by Multivariate Analysis *P*-Value, Hazard Rate and Cumulative Intervals

Prognostic factor	Sig.	HR	95% CL	
Karnofsky score < 70	0	2.955	1.894	4.61
Pelvis	0.026	0.4	0.178	0.899
Upper limb	0.053	0.612	0.373	1.006
Operation strategy other than en bloc resection	0.039	1.833	1.032	3.255

metastases were so seldom, the statistical justification was lost in all other primary tumors except in kidney cancer. In kidney cancer, patients undergoing en-bloc resection of a solitary metastasis had fourfold better survival when compared to patients with a solitary metastasis undergoing intralesional surgery. This statistical significance remained in the multivariate analysis. En bloc resection of a metastasis in patients with multiple metastases did not increase the survival when compared with intralesional surgery (Table VII).

TABLE VII. Possible Prognostic Factors, Median Survival by Kaplan–Meier With Cumulative Intervals and *P*-Values After Operation of 122 Skeletal Metastases in Kidney Cancer

Factor	n	Survival	95% CL	*P*-value
Age (yrs)				
<65	60	12.846	6.161–19.531	0.377
>65	62	10.743	3.195–18.292	
Karnofsky score				
≥70	66	24.312	11.223–37.402	**0**
<70	56	4.994	3.737–6.251	
Number of lesions				
One	55	19.187	5.152–33.222	**0.002**
Multiple	67	6.177	2.979–9.374	
Organ metastases				
Absent	64	15.901	5.213–26.590	**0.022**
Present	58	7.721	2.564–12.878	
Localization				
Lower limb	71	9.232	5.548–12.916	**0.034**
Pelvis	13	25.856	0.000–58.064	
Upper limb	38	15.113	0.000–45.404	
Pathological fracture				
Yes	80	9.593	5.018–14.169	0.133
No	42	23.228	10.619–35.837	
Radiation				
No	98	14.094	9.886–18.303	**0**
Yes	20	5.848	2.728–8.968	
Missing	4			
Operation strategy				**0.002**
En bloc	27	46.719	19.419–74.018	
Other	95	9.232	5.994–12.470	
solitarymet. + enbloc	21	50.201	16.006–84.396	**0.014**
solitarymet. + other	34	15.113	8.754–21.472	
multiplemet. + enbloc	6	12.846	0–32.247	0.355
multiplemet. + other	61	5.651	2.245–9.057	
Time between primary diagnosis → metastases				
≤2 years	86	8.772	5.214–12.330	**0.011**
>2 years	32	30.719	16.445–44.992	
Missing	4			
Metastasis diagnosis → operation				
≤6 months	94	12.846	8.935–16.757	0.696
>6 months	26	6.177	0.00–12.776	
Missing	2			
Primary diagnosis → operation				
≤6 months	57	13.536	8.924–18.148	0.462
>6 months	61	10.382	3.642–17.117	
≤2 years	81	9.232	6.293–12.171	**0.039**
>2 years	37	25.856	5.505–46.207	
≤5 years	96	9.232	5.771–12.693	**0.016**
>5 years	22	30.719	17.582–43.855	
≤10 years	109	11.039	6.012–16.066	0.542
>10 years	9	12.09	8.155–16.026	
Missing	4			

Complications reported were infections, mechanical complications, nerve problems, nail breakage, non-unions, tumor progression, and embolism. Rates were not high and there were no differences in complication rates between different primary tumors. Preoperative RT was associated with a higher complication rate. The complication percentages in patients not receiving preoperative RT were 5%, 12%, 10%, and 8% in lung cancer, in prostate cancer, in breast cancer and in kidney cancer, respectively; while the corresponding complication percentages in patients receiving preoperative RT were 15%, 15%, 15%, and even 35%, respectively. This same effect was also seen when different operation methods were studied; for example after plating and nailing procedures, the patients receiving preoperative RT had more often complications (18%, 14/78) than patients who did not receive preoperative RT (9%, 20/234). This was also seen in rates of prosthetic complications (11%, 9/82 vs. 4%, 6/172), nail-breakages (5.1%, 4/78 vs. 1%, 3/172), non-unions (5%, 4/78 vs. 2%, 4/234) and also in wound and deep infections (9%, 7/82 vs. 4%, 7/172). The complication rate was lower after en bloc resection. In the solitary metastases, the complication percentage was 10% (3/29) after en bloc resection and 14% (12/87) after other operation strategies. In multiple skeletal metastases, the complication percentage was 7% (1/14) after en bloc resection and 11% (62/542) after other operation strategies. A total of seven systemic complications were reported in all cancers investigated.

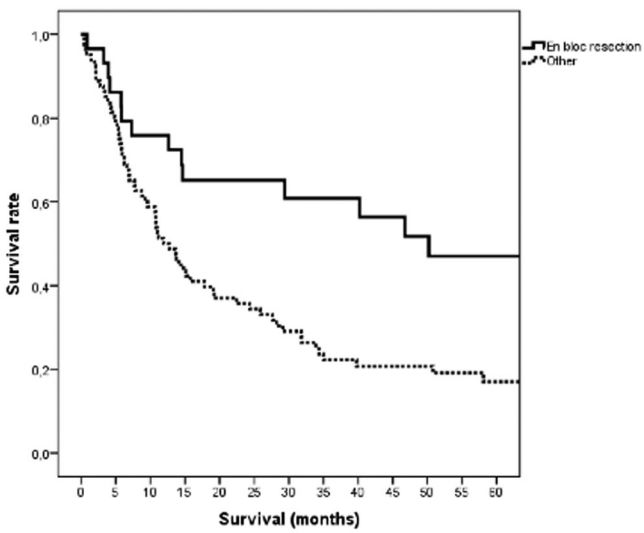

Fig. 1. En bloc resection in solitary bone metastases had a significant effect on the overall postoperative survival rate when compared to other operation strategies.

The number of reoperations was similar in different primary tumors. The reoperation percentages in patients with breast, lung, prostate, and kidney cancers were 6% (19/306), 2% (2/97), 6% (9/136), and 7% (9/122), respectively. There were also more reoperations after preoperative RT, 9% (9/99), 15% (2/41), and 20% (4/20) in breast, prostate, and kidney cancer patients, respectively. The reasons for reoperations did not vary between different primary tumors. The reported reasons for reoperations were non-unions, local recurrences, stress fractures, immediate fails/technical errors, and infections. All local recurrences were operated on in patients where the primary indication for surgery was an impending fracture, and none of these patients received preoperative RT. The reoperation rates were low after en bloc resection. In solitary metastases, the reoperation rate was 7% (2/29) after the en bloc resection and 12.6% after other operation strategies. In multiple skeletal metastases, there were no reoperations after en bloc resection and the reoperation rate was 5% (26/542) after other operation strategies.

DISCUSSION

More personalized survival data for patients with metastasized cancer is needed to improve the understanding of prognostic factors and aid physicians who are confronted with the difficult problem of managing pathologic fractures [19]. The decision to operate should take into account the possible survival time, as long survivors should be treated more aggressively and short survivors with minimal surgery leading to more cost-effective use of health care resources [20,21].

Our results show that patients with surgery-demanding bone metastases should never be evaluated as one population. The present study identifies several predictors of survival. The most interesting finding was that in solitary bone metastases, the type of surgery significantly influenced patients' survival. En bloc resection of solitary bone metastases increased survival in all primary cancer groups; although, with the exception of kidney cancer, the numbers of en-bloc resections in all other groups were so small that definite conclusions cannot be drawn. Only in kidney cancer, the survival in en-bloc resection patients was statistically significant increased (fourfold) compared with intralesional surgery. The subject of aggressive resection of bone metastases in cancer patients has raised controversies previously. In some studies, wide resection was a positive prognostic factor for improved survival [9,22], but other published data questions this [16,23,24]. The possible increased morbidity due to surgery and prolonged postoperative rehabilitation has also decreased the tendency towards aggressive surgery, as the benefit might be insignificant. Several studies reported that en bloc resection prevents local progression [22,23,25]. We found the mean survival after en bloc resections in solitary kidney cancer bone metastases was as long as 5 years. Another interesting finding in kidney cancer was that the patients with pathologic fractures in the pelvis had significantly better survival (25 months).

The time-point of bone metastases also influenced the overall survival. Known bone metastases are a sign of disease spread and the occurrence of skeletal metastases has a strong negative impact on survival. Interestingly, the onset of bone metastases had different impacts on survival in different primary tumors. As suspected, the occurrence of bone metastases in lung cancer had no impact on survival; whereas, in prostate cancer, early onset of a pathologic fracture after the primary diagnosis or with the primary diagnosis had a positive impact on survival. This is most probably because the disease is likely to respond to all therapy, mainly hormone therapy, at the beginning of the disease. In previous studies, a long disease-free interval has been a good prognostic factor in breast cancer and it is commonly believed that a breast cancer patient with long disease-free survival should be treated more aggressively [26–28]. However, in our results, a late onset of metastases in breast cancer did not affect the overall prognosis of these patients. Interestingly, in kidney cancer patients, a disease-free interval of more than 2 years had a positive impact on survival with statistical significance. The difference increased even more for patients with a disease-free interval of more than 5 years.

Some previous studies have shown that intralesional procedures have higher complication and reoperations rates than wide resection [13,29]. In addition to the increased survival, our current study could also confirm that en bloc resection prevents local progression of the disease and thereby mechanical complications, as well as reoperations. More interestingly, preoperative RT was associated with higher complication and reoperation rates. This was seen among all primary cancer types, but most strongly with kidney cancer patients. The surgical complication rate in kidney cancer metastases was as high as 35% after preoperative RT. The impact was seen in all surgical procedures, like nailing and plating, as well as in prosthetic replacement procedures.

The large SSG metastasis registry database is international and multicenter and it provides excellent opportunities to investigate the association between pathological fractures and survival. Even though the database is quality-controlled, it is a retrospective study in nature and has its limitations. The exact indications for operative treatment varied during the study period and there could be patient and treatment selection biases. Yet, as a multicenter and retrospective study, we had a large cohort and long follow-up times. With these advantages, we could differentiate statistical differences between different cancers and different variables.

It is important that patients with metastatic bone disease undergo the best possible surgical treatment. By collecting more information on patients who have been operated on because of skeletal metastases, we can proceed towards more personalized treatment strategies. In this study, we wanted to show how these bone-seeking tumors greatly differ at the time of pathologic fracture and how this has a significant role in survival.

In summary, the most important significant factors affecting survival are the primary tumor, presence of organ metastases, overall health status, and number of bone metastases. En bloc resection remains preferable for the treatment of a solitary metastasis, especially for kidney cancer patients with late onset of metastases and good overall health status, and it is the most reliable means for providing long survival and durable local control with lowered complication and reoperation rates. Preoperative RT seems to increase the postoperative complication rate especially in intralesional surgery. The findings from this study are important and should be considered when determining the surgical treatment of each patient.

REFERENCES

1. Howlader N, Noone AM, Krapcho M, et al.: SEER Cancer Statistics Review, 1975–2008. National Cancer Institute; Bethesda, MD: http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site, 2011.
2. Vasudev NS, Brown JE: Medical management of metastatic bone disease. Curr Opin Support Palliat Care 2010;4:189–194.
3. Tubiana-Hulin M: Incidence, prevalence and distribution of bone metastases. Bone 1991;12:S9–10.
4. Rove KO, Crawford ED: Metastatic cancer in solid tumors and clinical outcome: Skeletal-related events. Oncology 2009;23:21–27.
5. Hansen BH, Keller J, Laitinen M, et al.: The Scandinavian Sarcoma Group Skeletal Metastasis Registry. Functional outcome and pain after surgery for bone metastases in the pelvis and extremities. Acta Orthop 2009;334:85–90.
6. Hansen BH, Keller J, Laitinen M, et al.: The Scandinavian Sarcoma Group Skeletal Metastasis Register. Survival after surgery for bone metastases in the pelvis and extremities. Acta Orthop Scand Suppl 2004;75:11–15.
7. 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.

8. Kachnic L, Berk L: Palliative single-fraction radiation therapy: How much more evidence is needed? J Natl Cancer Inst 2005;97: 786–788.
9. Fottner A, Szalantzy M, Wirthmann L, et al.: Bone metastases from renal cell carcinoma: Patient survival after surgical treatment. BMC Musculoskelet Disord 2010;11:145.
10. Sugiura H, Yamada K, Sugiura T, et al.: Predictors of survival in patients with bone metastasis of lung cancer. Clin Orthop Relat Res 2008;466:729–736.
11. Sathiakumar N, Delzell E, Morrisey MA, et al.: Mortality following bone metastasis and skeletal-related events among women with breast cancer: A population-based analysis of U.S. Medicare beneficiaries, 1999–2006. Breast Cancer Res Treat 2012;131:231–238.
12. Decroisette C, Monnet I, Berard H, et al.: Epidemiology and treatment costs of bone metastases from lung cancer: A French prospective, observational, multicenter study (GFPC 0601). J Thorac Oncol 2011;6:576–582.
13. Steensma M, Boland PJ, Morris CD, et al.: Endoprosthetic treatment is more durable for pathologic proximal femur fractures. Clin Orthop Relat Res 2012;470:920–926.
14. Moholkar K, Mohan R, Grigoris P: The Long Gamma Nail for stabilisation of existing and impending pathological fractures of the femur: An analysis of 48 cases. Acta Orthop Belg 2004;70:429–434.
15. Chavey D, Lewis VO, Moon BS, et al.: Durability of cephalomedullary nail fixation for treatment of metastatic peritrochanteric femoral lesions. Lecture abstract. MSTS 2012 Annual Meeting, session III;2012.
16. Lin PP, Mirza AN, Lewis VO, et al.: Patient survival after surgery for osseous metastases from renal cell carcinoma. J Bone Joint Surg Am 2007;89:1794–1801.
17. Ratasvuori M, Wedin R, Keller J, et al.: Insight opinion to surgically treated metastatic bone disease: Scandinavian Sarcoma Group Skeletal Metastasis Registry report of 1195 operated skeletal metastasis. Surg Oncol 2013;22:132–138.
18. Nathan SS, Healey JH, Mellano D, et al.: Survival in patients operated on for pathologic fracture: Implications for end-of-life orthopedic care. J Clin Oncol 2005;23:6072–6082.
19. Coleman RE: Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res 2006;12:6243s–6249s.
20. Bauer HC: Controversies in the surgical management of skeletal metastases. J Bone Joint Surg Br 2005;87:608–617.
21. Ministry of Social Affairs and Health of Finland. A working group report about development of cancer in 2010–2020; 2000;82:62–67.
22. Baloch KG, Grimer RJ, Carter SR, et al.: Radical surgery for the solitary bony metastasis from renal-cell carcinoma. J Bone Joint Surg Br 2000;62–67.
23. Evenski A, Ramasunder S, Fox W, et al.: Treatment and survival of osseous renal cell carcinoma metastases. J Surg Oncol 2012;106: 850–855.
24. Durr HR, Maier M, Pfahler M, et al.: Surgical treatment of osseous metastases in patients with renal cell carcinoma. Clin Orthop Relat Res 1999;283–290.
25. Les KA, Nicholas RW, Rougraff B, et al.: Local progression after operative treatment of metastatic kidney cancer. Clin Orthop Relat Res 2001;206–211.
26. Insa A, Lluch A, Prosper F, et al.: Prognostic factors predicting survival from first recurrence in patients with metastatic breast cancer: Analysis of 439 patients. Breast Cancer Res Treat 1999; 56:67–78.
27. Coleman RE, Smith P, Rubens RD: Clinical course and prognostic factors following bone recurrence from breast cancer. Br J Cancer 1998;77:336–340.
28. James JJ, Evans AJ, Pinder SE, et al.: Bone metastases from breast carcinoma: Histopathological—radiological correlations and prognostic features. Br J Cancer 2003;89:660–665.
29. Van der Linden YM, Dijkstra PD, Kroon HM, et al.: Comparative analysis of risk factors for pathological fracture with femoral metastases. J Bone Joint Surg Br 2004;86:566–573.

Surgery of non-spinal skeletal metastases in renal cell carcinoma

No effect of preoperative embolization?

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Background and purpose — Surgery for metastases of renal cell carcinoma has increased in the last decade. It carries a risk of massive blood loss, as tumors are hypervascular and the surgery is often extensive. Preoperative embolization is believed to facilitate surgery. We evaluated the effect of preoperative embolization and resection margin on intraoperative blood loss, operation time, and survival in non-spinal skeletal metastases of renal cell carcinoma.

Patients and methods — This retrospective study involved 144 patients, 56 of which were treated preoperatively with embolization. The primary outcome was intraoperative blood loss. We also identified factors affecting operating time and survival.

Results — We did not find statistically significant effects on intraoperative blood loss of preoperative embolization of skeletal non-spinal metastases. Pelvic localization and large tumor size increased intraoperative blood loss. Marginal resection compared to intralesional resection, nephrectomy, level of hemoglobin, and solitary metastases were associated with better survival.

Interpretation — Tumor size, but not embolization, was an independent factor for intraoperative blood loss. Marginal resection rather than intralesional resection should be the gold standard treatment for skeletal metastases in non-spinal renal cell carcinoma, especially in the case of a solitary lesion, as this improved the overall survival.

The incidence of renal cell carcinoma (RCC) has been increasing (Engholm et al. 2010). RCC is characterized by an absence of early warning signs, especially since small tumors rarely produce symptoms. Thus, diagnosis can be delayed until the disease has metastasized (Motzer et al. 1996). The lung and bone are the most common sites for metastases (Han et al. 2003). Studies have shown that 30–40% of patients either have bone metastases at initial presentation of disease or they develop these later (Schlesinger-Raab et al. 2008, Woodward et al. 2011). New therapeutic options such as multimodal-targeted therapies have improved the treatment of RCC (Motzer et al. 2009). Medical therapy and radiotherapy are the first-line treatments for metastatic RCC. However, as metastases of RCC are relatively resistant to these treatments, surgery may be considered for skeletal metastases (Hwang et al. 2014). Indications for surgery with local tumor control are severe pain, restricted function, and impending or pathological fracture. According to a recent study, the proportion of patients with metastatic RCC who receive surgical therapy has increased from 4% to 6% in the last decade (Antczak et al. 2014).

The 5-year survival in RCC has been reported to be 77–92% for non-metastatic disease (Ito et al. 2015), decreasing to 21% after diagnosis of metastases (Schlesinger-Raab et al. 2008). The 5-year survival rate after the first operation for bone metastasis is 11% (Lin et al. 2007). There have been several studies on factors that affect survival after metastatic bone disease. In general, nephrectomy, the absence of visceral metastases, and solitary bone metastases improve survival (Toyoda et al. 2007, Yuasa et al. 2011, Hwang et al. 2014). Resection of a solitary skeletal lesion with a tumor-free margin appears to increase the survival rate (Baloch et al. 2000, Jung et al. 2003, Ratasvuori et al. 2014).

Surgical treatment of skeletal metastases from RCC carries a risk of massive blood loss, as tumors are hypervascular and

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the surgery is often extensive (Wilson et al. 2010, Robial et al. 2012). Preoperative embolization is often used; most authors agree that this reduces intraoperative blood loss substantially, making surgery easier and facilitating radical removal (Chatziioannou et al. 2000, Wirbel et al. 2005, Nair et al. 2013, Pazionis et al. 2014). Preoperative embolization in spinal RCC metastases is performed frequently, despite inconsistent effect (Wilson et al. 2010, Robial et al. 2012, Thiex et al. 2013, Quraishi et al. 2013, Clausen et al. 2015). Similarly, there is no consensus regarding non-spinal metastases. Some studies support the belief that preoperative embolization reduces intraoperative blood loss (Chatziioannou et al. 2000, Wirbel et al. 2005). Other authors have suggested that feeding vessels that are clearly identified during operation are easily ligated (Baloch et al. 2000, Lin et al. 2007). However, most of these studies have included only a few patients.

We therefore determined the effect of preoperative embolization and resection margin on intraoperative blood loss and operating time in a large cohort of patients suffering from RCC with non-spinal skeletal metastases. We also investigated factors that influence postoperative survival.

Patients and methods

Patients were identified from prospectively maintained databases at 4 Nordic bone tumor centers (Aarhus, Denmark; Bergen, Norway; Stockholm, Sweden; and Tampere, Finland). All the patients had had surgery for non-spinal skeletal metastases from RCC between October 1999 and June 2014. Metastatic RCC was confirmed histologically. Patient demographics included: age at presentation of pathological fracture, sex, comorbidities (diabetes and heart disease), American Society of Anesthesiologists classification, smoking habits, size (cm) and site of metastases (humerus, femur, pelvis), preoperative diagnostic procedures, hemoglobin value, number of skeletal metastases, and preoperative radiotherapy to the site of metastasis. Treatment of the primary tumor (including nephrectomy) and the presence of organ metastases were also recorded. Information on the surgical resection procedure for metastases, including margins of resection, methods of reconstruction, use of tourniquet, estimated intraoperative blood loss (IBL), and operating time, was taken from the anesthesia forms. Surgical margins were defined as being intralesional in cases where macroscopic tumor was left—as in nailing—or as being marginal in cases were margins were tumor-free. Details on the preoperative embolization procedure were recorded for each patient. There was no strict protocol for when to use preoperative embolization, but the size of the tumor was similar in embolized and non-embolized patients. If a patient underwent preoperative embolization, surgery was always performed within 72 h of the embolization.

Preoperative embolization was performed via ipsilateral or contralateral groin puncture. Feeding arteries (1–7 arteries) were accessed with microcatheters and occluded using various techniques, according to operator and institutional preferences. Detachable platinum coils, liquid embolization materials (acrylic glues), particles (polyvinyl alcohol), gelatin foam powder, or a combination of these methods were used. Most tumors were embolized with platinum coils, particles, or a combination of these. The success of the embolization was evaluated by comparing the pre-embolization and post-embolization angiography images after completion of the procedure. The interventional radiologist who performed the procedure evaluated and classified the degree of devascularization as adequate (approximating more than 75% tumor devascularization based on visual inspection of residual tumor enhancement), suboptimal (between 50% and 75% devascularization), or inadequate (less than 50% devascularization). We analyzed post-embolization and postoperative complications.

Statistics

The primary outcome of the study was intraoperative IBL. The amount of intraoperative IBL was not normally distributed, so logarithmic transformation was used. The variables used in the analyses included the surgical resection margin, preoperative embolization, tumor size, operating time, patient age, comorbidities, preoperative hemoglobin value, operative method, and site of metastases. The Mann-Whitney U-test was used to evaluate differences between the groups with or without embolization. The operating time was also considered to be a dependent factor. Patient survival was assessed using the Kaplan-Meier method and the log-rank test, and Cox regression analysis was used to identify independent factors affecting survival. The patients for whom the date of death was missing—either because the patient was still alive or had been lost to follow-up—were censored at the last time they were known to be alive. If the reason for death was not cancer, the case was censored. Proportional hazards assumption was taken into account. All the variables were checked with Kaplan-Meier curves. We plotted the cumulative hazards functions for the covariates and checked that lines did not cross each other. Statistical significance was assumed with p-values less than 0.05. All statistical analyses were performed using IBM SPSS version 20.0.

Results

There were 148 operations in 144 patients, 99 male and 45 female, with a mean age of 67 (40–90) years at first operation of bone metastasis. 56 of the 148 tumors (38%) were embolized preoperatively. Baseline data for patients with and without embolization were similar (Table 1). Adequate post-embolization results were achieved in 46 cases, suboptimal results in 9 cases, and an inadequate result in 1 case (Figures 1–3).

Table 1. Baseline characteristics of patients with and without preoperative embolization for skeletal metastases from RCC

Variable	Total	With embolization	Without embolization
No. of cases	148	56	92
Mean age (range)	67	67 (43–90)	67 (40–86)
Sex			
Male	102	38	64
Female	46	18	28
Mean ASA	2.7	2.7	2.7
Nephrectomy	98	37	61
Organ metastases present	72	28	44
Solitary skeletal metastases	78	33	45
Mean tumor size (range), cm	6.4	7.1 (3–13)	6.0 (2–14)
Localization			
Femur	82	30	52
Pelvis	15	9	6
Humerus	37	14	23
Other	14	5	11
Operation method			
Marginal resection	45	20	25
Intralesional resction	103	36	67
Type of surgery			
Tumor prosthesis	34	17	17
Prosthesis	42	22	20
Nailing	43	11	32
Other	26	5	21
Preoperative hemoglobin, g/L (range)		121 (88–197)	122 (82–175)
Mean estimated blood loss, L (range)	1.0	1.1 (0.005–5.7)	1.0 (0.005–12)
Mean operating time, min (range)	135	157 (65–420)	120 (45–420)
Mean survival time (range), months	12	11 (0–90)	14 (0–150)

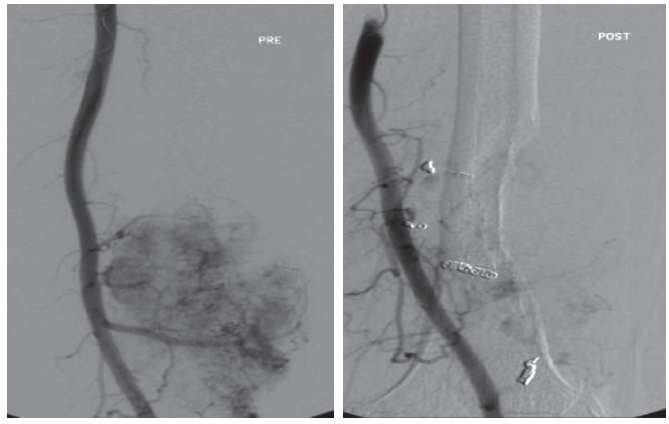

Figure 1. Preoperative embolization performed on a tumor measuring 13 cm located in the distal femur. Since only some residual peripheral tumor enhancement was seen, this was considered to be an adequate embolization outcome. A marginal resection and endoprosthetic replacement resulted in an IBL of 1.3

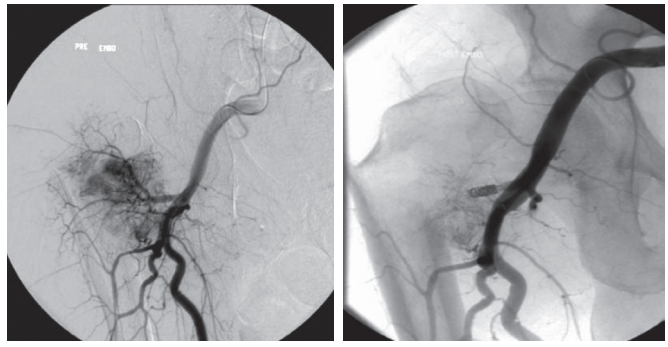

Figure 2. Preoperative embolization performed on a tumor with fracture in the proximal femur measuring 9 cm. Since a clear region of tumor enhancement (about 40% of the tumor) was seen in the lower parts of the tumor, this was considered to be a suboptimal embolization result. An intralesional resection and endoprosthetic replacement resulted in an IBL of 0.2 L.

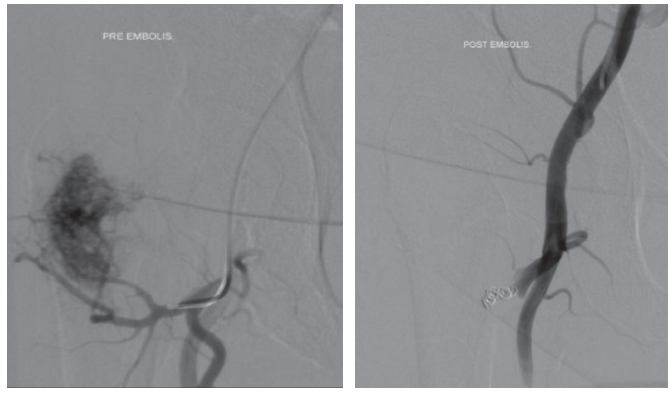

Figure 3. Preoperative embolization performed on a proximal femur tumor measuring 5 cm. In the absence of any tumor enhancement, this was classified as an adequate embolization result. Intralesional resection and endoprosthetic replacement resulted in an IBL of 0.5 L.

There were 140 patients, 86 without embolization and 54 with embolization, with information on IBL. Pelvic location (Mann-Whitney U-test, $p < 0.01$) and increasing tumor size ($p < 0.01$) were associated with increased IBL. There were no interactions between these variables. Factors such as age, liver metastasis, overall metastatic load, solitary skeletal metastasis, preoperative hemoglobin value, use of a tourniquet, operating time, operation method, resection margin, and preoperative embolization (including adequate cases) had no apparent effect on IBL (Table 2). Embolization did not have a statistically significant positive effect on operating time (Table 3, see Supplementary data). Operating time was significantly shorter with no embolization for tumors in the humerus.

There were no procedure-related complications during or after embolization. Postoperative complications were reported in 23 cases (16%), including tumor progression (4), nerve damage (1), nail failures (3), massive blood loss (1), prosthetic dislocations (2), wound healing problems (5), non-unions (2), pulmonary embolisms (3), and deep venous thrombosis (1). The embolization procedure did not predispose patients to complications.

The median postoperative survival was 13 (0–150) months. Marginal resection rather than intralesional resection, solitary skeletal metastasis, the absence of organ metastases, a hemoglobin level over 100 g/L, and nephrectomy were

Table 2. A comparison of the factors affecting intraoperative blood loss (IBL) in the different subgroups of cases with and without preoperative embolization, performed using the Mann-Whitney U-test

	With embolization			Without embolization			
	n	Median	Q1–Q3	n	Median	Q1–Q3	p-value
Pelvis	9	1,800	(1,100–5,000)	6	1,525	(836–2,800)	0.5
Humerus	14	525	(340–625)	23	600	(200–1,020)	0.6
Femur	29	400	(275–850)	47	600	(200–900)	0.8
Prosthesis	22	500	(300–500)	20	875	(612–2,400)	0.2
Tumor prosthesis	17	600	(350–1,050)	17	400	(200–910)	0.2
Nailing and plating	9	200	(75–525)	26	375	(200–625)	0.2
Marginal resection	20	550	(350–875)	24	400	(200–725)	0.2
Intralesional removal	34	500	(300–1,650)	62	600	(238–1,210)	0.8

Table 5. Factors associated with survival (Cox regression analysis)

Variable	Exp. [a]	95% CI	p-value
Hemoglobin under 100 g/L	2.0	1.2–3.5	0.01
Intralesional removal	2.2	1.4–3.3	0.001
Multiple bone metastases	1.5	1.1–2.2	0.03
No previous nephrectomy	1.7	1.2–2.6	0.008

[a] Exp: HR = Hazard rate

associated with better survival rates, but age, tumor size, tumor location, IBL, and preoperative embolization were not (Table 4, see Supplementary data). In the Cox model, solitary metastasis, marginal resection, hemoglobin level over 100 g/L, and nephrectomy were independently associated with better survival rates (Table 5).

Discussion

In this retrospective study, we could not find statistically significant effects of preoperative embolization of skeletal non-spinal metastases on intraoperative blood loss, irrespective of whether or not there was an adequate embolization result. This contrasts with several studies that have advocated preoperative embolization of bone metastases from RCC as an effective procedure for minimization of intraoperative bleeding (Olerud et al. 1993, Barton et al. 1996, Chatziioannou et al. 2000). By contrast, 1 study found greater IBL in embolized patients but suggested that this was because of patient selection bias, since embolization was used in larger, more central tumors and at sites where a tourniquet could not be applied to control IBL (Lin et al. 2007). In our study, tourniquet use did not have any apparent effect on IBL and the tumors in the embolized and non-embolized groups were similar in both size and location.

The studies that have shown any effect of embolization on reducing IBL have had several limitations, including small numbers of patients and the use of statistical methods that were not sensitive to selection bias. Except for its large number of patients, the present study also had similar limitations, including the retrospective design and the possibility of selection bias. There may have been selection bias due to the different medical treatments, which varied considerably, making the numbers of patients in different treatment categories too small for meaningful statistical analysis. There may also have been bias in selecting the types of surgical procedures, in selecting patients for preoperative embolization, and in the different embolization methods. The strength of our study lies in the number of patients: to date, this is the largest published series of patients with non-spinal RCC metastases to be treated surgically with preoperative embolization.

There was a significant correlation between tumor size and IBL irrespective of whether or not there was embolization. This has also been reported in previous studies. Pazionis et al. (2014) found a correlation between tumor size and IBL and operating time. In their case-control study, the association between embolization and reduced blood loss was only seen in femoral procedures, but in a multivariable analysis, tumor size was the only significant factor affecting IBL. In our study, pelvic location was found to be a statistically significant predictor of excessive blood loss, and was probably associated with tumor size because pelvic metastases tended to be larger.

Although IBL is a commonly used outcome measure in evaluation of the efficacy of preoperative embolization, the amount of bleeding is difficult to quantify and may not be an optimal measure for evaluation of the benefits of embolization. Although we adjusted for several confounding factors including resection margin, location of the metastases, and operation method, we did not find any statistically significant differences in IBL between cases with embolization or cases without. No benefit of preoperative embolization in facilitating the operative treatment has been convincingly shown. In our study, preoperative embolization did not reduce operating time—irrespective of the location of the tumor or the method of operation.

Embolization is believed to be a safe procedure. In a study involving 228 embolizations of a variety of tumors, only 1

case with a large groin hematoma and 1 cardiac arrest due to general anesthesia were reported (Nair et al. 2013). In our study, there were no major complications related to the embolization procedures. Although embolization is a safe procedure, it is invasive, time-consuming, and expensive. Because we found similar operating times, IBL, and survival between groups with or without embolization, we do not recommend it as a routine procedure. Further research may help to define specific patient groups that might benefit from embolization. Also, the use of embolization for pain control requires further investigation.

Our study confirms the results of previous studies that have demonstrated improved survival with a tumor-free margin of a metastatic lesion in RCC (Baloch et al. 2000, Lin et al. 2007, Fottner et al. 2010). In the present study, several confounding factors such as age, tumor size, and operation method were also taken into account. Even though radiotherapy of skeletal metastases can be used for pain control (Reichel et al. 2007), surgery is more effective in restoring function and in preventing local tumor progression (Laitinen et al. 2015). Moreover, the metastatic pattern with solitary skeletal metastasis, type of surgery with a tumor-free margin, and prosthetic replacement substantially influence the overall patient and reconstruction survival after surgery for RCC metastases (Jung et al. 2003, Fuchs et al. 2005, Alt et al. 2011, Laitinen et al. 2015). In the present study, there were 12 cases in which marginal resection was done even though patients had multiple skeletal metastases. Even in this limited group, marginal resection resulted in significantly better survival than an intralesional resection. The role of nephrectomy in patients with disseminated disease is debatable. It has been reported that nephrectomy increases survival in patients with skeletal metastases (Evenski et al. 2012). This could not be analyzed in our material because of the number of patients in appropriate subgroups being too small. However, since our data show that marginal resection improves survival both in patients with solitary metastasis and in those with multiple skeletal metastases, we recommend that in RCC with skeletal metastases, a marginal and not an intralesional resection should be aimed for.

In conclusion, we were unable to show any benefit of preoperative embolization in preventing intraoperative bleeding and in improving surgical or oncological outcome. A select group of patients may benefit from preoperative embolization, especially if the metastatic lesion is located in the pelvis. This should be addressed in future investigations. In order to improve overall survival, marginal resection—and not intralesional resection—should be the gold standard for surgical management of skeletal metastases in RCC, especially if there are solitary lesions.

Supplementary data

Tables 3 and 4 is available on the Acta Orthopaedica website at www.actaorthopaedica.org, identification number 9216.

MR and ML designed the study. MR, ML, RW, BHH, and CT participated in data collection. MR performed the statistical analysis, wrote the first draft, and took care of manuscript revisions. NS offered expert comments on the embolization procedures. All the authors contributed to preparation of the manuscript.

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No competing interests declared.

Alt A L, Boorjian S A, Lohse C M, Costello B A, Leibovich B C, Blute M L. Survival after complete surgical resection of multiple metastases from renal cell carcinoma. Cancer 2011; 117 (13): 2873-82.

Antczak C, Trinh V Q, Sood A, Ravi P, Roghmann F, Trudeau V, Chang S L, Karakiewicz P I, Kibel A S, Krishna N, Nguyen P L, Saad F, Sammon J D, Sukumar S, Zorn K C, M Sun, Trinh Q D. The health care burden of skeletal related events in patients with renal cell carcinoma and bone metastasis. J Urol 2014; 191 (6): 1678-84.

Baloch K G, Grimer R J, Carter S R, Tillman R M. Radical surgery for the solitary bony metastasis from renal-cell carcinoma. J Bone Joint Surg Br 2000; 82 (1): 62-7.

Barton P P, Waneck R E, Karnel F J, Ritschl P, Kramer J, Lechner G L. Embolization of bone metastases. J Vasc Interv Radiol 1996; 7 (1): 81-8.

Chatziioannou A N, Johnson M E, Pneumaticos S G, Lawrence D D, Carrasco C H. Preoperative embolization of bone metastases from renal cell carcinoma. Eur Radiol 2000; 10 (4): 593-6.

Clausen C, Dahl B, Frevert S C, Hansen L V, Nielsen M B, Lonn L. Preoperative embolization in surgical treatment of spinal metastases: single-blind, randomized controlled clinical trial of efficacy in decreasing intraoperative blood loss. J Vasc Interv Radiol 2015; 26 (3): 402-12 e1.

Engholm G, Ferlay J, Christensen N, Bray F, Gjerstorff M L, Klint A, Kotlum J E, Olafsdottir E, Pukkala E, Storm H H. NORDCAN--a Nordic tool for cancer information, planning, quality control and research. Acta Oncol 2010; 49 (5): 725-36.

Evenski A, Ramasunder S, Fox W, Mounasamy V, Temple H T. Treatment and survival of osseous renal cell carcinoma metastases. J Surg Oncol 2012; 106 (7): 850-5.

Fottner A, Szalantzy M, Wirthmann L, Stahler M, Baur-Melnyk A, Jansson V, Durr H R. Bone metastases from renal cell carcinoma: patient survival after surgical treatment. BMC Musculoskelet Disord 2010; 11: 145.

Fuchs B, Trousdale R T, Rock M G. Solitary bony metastasis from renal cell carcinoma: significance of surgical treatment. Clin Orthop Relat Res 2005; (431): 187-92.

Han K R, Pantuck A J, Bui M H, Shvarts O, Freitas D G, Zisman A, Leibovich B C, Dorey F J, Gitlitz B J, Figlin R A, Belldegrun A S. Number of metastatic sites rather than location dictates overall survival of patients with node-negative metastatic renal cell carcinoma. Urology 2003; 61 (2): 314-9.

Hwang N, Nandra R, Grimer R J, Carter S R, Tillman R M, Abudu A, Jeys L M. Massive endoprosthetic replacement for bone metastases resulting from renal cell carcinoma: factors influencing patient survival. Eur J Surg Oncol 2014; 40 (4): 429-34.

Ito N, Kojima S, Teramukai S, Mikami Y, Ogawa O, Kamba T. Outcomes of curative nephrectomy against renal cell carcinoma based on a central pathological review of 914 specimens from the era of cytokine treatment. Int J Clin Oncol 2015; [Epub ahead of print] doi: 10.1007/s10147-015-0840-5.

Jung S T, Ghert M A, Harrelson J M, Scully S P. Treatment of osseous metastases in patients with renal cell carcinoma. Clin Orthop Relat Res 2003; (409): 223-31.

Laitinen M, Parry M, Ratasvuori M, Wedin R, Albergo J I, Jeys L, Abudu A, Carter S, Gaston L, Tillman R, Grimer R. Survival and complications of skeletal reconstructions after surgical treatment of bony metastatic renal cell carcinoma. Eur J Surg Oncol 2015; 41(7): 886-92.

Lin P P, Mirza A N, Lewis V O, Cannon C P, Tu S M, Tannir N M, Yasko A W. Patient survival after surgery for osseous metastases from renal cell carcinoma. J Bone Joint Surg Am 2007; 89 (8): 1794-801.

Motzer R J, Bander N H, Nanus D M. Renal-cell carcinoma. N Engl J Med 1996; 335 (12): 865-75.

Motzer R J, Hutson T E, Tomczak P, Michaelson M D, Bukowski R M, Oudard S, Negrier S, Szczylik C, Pili R, Bjarnason G A, Garcia-del-Muro X, Sosman J A, Solska E, Wilding G, Thompson J A, Kim S T, Chen I, Huang X, Figlin R A. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009; 27 (22): 3584-90.

Nair S, Gobin Y P, Leng L Z, Marcus J D, Bilsky M, Laufer I, Patsalides A. Preoperative embolization of hypervascular thoracic, lumbar, and sacral spinal column tumors: technique and outcomes from a single center. Interv Neuroradiol 2013; 19 (3): 377-85.

Olerud C, Jonsson H, Jr, Lofberg A M, Lorelius L E, Sjostrom L. Embolization of spinal metastases reduces peroperative blood loss. 21 patients operated on for renal cell carcinoma. Acta Orthop Scand 1993; 64 (1): 9-12.

Pazionis T J, Papanastassiou I D, Maybody M, Healey J H. Embolization of hypervascular bone metastases reduces intraoperative blood loss: a case-control study. Clin Orthop Relat Res 2014; 472 (10): 3179-87.

Quraishi N A, Purushothamdas S, Manoharan S R, Arealis G, Lenthall R, Grevitt M P. Outcome of embolised vascular metastatic renal cell tumours causing spinal cord compression. Eur Spine J 2013; 22 Suppl 1: S27-32.

Ratasvuori M, Wedin R, Hansen B H, Keller J, Trovik C, Zaikova O, Bergh P, Kalen A, Laitinen M. Prognostic role of en-bloc resection and late onset of bone metastasis in patients with bone-seeking carcinomas of the kidney, breast, lung, and prostate: SSG study on 672 operated skeletal metastases. J Surg Oncol 2014; 110 (4): 360-5.

Reichel L M, Pohar S, Heiner J, Buzaianu E M, Damron T A. Radiotherapy to bone has utility in multifocal metastatic renal carcinoma. Clin Orthop Relat Res 2007; 459: 133-8.

Robial N, Charles Y P, Bogorin I, Godet J, Beaujeux R, Boujan F, Steib J P. Is preoperative embolization a prerequisite for spinal metastases surgical management? Orthop Traumatol Surg Res 2012; 98 (5): 536-42.

Schlesinger-Raab A, Treiber U, Zaak D, Holzel D, Engel J. Metastatic renal cell carcinoma: results of a population-based study with 25 years follow-up. Eur J Cancer 2008; 44 (16): 2485-95.

Thiex R, Harris M B, Sides C, Bono C M, Frerichs K U. The role of preoperative transarterial embolization in spinal tumors. A large single-center experience. Spine J 2013; 13 (2): 141-9.

Wilson M A, Cooke D L, Ghodke B, Mirza S K. Retrospective analysis of preoperative embolization of spinal tumors. AJNR Am J Neuroradiol 2010; 31 (4): 656-60.

Wirbel R J, Roth R, Schulte M, Kramann B, Mutschler W. Preoperative embolization in spinal and pelvic metastases. J Orthop Sci 2005; 10 (3): 253-7.

Woodward E, Jagdev S, McParland L, Clark K, Gregory W, Newsham A, Rogerson S, Hayward K, Selby P, Brown J. Skeletal complications and survival in renal cancer patients with bone metastases. Bone 2011; 48 (1): 160-6.

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Full Length Article

Venous thromboembolism after surgical treatment of non-spinal skeletal metastases — An underdiagnosed complication

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ABSTRACT

Introduction and aim: Venous thromboembolism (VTE) is a severe complication associated both with major orthopaedic surgery and cancer. However, survival and postoperative complications of skeletal metastases despite their thrombogenic potential, have received little attention in both the clinical management and research setting. This single-centre observational cohort study aimed to evaluate the incidence and impact of VTE in association with cancer surgery targeted to the management of fractures secondary to skeletal metastases.
Methods: Data were collected retrospectively from the medical database. We included consecutive 306 patients operated for 343 non-spinal skeletal metastases during a 15-year period (1999–2014).
The incidence of VTE and its risk factors were assessed using binary logistic regression analysis. Kaplan–Meier and Cox regression analyses were used to evaluate variables affecting survival.
Results: The rate of symptomatic VTE was 10% (30/306) during the 3-month postoperative period, while 79% received thromboprophylaxis. Fatal pulmonary embolism (PE) rate was high, 3.3% (10/306) after surgery. Intraoperative oxygen saturation drop, pulmonary metastases and intramedullary nailing were independent risk factors for VTE. Indicators of decreased survival were lung cancer, intramedullary nailing, multiple skeletal and pulmonary metastases, anaemia, leukocytosis, and PE.
Conclusion: Relationship between fractures secondary to skeletal metastases and VTE needs further clinical attention. Whether the survival of patients with fractures secondary to skeletal metastases can be improved by targeted thromboprophylactic means should be studied further.

1. Introduction

Cancer is a well-known risk factor for venous thromboembolism (VTE) events, including deep vein thrombosis (DVT) and pulmonary embolism (PE). It is estimated that the overall risk of a VTE is increased seven-fold in patients with a malignancy compared with those without malignancy [1]. In patients with cancer, each of the three components of Virchow's triad (blood composition, vessel wall components and blood flow) represents abnormalities that predispose to thrombus formation. Additionally, abnormal angiogenesis is involved in tumour growth, resulting in a prothrombotic state [2]. Several other risk factors for VTE in cancer patients have been reported, including a history of VTE, female gender, older age, leukocytosis, and thrombocytosis [3,4]. Patients who are treated with chemotherapy or have metastatic disease have additional risks for VTE [1,2]. Patients with distant metastases and those undergoing chemotherapy are reported to have a two-fold increased risk compared with those without metastases or not undergoing chemotherapy [1]. One survey found that 5–10% of patients with breast cancer undergoing adjuvant chemotherapy and up to 15% of those with metastatic disease had VTE [5]. Different models for predicting chemotherapy-associated VTE have been developed. One model, the Khorana score, includes the following variables: site of cancer, platelet count, haemoglobin, leukocyte count, and BMI [6].

Trauma and orthopaedic surgery are also well-known risk factors for VTE [7,8]. However, the reported symptomatic VTEs have been few, as during the 90 days after the primary total hip arthroplasty symptomatic DVT occurs in 0.7% and PE in 0.3% of the patients. [9] In one large study including 199,952 patients with pelvic and lower-extremity fracture symptomatic PE was identified only in 0.5% of patients. [10] Cancer surgery seems to significantly increase the risk of postoperative VTE, as well as risk of fatal PE when compared to similar procedures in non-cancer patients (0.33% vs. 0.09%) [11]. Moreover, both cancer and trauma and their management may otherwise contribute to the prothrombotic state, including bed rest, infection, and certain chemotherapies.

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VTE is a severe complication in all hospitalized patients [4]. In a population-based study matched for type of cancer, sex, age, and the year of diagnosis, the 1-year survival of patients diagnosed with VTE and malignancy was 12% compared with those patients without VTE, whose survival rate was three-fold higher [12]. Mortality rates are three times higher in the first 6 months after VTE in patients with cancer than in those without cancer [13]. A necropsy study revealed that 10% (648 of 6197) of patients who died of cancer had PE [14]. After major surgery as much as 10–40% of the deaths were related to PE. [15].

Even though a number of studies have shown the importance of VTE after orthopaedic surgery and disseminated cancer, little attention has been given to the incidence of thrombosis in patients after pathological fractures secondary to skeletal metastases. Therefore, the aim of this observational study was to determine (1) the incidence and impact of symptomatic VTE postoperatively, (2) the risk factors for VTE, (3) whether the Khorana score itself or its haematological elements separately could predict VTE in this surgical patient cohort, and (4) risk factors for decreased survival after operation.

2. Patients and methods

Patients for this observational cohort study were identified from a prospectively maintained database in one referral centre. All consecutive patients, included in the study were treated surgically for non-spinal skeletal metastases, in the vast majority due to pathological fractures, between the 1st of April 1999 and the 31st of July 2014. The institutional ethical review board approved the study. Data were retrospectively collected from the medical records. All patients had metastatic stage IV cancer and all the patients were living independently before surgery. Patients whose survival was estimated to be less than four weeks were not operated. Surgical procedures included osteosynthesis with plate, intramedullary nailing with or without cementing, total arthroplasty, endoprosthetic replacement and Harrington procedure.

Symptomatic DVT was identified by ultrasound scan of lower extremities and PE was diagnosed with computer tomography or autopsy. Data regarding deaths were verified from death certificates or autopsy reports at our institution. Data of patients who died outside the hospital were obtained from Statistics Finland, which is the exclusive Finnish public authority holding data regarding causes of death and post mortem death certificates. Unfortunately, the mortality data are routinely updated 1 year later, thereby underestimating the true rate of occurrence towards the end of the study.

In year 2004 the national guidelines for postoperative thromboprophylaxis were introduced. After this recommendation all major orthopaedic patients had postoperative prophylaxis, enoxaparin 40 mg or dalteparin 5000 IU started 6–12 h postoperatively continuing on once daily basis, unless a bleeding complication or major bleeding risk ensued. No mechanical prophylaxis was used. Surgical techniques and operating times have remained stable in this 15-year period.

2.1. Statistical analysis

Univariate analysis was performed for risk factors of VTE. The chi-square test or Fisher's exact test in the case of proportions and by the *t*-test in the case of continuous variables was used. Using multivariable analysis with binary logistic regression we assessed independent risk factors for VTE and PE. Survival was assessed using the Kaplan-Meier method with a log-rank test for univariate analysis while Cox regression analysis was used to identify independent factors affecting patient survival. In survival analyses we censored patients still alive at the time of study and patients who died for other reasons than cancer. The following variables were evaluated: gender, age, primary diagnosis, number of skeletal metastases (solitary/multiple), metastatic load and sites (lung and liver), intraoperative haemorrhagic events, operation time, intraoperative oxygen saturation drop during application of nails or stems (no vs. minor drop of 5–15% and major drop >15%), fracture localisation (humerus, radius, ulna, scapula, pelvis, femur, or tibia), specific operation method (intramedullary nailing vs. others) and use of low-molecular-weight heparin (LMWH) (28-day period as cut off). The Khorana score as such and its separate haematological variables were analysed to investigate the prediction of VTEs and survival among these patients (6). The variables from the Khorana score are as follows: site of cancer (2 points for very high-risk site, including pancreas and stomach; 1 point for high-risk site, including lung, lymphoma, gynaecologic, and genitourinary organs, excluding the prostate), platelet count ≥350 $\times$ 10^9/L, haemoglobin <100 g/L and/or use of erythropoiesis-stimulating agents, leukocyte count >11 $\times$ 10^9/L, and BMI ≥35 kg/m^2 (1 point each). These variables were analysed both together and independently, in particular to focus on the haematological variables. Specifically, leukocyte count was analysed for different cut-off values (8, 9, 10, and 12 $\times$ 10^9/L). The laboratory parameters were measured preoperatively. *P*-value <0.05 indicated statistical significance. Analyses were conducted with statistical software package IBM SPSS Statistics version 21.0.

3. Results

A total of 343 orthopaedic procedures were performed in 306 patients; 171 females (55.9%) and 135 males (44.1%). The study population comprised several different primary tumours (Table 1). Breast cancer, myeloma and renal cancer were the most common. Patients had a mean age of 67.2 (range 23.4–94.7) years at the time of the operation. Demographics of identifiable risk factors for VTE are reported in Table 2. Altogether 55 patients did not receive thromboprophylaxis. 15 of them were encountered after year 2004, and 13 of them were operated because of upper extremity fracture, one patient had pelvic surgery but because massive intraoperative bleeding complication postoperative thromboprophylaxis was not used. Two patients; one after femoral nailing and one after tibia plating did not have thromboprophylaxis due to unknown reasons.

Symptomatic VTE was identified in 35 patients (11.4%), of which PE was identified in 26 patients (8.5%). In 3-month postoperative period the VTE rate was 10%. Ten out of 306 patients (3.3%) had the diagnosis of PE as the cause of death in post mortem death certificate, established by autopsy. From the 26 patients who had PE, primary tumours were lung cancer ($n = 7$), breast cancer ($n = 6$), renal cancer ($n = 4$), prostate cancer ($n = 3$), myeloma ($n = 2$), lymphoma ($n = 1$), HCC ($n = 1$), primary bone sarcoma ($n = 1$) and in one case tumour origin

Table 1
Distribution of the types of cancer among the study population.

Primary tumour	n	%
Breast cancer	97	31.7
Myeloma	50	16.3
Renal cancer	38	12.4
Prostate cancer	35	11.4
Lung cancer	33	10.8
Colon cancer	8	2.6
Lymphoma	8	2.6
Sarcoma	7	2.3
Unknown	6	2.0
Melanoma	4	1.3
Thyroid cancer	4	1.3
Bladder cancer	3	1.0
GIST	3	1.0
HCC	2	0.7
Squamous cell cancer	2	0.7
Parotid cancer	1	0.3
Merkel cell cancer	1	0.3
Pancreatic cancer	1	0.3
Ventricle cancer	1	0.3
Leukaemia	1	0.3
Chordoma	1	0.3

GIST = gastrointestinal stromal tumour, and HCC = hepatocellular cancer.

Table 2
Characteristics of patients with VTE.

Characteristics	Total/306 patients	Number of patients without VTE	Number of patients with VTE	*p*-Value*
BMI >30 kg/m^2	45 (15%)	43	2	0.13
Anaemia (Hgb < 100 g/L)	49 (16%)	45	4	0.62
Leukocytosis >9 × 10^9/L	197 (65%)	181	16	**0.01**
Operation method nailing	104 (34%)	98	6	**0.03**
Pelvic lesions	45 (15%)	38	7	0.32
Femoral lesions	155 (51%)	136	19	0.72
Pulmonary metastases	71(23%)	57	14	**0.02**
Lung cancer	33 (11%)	25	8	**0.04**
Multiple skeletal metastases	266 (87%)	236	30	0.79
Saturation drop	87 (28%)	69	18	**0.002**
LMWH prophylaxis	241 (79%)	213	28	0.09

VTE = venous thromboembolism, and LMWH = low molecular weight heparin.
Bolded P-values are statistically significant, p-values > 0.05.
* *p*-Values are calculated with univariate analysis comparing patients with or without VTE in different risk factors.

was unknown. DVT occurred in 11 patients (3.6%). The mean time interval for symptomatic PE was 14 days and for DVT 20 days in 3-months postoperative period. The overall number of VTE and PE events according to time of their occurrence is illustrated in Fig. 1.

In univariate analysis the risk factors for VTE were lung cancer, intramedullary nailing, intraoperative saturation drop, leukocytosis and pulmonary metastases (Table 2). In multivariable analysis the risk factors for VTE were pulmonary metastases, intramedullary nailing and intraoperative saturation drop, whereas the risk factors for PE alone were pulmonary metastases and intraoperative saturation drop (Table 3). Khorana score did not predict VTE in this patient cohort.

Overall survival was 42.9% at 1 year and 23.9% at 2 years, declining to only 16.1% at 3 years. According to the Kaplan-Meier analysis, decreased survival associated with intraoperative oxygen saturation drop, PE diagnosis, haemoglobin below 100 g/L, leukocyte count exceeding 9 × 10^9/L, the presence of pulmonary metastases, LMWH use of <28 days, lung cancer, intramedullary nailing and multiple skeletal metastases (Table 4). All significant variables from the Kaplan-Meier analysis were further subjected to analysis in a Cox regression model. Lung cancer, intramedullary nailing, multiple skeletal metastases, anaemia, leukocytosis, pulmonary metastases and PE turned out as risk factors for decreased survival (Table 5). There were no interactions between variables.

From the separately analysed haematological risk factors, we found that the leukocyte count above 9 × 10^9/L and haemoglobin below 100 g/dL were significant risk factors. Survival markedly declined in patients suffering from PE (Fig. 2). Twenty patients suffered PE, despite receiving postoperative LMWH thromboprophylaxis. Twelve of these utilized prophylaxis for 28 days (range 2–35). Six patients died within 24 h postoperatively, five of them had oxygen saturation drop four having PE. The intraoperative oxygen saturation drop was observed more frequently in patients with lung cancer (51.5%; 17/33) compared with those with the other primary cancers that usually cause skeletal metastases, such as breast cancer (25.8%; 25/97) and renal cell cancer (28.9%; 11/38).

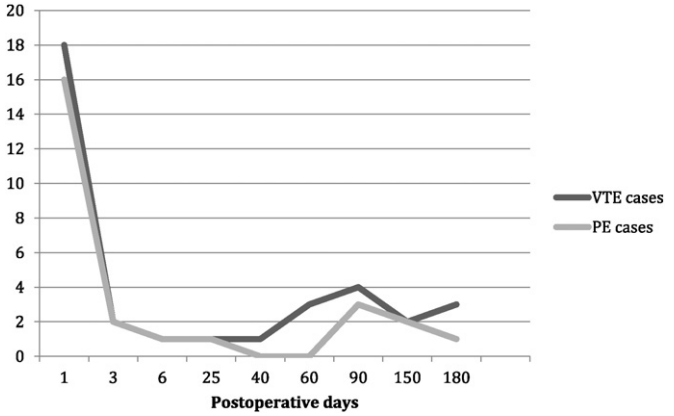

Fig. 1. Number of VTE and PE cases at the time of occurrence.

4. Discussion

During a 3-month postoperative period for cancer patients having undergone surgery for pathological fractures, we identified a striking occurrence of symptomatic VTE (10%), with an overall incidence of fatal PE of 3.3%. This is a relatively high incidence of VTE while 79% of patients had received postoperative thromboprophylaxis, albeit not of the recommended 4-week duration. This is the first study of its kind, with its focus on VTE and survival for 306 post-operative patients, surgically treated for pathologic fractures of non-spinal, skeletal metastases. In comparison to other studies of postoperative complications of skeletal metastases that found VTE complications to be uniformly low, or unstudied, we observed a high number of VTEs [16–19].

We identified several risk factors for VTE in univariate analyses, with multivariate analyses identifying intramedullary nailing, pulmonary metastases, and intraoperative saturation drop, as independent risk factors for VTE. Saturation drop during the cementing and nailing process was considered to be a significant risk factor, having ruled out other perioperative anesthesia-related causes (e.g. intraoperative bleeding). This finding agrees with the poor survival of patients who experience a reduction of intraoperative oxygen saturation, which correlates with the clinical severity of the embolism. [20,21].

In our study, symptomatic PE significantly contributed to premature death. The mean survival following PE was only 2 months, versus 10 months for patients who avoided this complication, who also benefited from a 5-fold greater overall survival. PE has been suggested to be one of the leading medical emergencies in clinical practice [22] with significant mortality [10]. Despite recognition of its severity, this topic has not received attention in survival studies for surgically treated skeletal metastases with pathologic fractures. The Khorana score is

Table 3
Multivariable logistic regression analysis of VTE and PE risk.

VTE			
Risk factor	OR	95 CI	*p*-Value
Pulmonary metastases	2.23	1.04–4.79	0.04
Intramedullary nailing	3.15	1.23–8.07	0.02
Saturation drop	3.28	1.56–6.88	0.002
PE			
Risk factor	OR	95 CI	*p*-Value
Pulmonary metastases	2.84	1.21–6.65	0.02
Intramedullary nailing	2.69	0.95–7.62	0.06
Saturation drop	4.03	1.72–9.41	0.001

Table 4
Kaplan-Meier survival analysis of the 306 operated skeletal metastases: prognostic factors, and median survival (months) with cumulative intervals and *p*-values.

Variable	n	Median	95 CI	*p*-Value
Pulmonary metastases				
Yes	71	5.2	3.4–6.9	0.001
No	235	11.4	8.2–14.5	
Primary disease				
Lung cancer	33	3.2	2.1–4.2	0
Other	273	10.7	7.9–13.6	
Number of skeletal metastases				
Solitary	38	17.3	7.0–27.5	0.002
Multiple	268	7.3	5.0–9.6	
Haemoglobin <100 g/L[a]				
Yes	254	11.4	8.9–13.9	0
No	49	2.7	0.3–5.1	
Leukocytosis $>9 \times 10^9$/L[a]				
Yes	106	4.0	2.8–5.3	0
No	197	12.9	10.8–14.9	
Operation method				
Intramedullary nailing	104	6.4	4.1–8.8	0.015
Other	202	10.5	7.1–14.0	
Intraoperative saturation drop				
Yes	86	4.1	2.1–6.2	0.009
No	220	11.4	8.4–14.4	
LMWH >27 days[b]				
Yes	155	14.3	10.8–17.8	0
No	84	5.8	1.4–6.1	
Pulmonary embolism				
Yes	26	2.0	0–4.3	0
No	280	9.7	6.9–12.6	

[a] Information missing in 3 patients.
[b] Information missing in 67 patients.

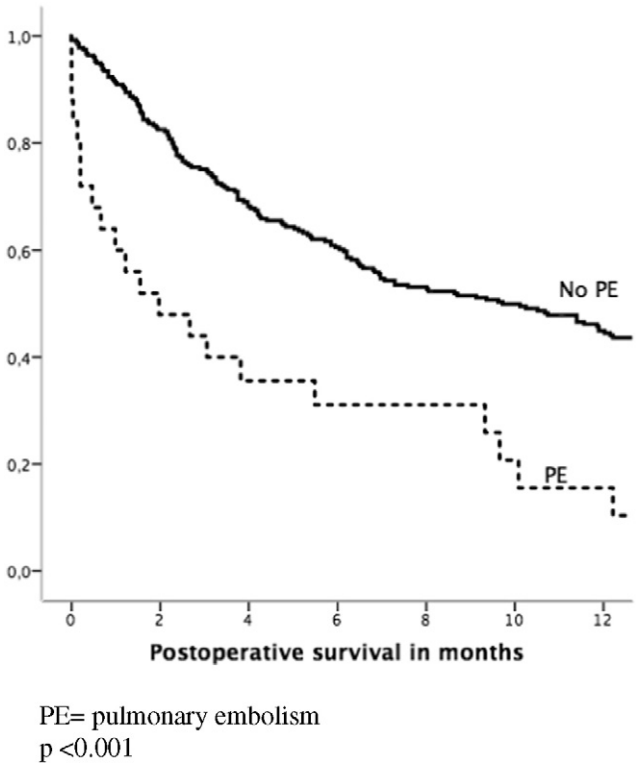

Fig. 2. Kaplan-Meier survival analysis showing the adverse effect of pulmonary embolism.

assumed to carry a predictive value for VTEs among cancer patients treated with chemotherapy. In our study with surgical management, we could find no correlation between high Khorana scores and VTE or survival. The predictive value of the Khorana score is most effective for patients with pancreatic or stomach cancers, or those with a high BMI. However, pancreatic and gastric cancers rarely metastasize to bone, and few patients suffering from disseminated cancer with skeletal metastases present with a high BMI. Therefore the total Khorana score is of little to no value for cancer patients with pathologic fractures.

In addition to PE, other significant variables associated with decreased survival were pulmonary metastases, lung cancer as primary disease, and multiple skeletal metastases, together with the haematological variants, i.e. leukocytosis and anaemia, as reported previously [23]. In addition, the operative nailing method was also associated with decreased survival. First, intramedullary nailing itself appears to carry a risk for VTE [24], thereby contributing to decreased survival. Second, when performing intramedullary nailing, the removal of a tumour with marginal resection cannot be achieved. Marginal resection of skeletal metastases has been shown to impair survival, at least for solitary skeletal metastases, as well as for metastases of renal cell carcinoma thereby contributing to decreased survival [25].

Interestingly, our study showed that lung cancer patients experienced the greatest number of intraoperative saturation drops and PE cases compared to patients with other primary cancers. The increased risk of VTE for lung cancer patients has already been described in the literature [24,26] as is their poor survival following surgery to remove skeletal metastases [27]. These adverse outcomes might reflect the strong association between thromboembolic events after surgical treatment of skeletal metastases. Interestingly, lung metastases were also a risk factor for PE in our study, suggesting that these two states may increase the risk for VTE by similar mechanisms, although it is acknowledged that the increased risk of VTE and decreased postoperative survival are multifactorial.

Table 5
Cox regression survival analysis: prognostic factors, risk ratios (RR), cumulative intervals and statistical analysis (*p*-values).

Factor	RR	95 CI	*p*-Value
Pulmonary metastases	1.49	1.09–2.04	0.013
Lung cancer	2.34	1.54–3.57	0
Multiple skeletal metastases	1.3	1.05–1.62	0.016
Anaemia (Hgb < 100 g/L)	2.7	1.91–3.81	0
Leukocytosis ($>9 \times 10^9$/L)	1.47	1.11–1.94	0.006
Intramedullary nailing	1.49	1.15–1.94	0.003
Pulmonary embolism	2.07	1.26–3.40	0.004

According to our study, a survival benefit was observed in univariate analyses following prophylactic use of LMWH for VTE for 28 days. However, it is noteworthy that 50% of patients (13/26 PE patients) still experienced PE despite this prophylaxis; additionally four patients developed PE despite warfarin use. Studies have shown that increasing DVT prophylaxis with LMWH for up to 30 days safely reduces the risk of postoperative thrombosis by 60% [28], especially in cancer patients [7]. The use of anticoagulants should be considered carefully when operating on patients with cancer, as they may be at high risk of bleeding complications because of their lowered blood cell count, chemotherapy, other drug interactions, renal impairment, and hepatic involvement with metastases [29].

This study has several limitations. First, our study design was observational, for which the most serious shortcoming is the selection bias [30]. However, in this observational study, as our cohort was derived from a single clinic and recruited consecutively, we feel that selection bias is an unlikely factor. Second, this study is retrospective, and lacks randomization. Additionally, there might be some bias in patient selection for surgery, although, as stated previously, patients were recruited consecutively. Despite its retrospective and observational nature, our study has its strengths. First, the patient information system is centralized, with all VTE events captured and registered, and standardized prophylaxis guidelines issued. Second, the total follow-up time was of considerable duration (15 years), and up to 1 year in most cases, which adds to the reliability of our findings. Third, Statistics Finland is the only Finnish public authority that gathers data regarding causes of death from its archive of death certificates. This facilitated

our comprehensive capture of data for patients who died of PE following discharge. Given that Statistics Finland updates "cause of death" data yearly, with the possibility that cancer related deaths could be coded as cancer rather than PE, we feel confident that, if anything, we are underestimating the true rate of VTE occurrence.

In conclusion, estimated VTE rates from autopsy studies differ from those analyzing postoperative complications of skeletal metastases treated surgically. Clinically diagnosed, symptomatic, and confirmed VTE rates are typically low. However, our study, focusing on postoperative VTE events, identified a much higher VTE rate of up to 10%. We provide evidence that VTE after surgery of skeletal metastases is under-diagnosed and adversely influences survival. A possible relationship between fractures associated with skeletal metastases and VTEs warrants further investigation. Collaborative efforts between hematologists and oncological orthopaedic surgeons are now needed to provide further insight into the pathophysiology, risk scoring, diagnosis, and treatment of VTE in patients suffering from this devastating disease. In the future, our aim is to prevent the excessive number of premature deaths currently caused by these under-documented thromboembolic events.

The authors state that they have no conflict of interest.

References

[1] J.W. Blom, J.P. Vanderschoot, M.J. Oostindier, S. Osanto, F.J. van der Meer, F.R. Rosendaal, Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: results of a record linkage study, J. Thromb. Haemost. 4l (2006) 529–535.

[2] G.Y. Lip, B.S. Chin, A.D. Blann, Cancer and the prothrombotic state, Lancet Oncol. 3l (2002) 27–34.

[3] M. Mandala, S. Barni, M. Prins, R. Labianca, C. Tondini, L. Russo, et al., Acquired and inherited risk factors for developing venous thromboembolism in cancer patients receiving adjuvant chemotherapy: a prospective trial, Ann. Oncol. 21l (2010) 871–876.

[4] A.A. Khorana, C.W. Francis, E. Culakova, N.M. Kuderer, G.H. Lyman, Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients, Cancer 110l (2007) 2339–2346.

[5] F.R. Rickles, M.N. Levine, Venous thromboembolism in malignancy and malignancy in venous thromboembolism, Haemostasis 28 (Suppl. 3 l) (1998) 43–49.

[6] A.A. Khorana, N.M. Kuderer, E. Culakova, G.H. Lyman, C.W. Francis, Development and validation of a predictive model for chemotherapy-associated thrombosis, Blood 111l (2008) 4902–4907.

[7] W.H. Geerts, R.M. Jay, K.I. Code, E. Chen, J.P. Szalai, E.A. Saibil, et al., A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma, N. Engl. J. Med. 335l (1996) 701–707.

[8] W.H. Geerts, K.I. Code, R.M. Jay, E. Chen, J.P. Szalai, A prospective study of venous thromboembolism after major trauma, N. Engl. J. Med. 331l (1994) 1601–1606.

[9] A.B. Pedersen, H.T. Sorensen, F. Mehnert, S. Overgaard, S.P. Johnsen, Risk factors for venous thromboembolism in patients undergoing total hip replacement and receiving routine thromboprophylaxis, J. Bone Joint Surg. Am. 92l (2010) 2156–2164.

[10] J. Godzik, C.M. McAndrew, S. Morshed, U. Kandemir, M.P. Kelly, Multiple lower-extremity and pelvic fractures increase pulmonary embolus risk, Orthopedics 37l (2014) e517–e524.

[11] A.K. Kakkar, S. Haas, H. Wolf, A. Encke, Evaluation of perioperative fatal pulmonary embolism and death in cancer surgical patients: the MC-4 cancer substudy, Thromb. Haemost. 94l (2005) 867–871.

[12] H.T. Sorensen, L. Mellemkjaer, J.H. Olsen, J.A. Baron, Prognosis of cancers associated with venous thromboembolism, N. Engl. J. Med. 343l (2000) 1846–1850.

[13] N. Levitan, A. Dowlati, S.C. Remick, H.I. Tahsildar, L.D. Sivinski, R. Beyth, et al., Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data, Medicine 78l (1999) 285–291.

[14] E. Svendsen, B. Karwinski, Prevalence of pulmonary embolism at necropsy in patients with cancer, J. Clin. Pathol. 42l (1989) 805–809.

[15] O.E. Dahl, J.A. Caprini, C.W. Colwell Jr., S.P. Frostick, S. Haas, R.D. Hull, et al., Fatal vascular outcomes following major orthopedic surgery, Thromb. Haemost. 93l (2005) 860–866.

[16] E.R. Henderson, J.S. Groundland, E. Pala, J.A. Dennis, R. Wooten, D. Cheong, et al., Failure mode classification for tumor endoprostheses: retrospective review of five institutions and a literature review, J. Bone Joint Surg. Am. 93l (2011) 418–429.

[17] R.J. Weiss, E. Tullberg, J.A. Forsberg, H.C. Bauer, R. Wedin, Skeletal metastases in 301 breast cancer patients: patient survival and complications after surgery, Breast 23l (2014) 286–290.

[18] M.S. Sorensen, K.G. Gregersen, T. Grum-Schwensen, D. Hovgaard, M.M. Petersen, Patient and implant survival following joint replacement because of metastatic bone disease, Acta Orthop. 84l (2013) 301–306.

[19] F. Camnasio, C. Scotti, G.M. Peretti, F. Fontana, G. Fraschini, Prosthetic joint replacement for long bone metastases: analysis of 154 cases, Arch. Orthop. Trauma Surg. 128l (2008) 787–793.

[20] R. Castelli, P. Bucciarelli, F. Porro, F. Depetri, M. Cugno, Pulmonary embolism in elderly patients: prognostic impact of the Cumulative Illness Rating Scale (CIRS) on short-term mortality, Thromb. Res. 134l (2014) 326–330.

[21] J. Christie, C.M. Robinson, A.C. Pell, J. McBirnie, R. Burnett, Transcardiac echocardiography during invasive intramedullary procedures, J. Bone Joint Surg. (Br.) 77l (1995) 450–455.

[22] T.A. Laack, D.G. Goyal, Pulmonary embolism: an unsuspected killer, Emerg. Med. Clin. North Am. 22l (2004) 961–983.

[23] M. Ratasvuori, R. Wedin, B.H. Hansen, J. Keller, C. Trovik, O. Zaikova, et al., Prognostic role of en-bloc resection and late onset of bone metastasis in patients with bone-seeking carcinomas of the kidney, breast, lung, and prostate: SSG study on 672 operated skeletal metastases, J. Surg. Oncol. 110l (2014) 360–365.

[24] B. Shallop, A. Starks, S. Greenbaum, D.S. Geller, A. Lee, J. Ready, et al., Thromboembolism after intramedullary nailing for metastatic bone lesions, J. Bone Joint Surg. Am. 97l (2015) 1503–1511.

[25] K.G. Baloch, R.J. Grimer, S.R. Carter, R.M. Tillman, Radical surgery for the solitary bony metastasis from renal-cell carcinoma, J. Bone Joint Surg. Br. Vol. 82l (2000) 62–67.

[26] J.W. Blom, C.J. Doggen, S. Osanto, F.R. Rosendaal, Malignancies, prothrombotic mutations, and the risk of venous thrombosis, JAMA 293l (2005) 715–722.

[27] K. Cetin, C.F. Christiansen, J.B. Jacobsen, M. Norgaard, H.T. Sorensen, Bone metastasis, skeletal-related events, and mortality in lung cancer patients: a Danish population-based cohort study, Lung Cancer (2014).

[28] D. Bergqvist, G. Agnelli, A.T. Cohen, A. Eldor, P.E. Nilsson, A. Le Moigne-Amrani, et al., Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer, N. Engl. J. Med. 346l (2002) 975–980.

[29] A.Y. Lee, M. Carrier, Treatment of cancer-associated thrombosis: perspectives on the use of novel oral anticoagulants, Thromb. Res. 133 (Suppl. 2 l) (2014) S167–S171.

[30] E.L. Hannan, Randomized clinical trials and observational studies: guidelines for assessing respective strengths and limitations, J. Am. Coll. Cardiol. Intv. 1l (2008) 211–217.