Survival after treatment of metastatic bone disease in the extremities

Evaluation of factors influencing survival and subsequent development and validation of a prediction model for postoperative survival

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SELECTED ABBREVIATIONS

MBD: Metastatic Bone Disease

MBDex: Metastatic Bone Disease in the extremities

SRE: Skeletal Related Event

CT: Computer Tomography

THA: Total Hip Arthroplasty

CRD: Capital Region of Denmark

MTC: Musculoskeletal Tumor Section

SSC: Secondary Surgical Center

DNPR: Danish National Patient Registry

DCRS: Danish Civil Registry System

OS: probability of Overall Survival

RFS: probability of Revision Free Survival

ASA: American Society of Anaesthiologist

95 C.I.: 95% Confidence Interval

OR: Odds Ratio

rTSA: reverse Total Shoulder Arthrosplasty

n/s: Not statistically Significant

SPRING: Sørensen PeteRsen, hINdsø, Gerds

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External validation and optimization of the SPRING model: a model for prediction of patient survival after surgery for bone metastasis of the extremities.

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ENGLISH SUMMARY

Background: Surgical management of metastatic bone disease (MBD) can be a devastating event for cancer patients whom are often very close to the end of life, where the desire for self-care must be balanced with the risk of surgical intervention aiming to perform one surgical procedure that will outlive the patient.
Main aim of the current thesis was to identify factors related to or influencing survival after surgery for MBD in the extremities (MBDex), and provide and validate a prediction model for postoperative survival.

Methods: Three cohorts comprised the material for the thesis, two retrospective cohorts (n=130 and 140) of patients having bone resection and reconstruction at a highly specialized center and one prospective multicenter population based cohort of all patients living in the Capital Region of Denmark (CRD) having surgical interventions for MBDex during a period of two years (n=164).

Main results: We found an estimated probability of one year overall survival after joint replacement surgery for MBDex in a cohort of patient treated at a highly specialized center to be 38% (study I). In comparison, overall one year survival in a multicenter study of population based cohort of patients treated for MBDex was 41% (study II). Survival decreased if treatment was performed at a secondary surgical center compared to patients treated at a highly specialized center (one year survival 34%). Patients was more likely to be referred for treatment at a highly specialized center if they had good prognostic factors for survival (younger age, good prognostic group of cancer, impending fracture, no visceral metastases, good performance status, low ASA score). Multiple regression analysis, adjusted for known risk factors for survival, showed a non-statistically significant (p=0.069) association with increased mortality if patients were treated outside a highly specialized center. The risk of undergoing surgery for MBDex if diagnosed with MBD was found to be 10% per year lived with MBD with an incidence of 48.6 MBDex lesions treated / million inhabitants / year in Denmark (study II). Eighty-eight percent of patients undergoing surgery for MBDex survived 30 days after the surgical trauma, were general health status, measured by Karnofsky performance status, and ASA score, was the only independent risk factors for mortality and no factors describing the extent of the surgical trauma (blood loss, surgery time or major bone

resection) were associated with increased mortality (study III). Patients receiving surgeries with prolonged surgical time seemed to have a non-statistical significant increased survival 30 days after surgery.

A model for prediction of survival 3, 6 and 12 months after surgery for MBDex was developed (SPRING model) using known prognostic variables for survival after surgery for MBDex (hemoglobin, primary cancer, Karnofsky performance status, ASA score, visceral metastases, multiple bone metastases, and complete or impending fracture) (study IV). The prediction model was refitted with a more modern cohort and external validated in an independent prospective population based cohort of patients having surgery for MBDex in multicenter settings. The model showed good calibration, accuracy and discrimination for prediction of survival at 3, 6 and 12 months after surgery. The refitted SPRING model (study V) performed better ($p<0.05$) at all three endpoints in ROC and Brier evaluation than the old model (study IV).

Conclusion: Survival of patients undergoing surgery for MBDex is different between treatment centers, were selected cohorts from highly specialized centers have an increased survival caused by selection bias of patients with good prognostic factors being referred for highly specialized treatment. A non-statistically significant association of increased mortality if surgery were performed at secondary surgical centers was found, and further investigation in study designs with more statistical power than the current is pending to clarify this probable relation.

Mortality in direct relation to the surgical trauma is purely depended on the patients' general health status, and not the size of the surgical trauma. We found some indication of prolonged surgeries may result in increased survival, and we speculate that this relation is due to a more durable implant that enables early mobilization and reduces the risk associated with immobilization. We speculate that internal fixation which is primarily performed at secondary surgical centers and have short surgery time is a risk factor for overall survival after surgery for MBDex, and further studies to clarify this is pending.

A model for preoperative prediction of survival after surgery for MBDex was developed and externally validated, providing the surgeon with a tool to provide the patient with one surgical solution for MBDex that will most probably outlive them.

DANSK RESUME

Baggrund: Når behovet for kirurgisk behandling af knoglemetastaser opstår, er patienterne oftest i den terminale fase af deres kræftforløb. Hvis behandlingen af knoglemetastaser ikke er optimal, kan det medføre invaliderende konsekvenser for patienterne. Balancen skal findes i at vælge det implantat som er holdbart nok til mekanisk at udleve patienterne, således at de undgår revisionskirurgiske indgreb, og uden at det kirurgiske indgreb bliver for omfattende og medfører en risiko for at dø. Hovedformålet for denne afhandling har været at identificere faktorer relateret til eller influerende på overlevelsen hos patienter som behandles kirurgisk for knoglemetastaser i ekstremiteterne og producere en model som kan forudsige hvor lang tid patienterne lever efter det kirurgiske indgreb således at det kirurgiske indgreb kan individualiseres.
Metode: Afhandlingen er opbygget af 3 patient kohorter. To retrospektive (n=130 og 140) og en prospektiv multicenter populationsbaseret kohorte (n=164) af patienter som modtog kirurgi for knoglemetastaser i ekstremiteterne.
Hovedresultater: Vi fandt at 38% af patienterne overlevede 1 år efter behandling med ledudskiftende kirurgi for knoglemetastaser på en højtspecialiseret tumor sektion (studie I). Til sammenligning fandt vi en 1 års overlevelse på 41% for den populationsbaseret kohorte, men at overlevelsen for patienter behandlet på ikke-højtspecialiseret ortopædkirurgisk afdelinger faldt til 34% (studie II). Patienter med faktorer der er forbundet med bedre overlevelse var mere tilbøjelige til at blive henvist til behandling på højtspecialiseret centre. Multiple regressionsanalyse identificerede behandlingscenter som værende associeret til øget dødelighed hvis behandlingen foregik udenfor et højtspecialiseret center (p=0.069). Incidensen for kirurgisk behandling af knoglemetastaser i ekstremiteterne var 48.6 metastaser behandlet /million indbygger / år i Danmark svarende til en 10 % risiko for at have behov for kirurgisk behandling hvis man lever et år med kendte knoglemetastaser. Risikoen for at dø umiddelbart efter det kirurgiske indgreb var 88% (studie III) og patienter med dårligt helbred (målt ved ASA og Karnofsky status score) havde øget dødelighed. Vi fandt ikke at stort blodtab, større knogleafskæring og rekonstruktion eller lang kirurgitid medførte øget risiko for tidlig død (studie III). Endvidere fandt vi at patienter allokeret til lang kirurgitid, som ses ved stor knogleafskæring og rekonstruktion, havde en bedre overlevelse, som dog ikke var statistisk signifikant. Ud fra kendte risikofaktorer (blodprocent, primærkræft, Karnofsky status score, ASA score, organmetastaser, flere knoglemetastaser og komplet fraktur vs.

truende fraktur) for dødelighed kunne vi producere en model (SPRING modellen) som kunne forudsige risikoen for død 3, 6 og 12 måneder efter det kirurgiske indgreb (studie IV). SPRING modellen for forudsigelse af overlevelse efter kirurgisk behandling af knoglemetastaser blev forbedret med en større patient kohorte behandlet i en nyere periode (studie V) og eksternt valideret i populationsbaseret multicenterbehandlet kohorte af patienter. Ekstern validering viste at den opdaterede SPRING model kunne forudsige med stor præcision hvad den enkelte patients sandsynlighed for at overleve 3, 6 and 12 måneder efter kirurgisk behandling for knoglemetastaser i ekstremiteterne var. Valideringen viste at den opdaterede SPRING model (studie V) præsterede bedre ($p<0.05$) end den gamle model (studie IV) evalueret med ROC og Brier score.

Konklusion: Overlevelse efter kirurgisk behandling af knoglemetastaser i ekstremiteterne er forskellig mellem behandlingscentre. Patienter med favorabel prognose bliver selekteret til behandling på højtspecialiseret center og vi fandt en ikke-statistisk signifikant association med øget mortalitet hvis man modtog behandling på et ikke-højtspecialiseret ortopædkirurgisk center. Endvidere fandt vi at dødelighed i forbindelse med det kirurgisk indgreb alene var afhængig af patienternes generelle helbredsstatus og ikke størrelsen af det kirurgiske indgreb hvor vi dog ikke kan udelukke at stor knogleafskæring og rekonstruktion kan medføre en bedret overlevelse. Vi vurderer at denne sammenhæng kan tilskrives at større knogleafskæring medfører indsættelse af et implantat i rask knogle hvilket gør konstruktionen mere stabil og patienterne mere mobile efter operationen og herved nedsætter risikoen for død associeret med nedsat mobilisering efter det kirurgiske indgreb. Vi mener at kirurgisk behandling efter almindelige fraktur principper hos knoglemetastase patienter (med skinne, skruer og lign.) som typisk udføres på ikke-højtspecialiseret centre med kort kirurgisk procedure tid, kan medføre øget dødelighed men yderligere studier bør i fremtiden afklare dette.

Endelig udviklede vi en model som kan forudsige sandsynligheden for død 3, 6 og 12 måneder efter det kirurgiske indgreb for metastatisk knoglesygdom i ekstremiteterne, og herved kan kirurgen bedre allokere den individuelle patient til en behandling som vil tjene dem bedst i deres restlevetid. SPRING modellen viste sig valid til brug i en uafhængig patient kohorte og er derved egnet til klinisk brug.

CONTENTS

1 INTRODUCTION

In the era of evidence based medicine we asked ourselves 10 years ago: are we really treating metastatic bone disease (MBD) in the extremities with the requisite knowledge of patient survival? This question initiated the current thesis.

The prevalence of MBD in the extremities (MBDex) is expected to rise mainly due to improvements in the treatment of primary cancers resulting in more patients living longer with cancer (1, 2).

We know from old autopsy studies of cancer patients that up to 30% will have MBD at the end of their lives (3) indicating that the disease is widely spread. Bone is the third most common place for dissemination of a primary cancer and is only surpassed by liver and lung (4). Forty percent of bone metastases will be located in the extremities (5) where the proximal femur is the most frequently affected site (4, 5). Cancers from breast, prostate, lung, and kidney as well as myeloma are the most common causing surgery for MBD (6).

Often MBD can be managed by bone stabilizing medication with an ability to delay or prevent a skeletal related event (SRE) (7-12). A SRE is defined as: a pathologic fracture, spinal cord compression, necessity for radiation to bone (pain or impending fracture) or surgery to bone (13). The true incidence of surgery for MBDex remains unknown as studies primary consist of single center studies rather than population based studies (14).

The risk of a SRE depends on the type of the primary cancer, but national registry data (15) indicates that the cumulative incidence of SRE is 45% - 55% one year after debut of MBD for prostate, lung and breast cancer patients, and patients will suffer a new SRE every 3-6 months for the rest of their residual survival (16, 17).

Radiation therapy as pain management is well documented for SRE but there is a lack of evidence of the healing potential of a metastatic lesion after radiation therapy. In case of complete fracture, orthopedic intervention is considered obligatory in the majority of cases (18, 19). With this in mind we must expect a larger number of surgeries for MBDex in the coming years.

Population based studies have identified dissemination of cancer to bone as a poor prognostic factor for overall survival (17, 20, 21) with a risk ratio as high as 10.5 for breast cancer patients (20). Survival after surgery for MBD has been reported with great variety in the literature and a review performed in 2016 by Kirkinis et al. (22) identified a one-year overall survival probability for patients undergoing surgery for MBD ranging from 17% to 70%. The widespread range of reported survival underlines the heterogeneity of patients included in various studies and suggests that the populations might be confounded by known risk factors for survival and selection bias. Kirkinis et al. (22) identified eight factors of importance for survival after MBD reported in the literature. The significance of these factors for survival is ambiguous, as some studies surprisingly find some factors to be risk factors while other studies find the same factors to be protective:

1. Primary cancer causing the lesion (6, 23-26)
2. Pathological fracture (26-28)
3. Visceral metastases (6, 23, 29-31)
4. Multiple vs. solitary osseous lesions (6, 30-32)
5. Performance status (6, 29)
6. Preoperative hemoglobin (23, 24, 29, 33)
7. Age (31)
8. Interval from cancer diagnosis to surgery for MBD (34, 35)

Survival estimation is a prerequisite to allocation of MBD patients to a surgical treatment that will outlive them without causing more harm than necessary (36). Throughout the last three decades prognostication of survival after surgery for MBD has been attempted using above mentioned factors, but no consensus has been achieved on a score for the prediction of survival after surgery for MBDex.

The spine is the most common place for MBD to occur and the most widely used score in prognostication of survival for patients suffering from spine metastases is the Tokuhashi score, which was presented in 1990 and revised in 2005 (37). This score is based on a cohort of patients referred for treatment, radiation therapy or surgery for MBD of the spine. In 1995 Bauer et al. (26) proposed three prognostic groups for patients treated surgically for

both spinal and extremity metastases acknowledging the importance of careful selection of patient cohorts in the attempt to prognosticate survival.

Well cited is the Katagiri score (25), presented in 2005 and revised in 2014 (38), which also addresses the prognostication of MBD patients. However, 93% of the original cohort consists of MBD patients having surgery for spinal MBD and the rest surgery for extremity metastases or no surgery at all. In 2005 Nathan (23) presented a nomogram offering individual risk assessment of mortality after surgery for MBD in spine and extremities. The same patient cohort was later used by Forsberg et al. (39) as a training cohort to explore which statistical method was best for clinical use. This led to the PATHFx model for prediction of survival after surgery for MBD, presented in 2011, using a Bayesian Belief Network. The PATHFx has been externally validated for use in mixed cohorts of patients having both spinal and extremity surgery for MBD (40-42). Prediction models offering estimation of individual risk of mortality for patients having surgery for MBDex is sparse, however, in 2015 Janssen et al. (24) presented and internally validated a nomogram based on a logistic regression – this model has never undergone external validation, though.

In spite of advances in surgical treatment of MBDex made over time, there remains a low awareness of treatment options in orthopedic oncology among primary and secondary treatment centers (43). Several guidelines for treatment regimens for MBDex have been published (14, 44-50), but one must face that the level of evidence for these is low (44). This is supported by a recent Delphi approach study aiming at determining top research priorities in orthopedic oncology. It was found that two out of four top priorities were related to the treatment of MBD (51).

2 BACKGROUND

2.1 Orthopedic intervention – WHEN, WHAT and RISK?

The incidence of SRE, however, do not give us the individual patient´s risk of undergoing surgery for MBDex. Need of surgery for MBDex for the general population will be difficult to determine as the indication for surgery will not only rely upon complete fracture or impending fracture, but also upon an evaluation of patient performance status, estimated residual life expectancy, anatomical location of the MBDex lesion, and lastly the patient´s and surgeon's preference (14, 45-47, 49, 50).

Optimally, treatment of MBDex should be preoperatively assessed by a multi-disciplinary team, thus ensuring a thorough radiologic assessment combined with an orthopedic evaluation. Also pathology and oncologic expertise are necessary prior to decision making regarding the indication for surgery and selection of the type of surgery (49). A database study from the Nordic countries (6) identified 14% of surgically treated MBDex to be the debut of a primary cancer and 12% the debut of a cancer relapse. Also, one should bear in mind the risk of primary malignant bone tumors, especially in patients with unknown primary cancer at the time of surgery, and multi-disciplinary team evaluation is especially important in these cases.

2.1.1 WHEN: Indications for orthopedic intervention

Most of the patients suffering from MBDex are at the end of life, and therefore the selected treatment must balance this reality. However, since most patients still have a desire for being mobile and self-supporting, it is important not to undertreat them. Thus, the aim for the orthopedic surgeon when treating MBDex is to relieve pain and preserve the highest level of limb function for the maximum of time (the implant should outlive the patient) (49, 50, 52).

2.1.1.1 Risk analysis of impending fracture and progression to fracture – can the need for surgery be predicted?

Surgical treatment of an impending fracture is associated with shorter hospital stay, an increased chance of discharged to home versus extended care and improved chances of support-free ambulation (53, 54). Thus, identifying and treating an impending fracture prior to progression to complete fracture is of patient and healthcare interest.

Literature describes, one can never expect a pathological fracture to heal (18, 19) and therefor identifying lesions in risk of fracture would be clinical relevant.

Several rating systems to estimate if a metastatic lesion will develop into a complete fracture or remain stable under radiation therapy have been described, and the Mirel´s score (55) is considered the golden standard (56). Provided with such a scoring system, surgeons would theoretically be able to allocate patients to prophylactic surgical treatment with stabilization (and hereby a potential better clinical outcome) or allocate patients with lesions that will never progress to a complete fracture to radiation therapy treatment alone.

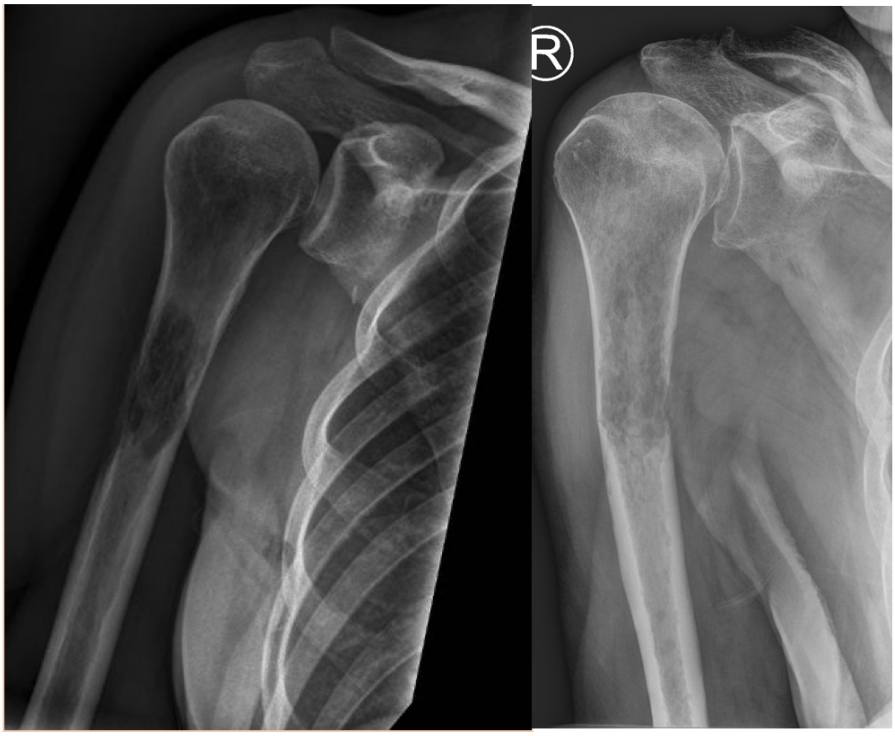

Figure 2.1.1.1: Illustrating an impending (left) and complete (right) pathological fracture of the humerus. In the complete fracture, breakage of cortices is present as oppose to the impending.

Although Mirel´s score is reported very reproducible (Kappa 0.292-0.752 for the five components of the score), it does not perform well in external validation of the ability to predict whether a metastatic lesion progresses to a complete fracture or not (specificity 35%) (57). Van der Linden et al. (58) performed a subgroup analysis of a randomized multicenter trial for the palliative effect of irradiation of bone metastases. Of the 1,157 patients randomized in the trial, 102 patients had a lesion of the femur, and 12 of these lesions progressed to a fracture in the study. Statistical analysis showed no association between patients scoring above 9 points and the risk of progression to fracture (univariate Cox regression p=0.36) and a specificity of only 13% (resulting in a positive predictive value of 14%). Benca et al. (56) also concluded that Mirel´s score leads to overtreatment, but they also argued that no other scorings have been validated in clinical settings and therefore was considered the best available tool. Evidence based methods for stratifying metastatic lesions to surgery or palliative treatment are therefore still missing. Clinical decision of treatment for the single patient continues to rely upon broad clinical knowledge in a multi-disciplinary team.

2.1.2 If surgery – WHAT to choose?

It has been established that pathological fractures in most cases should be surgically managed as they may otherwise never heal (19). Lesions that most likely will progress to fracture, but also lesions that remain to cause intractable pain and extensive bone loss (with an obvious risk of fracture) that does not respond to chemotherapy and/or radiation therapy should undergo surgical intervention as well (59-61).

Bauer (46) underlines that assessment of success for orthopedic interventions evaluated by functional outcome scores seems meaningless for MBDex patients, as factors not related to the surgical implant influences the function of the limb (spinal cord compression influences ambulatory function more than a failed arthroplasty). This makes it difficult to assess the clinical impact of different treatment implants in MBDex. Even though treatment guidelines have been available for more than a decade, Harvie (48) finds that the basic principle for orthopedic treatment of MBD is not fulfilled in every day clinical cases, leading to a decrease in patient survival and quality of life.

Prior to choosing an orthopedic implant, a thorough assessment of the patient's cancer staging must be performed as studies indicate that some lesions can be treated with curative intent in mind. This is the case for solitary metastatic lesions of renal cell cancer, and the literature suggests that this is also possible in some cases of breast cancer (59, 62, 63). Otherwise, surgical treatment of MBDex is considered palliative and Eastley et al. (50) describe that the main scope of treatment must be relief of pain, and to restore or maintain function and mobility, thus hopefully leading to an improvement in the quality of life.
The basic principles that should be taken into consideration when performing surgery on skeletal metastases have been described by Damron and Sim (52):

1. Life expectancy – choosing an implant that will outlive the patient
2. An implant that allow full weight bearing and encourage early mobility
3. All lesions of the treated bone must be identified and addressed
4. Postoperative irradiation should be performed in all cases to minimize progression.

These principles may differ from usual fracture management. Poor healing abilities of metastases and remaining bone may prevent absolute stability when using internal fixation devices (14, 64), especially in metastases located in the proximal femur (65-67).

2.1.2.1 Surgical approaches

Treatment philosophies in the surgical treatment of MBDex are to ensure that the implant used, together with the metastatic host bone, achieve the structural stability that the metastatic bone lacks. Allografts are considered obsolete as they rely on bone healing (14). If absolute stability of the bone cannot be achieved by implant devices it is recommended to obtain this by bone cementation (68).
Internal fixation is a widely used principle in ordinary fracture treatment. Generally, devices used for conventional fracture treatment are designed to stabilize the bone until osseous healing occurs. All fixation materials have a finite numbers of load cycles until failure occurs. If bone healing is not accomplished, risk of failure will depend on how long the patient survives after surgery. Authors in favor of internal fixation for MBDex claim that it is a simple and easy procedure without a long rehabilitation period, and there should be no concern to

local progression as it is a rare event (69), precaution in using internal fixation methods should be taken if a lesion is placed under full weight bearing or if osteolytic lesions are widely spread (45). For lesions of the medial neck of the femur, metastases can be treated by endoprosthesis used in ordinary fracture treatment if the calcar area is unaffected. In case of a large osteolytic defect, especially in the metaphyseal part, bone resection and reconstruction with a tumor prosthesis is advised (44, 45).

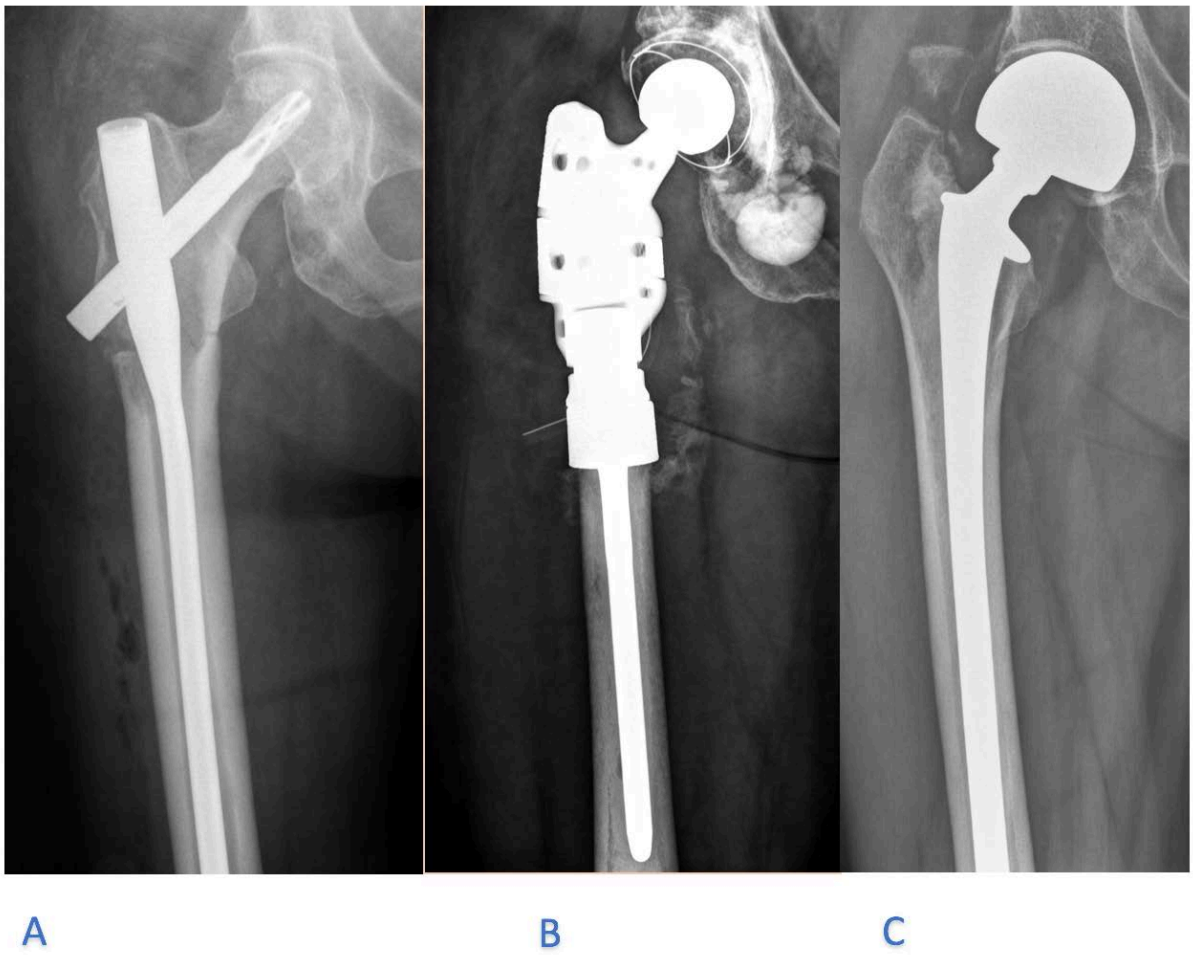

Figure 2.1.2.1: Surgical implant solutions for proximal femur lesions. A) Internal fixation method using an IHMS nail (Smith & Nephew), B) a cemented total hip arthroplasty (THA) with major resection below the lesser trochanter using a modular tumor prosthesis (Segmental, Zimmer Biomet) C) a long stemmed cemented hemi arthroplasty (SP 2, Link) with bipolar head.

Errani et al. (44) performed a systematic review of treatment of MBD of the long bones and concluded that:

1. Solitary lesions from renal cancer should preferentially be resected with a large margin and reconstructed by either tumor prostheses for the meta- and epiphyseal areas or plate and bone cement for diaphysial areas.
2. Tumor prostheses for lesions of the proximal humerus and intramedullary nails for diaphyseal lesions
3. Plate and cement in proximal tibia lesions and intramedullary nails for the diaphyseal part
4. Endoprostheses for the head and neck of femur, tumor prostheses for the metaphyseal and distal femur and intramedullary nails for the diaphyseal lesions.

However, no absolute consensus and treatment algorithm upon treatment strategy has been accomplished within the field of orthopedic oncology.

2.1.3 Does surgery increase the RISK of mortality?

If an implant has a tendency to fail, or just disables the patients to an extent that leaves them immobile, this would, at least in theory, cause increased mortality. Likewise, a surgical procedure that poses a major trauma to the patient may also add to an increased mortality. The question is if the surgical method/implant influences the patient's survival probability? Asking this question is important as; if surgical treatment or trauma does modify the survival probability, stratification should be considered in survival analysis and models for prediction of survival.

Pedersen(70) defined emergency surgery as a risk factor in a large study aimed at settling if the type of anesthesia modified the risk of postoperative complications or of mortality. The study, however, showed no relation between increased mortality in major surgical procedures compared to minor surgeries, but prolonged anesthesia was a risk factor for postoperative complications.

The influence of the surgical trauma on perioperative mortality has been sparsely described for MBDex patients, but indications of internal fixation (71), blood transfusion (71) and poor general health status of the patient(71, 72) have been reported to be related to increased mortality.

2.2 Moving towards personalized evidence based surgical treatment

In an era of improvement in medical management of cancer we are experiencing an increased survival of cancer patients and this improvement has not been reflected in increased healing of pathological fractures, thus the risk of hardware failure after internal fixation now plays a larger role (64, 73-75). When aiming to personalize the treatment for MBDex, survival prediction has been the main focus area for the last two decades. In 2000 Healey (47) advocated for a minimum residual life expectancy of one month, if surgery for an impending facture should be performed. Residual life expectancy that justifies surgical intervention has, however, been a subject of debate. When to allocate the patient to a more durable implant has been addressed in a survey (36) by musculoskeletal tumor surgeons who identified 6 months residual survival as the level of where to choose a more durable implant for the proximal femur.

Many attempts have been made to produce a reliable prediction model for survival after surgery for MBD (6, 23, 24, 26, 29, 76), but the majority include also non-surgically treated patients and spinal metastases. Validations of the models have been sparse, and only PATHFx has been properly externally validated, but only on a historic material (40-42).

3 HYPOTHESES AND OBJECTIVES

3.1 Overall aim of thesis

The overall aim of the present thesis was to identify factors related to (or influencing) survival after surgery for MBDex and furthermore to provide and validate a prediction model for postoperative survival.

3.2 Study I

Patient and implant survival following joint replacement because of metastatic bone disease. A cross-sectional study of 130 patients with 140 joint replacements.

The primary aim was to identify patient (and implant) survival in a retrospective patient cohort having had surgical treatment for MBDex using joint replacement surgery in a highly specialized orthopedic oncology center.

Since this study was a purely descriptive no specific hypotheses were tested statistically, but we wanted to compare the postoperative survival in our selected population to the survival seen in previously published studies.

3.3 Study II

Incidence of surgical interventions for metastatic bone disease in the extremities: A population based study.

The primary aim was to investigate the incidence of surgical interventions for MBDex and to identify the probability of patient survival after surgical treatment of MBDex in an unselected, population based prospective cohort. The secondary aim was to evaluate factors influencing the referral of patients to treatment at highly specialized centers.

We hypothesized that the large difference in survival after surgery for MBD as described in the literature is biased by selection of patients in cohorts.

3.4 Study III

Extent of surgery does not influence 30-day mortality in surgery for metastatic bone disease: An observational study of a historical cohort.

We aimed at settling if the extent of the surgical trauma influences 30-day survival in MBDex patients.

We hypothesized that the extent of the surgical trauma when treating MBDex did not influence survival, and that postoperative survival was solely dependent on the general health status of the patient prior to surgery.

3.5 Study IV and V

Prediction of survival after surgery due to skeletal metastases in the extremities.

and

External validation and optimization of the SPRING model: a model for prediction of patient survival after surgery for bone metastases of the extremities.

The aim of the studies was to produce a valid prediction model for patient survival after surgery for MBDex and to externally validate the model.

As many prediction models for postoperative survival after surgery for MBDex have been described, we hypothesized that a cohort consisting of high quality data of only MBDex patients undergoing surgery would result in better prediction models than registry data based models with a mixture of patients having surgery for MBDex, spinal metastasis and non-surgical treatment.

4 MATERIAL AND METHODS

4.1 Settings

All five studies were analyzed and managed in the Capital Region of Denmark (CRD) and comprised three cohorts (Figure 4.1).

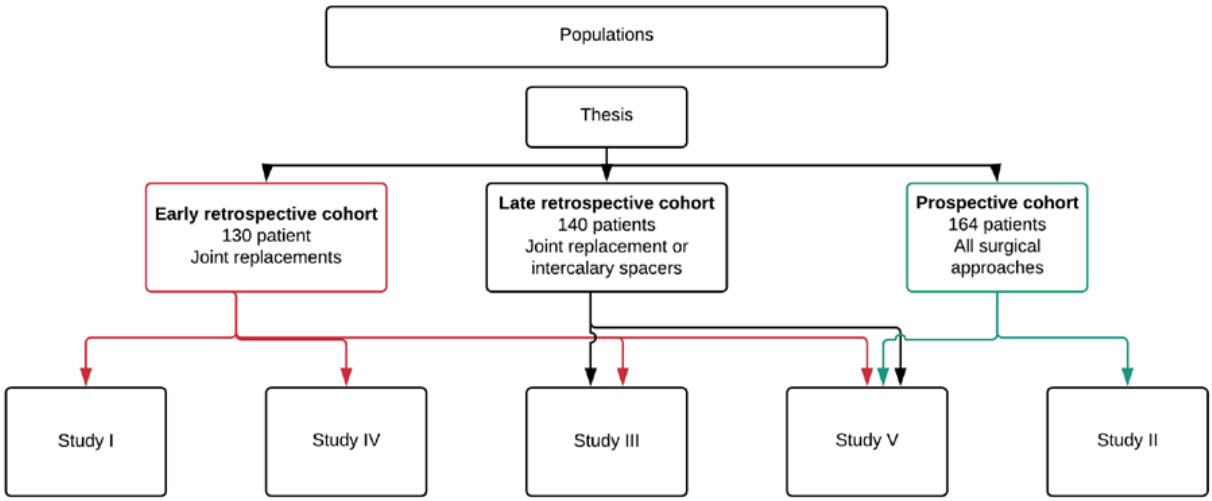

Figure 4.1. Summary of relation between cohorts and studies.

The prospective cohort was constituted of all patients having surgery for MBDex in CRD (1.812 million inhabitants (77)) during a 2-year period. The two retrospective cohorts were comprised of all patients having joint replacement surgery (or intercalary spacers (only included in the late retrospective cohort)) with or without wide bone resection for MBDex during two different time periods at the musculoskeletal tumor center (MTC) at Rigshospitalet. MTC Rigshospitalet treats all patients in need of specialized musculoskeletal surgical oncologic treatment (bone and soft tissue sarcomas, bone metastases with advanced bone loss, aggressive benign tumors of bone and soft tissue) in the eastern and southern part of Denmark (CRD, Region Zealand, The Region of Southern Denmark) and the Faroe Islands and Greenland, comprising a population of 3.982 million people (77).

All citizens in Denmark are entitled to free government paid medical treatment in a tax financed medical care system, and thus all patients having surgical treatment for MBDex in Denmark will be treated in an orthopedic department of a public hospital.
MBDex patients in our catchment areas can receive treatment at either a secondary surgical center (SSC) or a MTC depending upon the attending orthopedic surgeon's evaluation of the patient and the metastatic lesion. In the majority of cases, patients suffering from extensive bone loss will be referred to the MTC from SSCs.
Patients suffering from MBDex treated at the MTC Rigshospitalet are mainly treated with joint replacement surgery including intercalary spacers. If possible, wide resection of the bony lesions are performed allowing implant fixation to unaffected bone.
In the CRD 1.812 million inhabitants are offered orthopedic treatment at six SSCs (Trauma Section Rigshospitalet, Bornholms Hospital, Hvidovre/Amager Hospital, Herlev/Gentofte Hospital, Frederiksberg/Bispebjerg Hospital and Nordsjællands Hospital). MBDex in these hospitals will be treated with internal fixation devices or implants designed for primary hip joint replacement surgery.
In the current thesis, hematological diseases affecting the bone leading to surgical intervention will be included as bone metastases like metastases arising from e.g. carcinomas as treatment strategies are the same.

4.2 Design

Studies I, III and IV are cross sectional historical cohort studies based on data from medical records and/or from the Danish National Patient Registry (DNPR) from a single center (all patients treated at MTC, Rigshospitalet). Studies II and V are prospective cohort studies from an unselected cross section of the Danish population (all patients living in the CRD and treated at the orthopedic departments in the CRD including MTC Rigshospitalet). Study V is a validation study of findings from study IV.

4.3 Study populations

This thesis is based upon three study populations:

4.3.1 Cross sectional historic cohorts:

1. An **early consecutive retrospective cohort** of patients having joint replacement surgery during January 1st, 2003, to December 31st, 2008, at MTC Rigshospitalet. Rigshospitalet (n=130). Patients were identified on the basis of a meticulous review of operation booking lists and patient records.
    - Inclusion criteria
        - MBD lesion identified by histopathology of resected lesion or biopsy
    - Exclusion criteria
        - Other surgical types of treatment than endoprostheses (e.g. internal fixation, intercalgery spacer or resection without reconstruction)
        - Surgeries performed for failed devices in metastatic lesions
        - Age under 18 years

    Patients were followed until death or the end of study (March 29th, 2011, for study I and December 31th, 2014, for studies III, IV and V). Survival was identified from the Danish Civil Registry System (DCRS) (78) and complications to surgery was identified from the DNPR (79) and patient records.

As complete records of patients not treated with an endoprosthesis or intercalary spacer are not kept (but the number of patients treated was estimated to be very small), it was chosen to exclude these patients in an attempt to minimize selection bias.

2. A **late consecutive retrospective cohort** of patients having joint replacement surgery or intercalary spacer during January 1st, 2009, to December 31st, 2013, at MTC Rigshospitalet) (n=140). Identification, inclusion and exclusion criteria did not differ from the early retrospective cohort with the exception that patients with intercalary spacers were not excluded.

    Patients were followed until death or end of study (December 31th, 2014).

4.3.2 Prospective cohort:

3. A **prospective cohort** of all patients living in the CRD having orthopedic surgical treatment for MBDex in the CRD from May 19th, 2014, to May 18th, 2016. Patients were identified by systematic screenings of preoperative imaging for orthopedic procedures performed at any orthopedic center in the CRD excluding spine, foot and hand surgery. To ensure no loss to inclusion, all centers reported to MSS if a metastatic lesion was treated at their center. If a pathologic fracture or bony lesion was suspected, mechanism of injury was explored and in case of reasonable doubt of a malignant lesion, the patient was included. However, if histopathology later excluded a malignant diagnosis, the patient was excluded from the study. As the present study was observational, no influence on the selected treatment was performed. As a consequence, surgeons were not encouraged to perform histopathology explaining that some patients - without a previous history of cancer but a suspected pathological fracture - had no material from the lesion analyzed by histopathology. In such cases, the patient was followed for 6 months or until death, and if no cancer was diagnosed and the lesion did not progress, it was considered non-metastatic and excluded from the study.
   Another exclusion criterion was surgery performed because of failed devices involving a metastatic lesion. Patients were followed until death or end of study (May, 18th, 2017) resulting in complete one year follow-up of patients still alive one year postoperatively.

4.4 Data sources

Data was obtained from administrative and clinical registries, medical records and by patient interviews. Table 4.4 illustrates data source and use.

Data source	Data	Study
Medical record	Clinical information	Studies I-VI
	Complications to surgery	Study I
Surgical record	Sampling of study cohort	Studies I, II, III, IV
	Surgical information	Studies I, III, IV
The Danish National Patient registry	Complications to surgery	Studies I, II
The Danish Civil Registry System	Survival status, date of death	Studies I-VI
Patient interview	Clinical information	Study II

Table 4.4: Data source and data origin used in studies

4.4.1 The Danish Civil Registry system (DCRS)

The registry was introduced nationwide in 1968 by assigning a unique personal identification number (Central Person Register (CPR) – number) to all persons living in Denmark. The registry links information of registries in Denmark. The DCRS contains information regarding name, date of birth, sex, address, citizenship, vital status, date of death or emigration (78).

4.4.2 The Danish National Patient Registry (DNPR)

The registry was founded in 1976 and includes data from all hospital admissions (1977) and outpatient clinic visits in Denmark (since 1995). Data registered include: hospital ward, diagnoses, and treatments performed (79). In study I, all diagnose codes and procedure codes were obtained from the complete cohort, and by manual investigation, clinical relevant procedures and diagnose codes for the surgical treatment were extracted and complications were hereby identified.

In study II, the prevalence (18th May, 2016) and person years lived with MBD in the study period was obtained for patients living with ICD-10 code DC79.5 (neoplasma malignum osseus metastaticum all anatomical locations) in order to calculate the risk of undergoing surgery, if a patient is diagnosed with MBD.

4.5 Variables and outcome measures

In survival analysis, probability of overall survival (OS) was used as we did not expect patients to succumb for any other reason than the primary cancer disease for which they were included into the study.

Table 4.5 provides an overview of variables used in analysis and outcome measures.

Study	Period	End of follow-up	Variables	Outcomes
I	2003-2008	March 29th 2011	Clinical factors	OS
			Surgical factors	RFS
				Revisions
II	2014-2016	May 18th 2017	Clinical factors	Referral pattern
				OS
			Surgical factors	Incidence
III	2003-2013	30th December 2014	Clinical factors	OS
			Surgical factors	OS
IV	2003-2008	31th December 2009	Clinical factors	Survival prediction
V	2003-2008	31th December 2014	Clinical factors	Survival prediction
	2014-2016	18th, May, 2017	Clinical factors	Validation

OS: probability of Overall Survival

RFS: probability of Revision Free Survival

Table 4.5: Summarizing study populations, included variables and outcome measures

4.5.1 Clinical factors

For all studies, clinical variables for demographics were used (age, gender, primary cancer). Blood hemoglobin concentration was also evaluated and considered missing, if not measured within 7 days prior to surgery. Presence of visceral and other bone metastases was obtained from various imaging results available.

In study II, admission days prior to surgery were counted from the day the patient was admitted to any hospital (not just the hospital where the patient received MBDex surgery).

4.5.1.1 Primary cancer

The primary cancer was identified for every patient from the Danish Pathology Registry. Usually MBDex patients present a high degree of heterogeneity regarding the primary cancer and it is common to stratify the primary cancers into prognostic groups (24, 25, 76). In the literature, it has been done with great variations (some report two diagnostic groups (6, 24), others three (25, 76) and some refer to the individual cancers (23, 26).
In the present thesis, primary cancer causing the MBDex was grouped according to Katagiri et al. (25) with a modification based on survival observations for the cancer types in the early cohort (Table 4.5.1.1 and Figure 4.5.1.1).

PROGNOSTIC GROUP	PRIMARY CANCERS
FAST GROWING	Bladder, colorectal, hepatocellular, lung, malignant melanoma, unknown, others
MODERATE GROWING	Prostate, renal, sarcoma
SLOW GROWING	Breast, lymphoma, myeloma

Table 4.5.1.1: Primary cancers categorized into risk groups according to patient survival after surgery for MBDex, inspired by Katagiri (25)

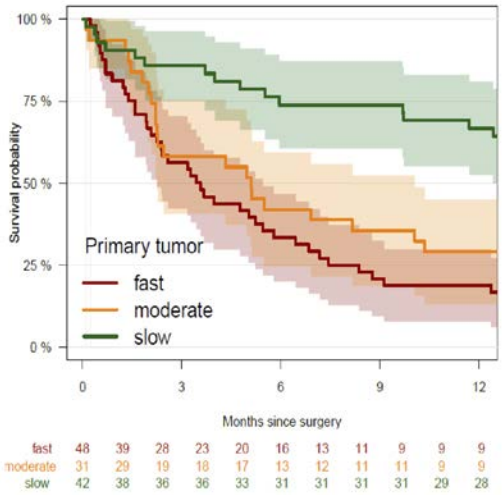

Figure 4.5.1.1.: Kaplan-Meier curve for overall survival after surgery for MBDex dependent on primary cancer group defined in the early cohort with 95 C.I.

4.5.1.2 American Society of Anesthesiologist score (ASA score)

The ASA score was evaluated preoperatively by the anesthesiologist assessing the physical status of patients *prior* to surgery aiming to assess the anesthetic risk. The first draft for the ASA score we know today was published in 1941. The score was presented in 1961 as a five-category physical classification score and a sixth category (brain dead) was later added resulting in a score from 1-6 (80):

1. Healthy patient
2. Mild systemic disease
3. Severe systemic disease
4. Severe systemic disease with a constant threat to life
5. Moribund patients not expected to survive 24 hours without surgery
6. A declared brain-dead patient

The score has proven to relate to both survival and surgical complication as outcome (81, 82).

4.5.1.3 Karnofsky Performance Scale Score

The Karnofsky Performance Scale score was developed to determine the patients´ performance status with the aim of allocating them to be eligible to receive chemotherapy or not (83). It is a ranking score from 0 -100 where:

- 0 - dead
- 60 - require occasional assistance from others but are able to care for most of their personal needs
- 70 - care for themselves; unable to carry on normal activity or do active work
- 100 - Normal; no complaints; no evidence of disease.

Karnofsky performance score was reported as performance status prior to acute fracture of the metastatic lesion aiming not to bias the score by fracture or in case of impending fracture, performance status was measured as the score it was one month prior to surgery.

4.5.2 Surgical factors

In studies I and II we looked at the surgical technique, implants used, and anatomical location. Perioperative bleeding was estimated by measuring blood volume in surgical drains and napkins. No calculation of perioperative blood loss was calculated from pre- and postoperative hemoglobin in an attempt to eliminate bias of pre/perioperative optimization (rehydration that may have caused dilution). Surgery with bone tumor resection was defined

in study I (and the definition was also used in studies II and III) and major resection was considered:

1. Hip: resection through or distal to the lesser trochanter.
2. Knee: resection proximal to the femoral condyles at the knee.
3. Shoulder: resection distal to the surgical neck of the humerus.
4. Elbow: resection proximal to the humeral epicondyles.

Surgery time was obtained from the surgical planning and documentation program (ORBIT (EVRY healthcare systems AB)) and was calculated from the time of the knife perforating the skin to the point when complete wound closure was archived.

4.5.3 Outcome

4.5.3.1 Study I

In study I, patient survival was the primary outcome and it was defined as the probability of overall survival (OS) calculated as number of days from date of surgery to death of all causes or end of study (March 29th, 2011).

The secondary outcome was probability of implant survival and probability of revision free survival (RFS). Any additional surgical intervention of the affected joint after index surgery was identified based on the procedure coding reported to the DNPR, thus ensuring that all surgical interventions were identified and validated by cross checking with patient records (electronically if surgery was performed after 01.01.09 or in paper if revision was done prior to this date).

Implant survival time was defined as the time the implant survived without revision involving removal/replacement of bone anchored parts of the implant. Revision free survival was defined as the time the implant survived any surgical treatment in relation to the implant (including replacement of bushings, superficial and deep revision of soft tissue, skin necrosis etc.).

4.5.3.2 Study II

In study II, the primary outcome was the incidence (and patient demographics) of surgical treatment of MBDex of patients living in CRD performed in the period 19th May, 2014 - 18th May, 2016 and postoperative OS. End of study was 18th May, 2017. In addition, referral bias was investigated by analysis of patients referred from SSC to MTC.

4.5.3.3 Study III

Primary outcome was 30-day OS, calculated as number of days from the day of surgery to death or 30 days postoperatively, whichever came first. The 30-day timeline was chosen as the relevant period where surgery related mortality would occur. Secondary outcome was evaluation of risk factors for surgery related mortality (30-day survival after surgery).

4.5.3.4 Study IV

Primary outcome was the development of a prognostic score for estimating survival at 3, 6, and 12 months after surgery for MBDex. Secondary outcome was internal validation of prognostic score.

4.5.3.5 Study V

Primary outcome was to update and refit the prognostic score presented in study IV and secondary outcome was external validation of the score.

4.6 Statistics and ethical approvals

Ethical Committee, Data Protection Agency and National Board of Health approvals were obtained as summarized in Table 4.6.

	Data acquisition	Ethical approval	Data protection approval	Data obtained by
Studies I, IV	Retrospective	H-3-2010-130	2008-41-2819	MSS, MMP, KGG
Studies II, V	Prospective	H-4-2014-005	30-1222	MSS, PFH
Study III	Retrospective	3-2013-880/1/	2013-41-2591	MSS, THB

Table 4.6. Ethical and Data Protection approvals for the studies

In all studies, analyses were only performed for the index surgery during the study period (also if a patient underwent surgical treatment for different MBDex in the early and late retrospective cohort). Implants/surgeries were censored in the reoperation and revision analyses at the end of study or if the patient died (whichever came first) prior to experiencing the event of interest.

No patients were lost to survival follow-up due to the DCRS (and no patients emigrated), and none was lost to implant follow-up due to the use of electronic medical records and the DNPR. For the studies in general we used 95% confidence interval (95 C.I.) and the level of significance for rejecting the null hypothesis was set at $p<0.05$. Statistical analyses were performed in SPSS (84) and Excel in study I and R (85) in study II-V.

4.6.1 Study I

Patient and surgery characteristics were analyzed descriptively and presented as mean and range. OS and RFS were calculated by Kaplan-Meier survival analysis using right censoring and presented for one-, two- and three-year survival.

4.6.2 Study II

Patient and surgical treatment characteristics were analyzed descriptively and compared for statistical significance by Mann-Whitney test (continuous variables) and Chi^2 test (categorical

variables) between treatment center (MTC vs. SSC). Continuous variables were presented as mean and range. The incidence of surgery for MBDex was used to calculate the risk of undergoing surgery if a patient is diagnosed with MBD.

OS was estimated using the Kaplan-Meier analysis and difference in survival between treatment center was tested by log rank test using only right censoring. Survival estimates are presented for one, two and three-year postoperative survival.

A Cox regression analysis with adjustment for known confounders for survival was performed to analyze if treatment center (MTC vs. SSC) influenced mortality. A visual evaluation for the proportionality assumption was performed and posthoc power analysis (performed in PS – Power and Sample Size Calculator(86)) was used to identify statistical power of the regression model.

4.6.3 Study III

Patient demographics and surgery characteristics were presented by median and range. Dichotomy was performed based on findings in the literature or in case of lack hereof, by the median found in present study.

Kaplan-Meier survival analysis was used to estimate 30-day postoperative cumulative overall survival. Logistic regression was used to identify Odds Ratio (OR) for risk factors. Multivariate logistic regression was used for identifying independent risk factors for survival using stepwise backward elimination.

4.6.4 Study IV

Multivariate logistic regression analysis was used to identify associations between risk factors and survival outcome three, six and twelve months after surgery for MBDex. Patients with missing variables was eliminated in the multivariate analysis (no imputation of missing data was performed). All variables were included in the full model regardless of statistical significance level in the univariate analysis.

Validation of models were performed by 1000 cross validations of a bootstrap sample of the complete cohort (n=121). Results from internal bootstrap validation was evaluated by area

under the receiver operating characteristic curves (AUC). The risk score for three, six and twelve months postoperative survival was presented as nomograms.

4.6.5 Study V

Survival chances at three, six and twelve months were predicted from the result of a multivariate logistic regression analysis conducted as described in study IV.
Validation was performed in an independent cohort (external validation) and evaluated by the use of AUC, calibration blots and Brier score (87).

4.6.5.1 Brier score

The Brier score was presented by Brier in 1950 (87) and represents the square of the distance between the predicted and the observed survival of an individual. It is therefore given that the lower the Brier score is, the more accurate is the prediction model.

5 RESULTS

Current section of the thesis functions as a summary of the main findings in studies I-V. Detailed description and full analysis and results are available in the appended papers.

5.1 Study I

5.1.1 Survival outcome

One hundred and thirty patients received 140 joint replacements at the Musculoskeletal Tumor Section, Rigshospitalet, in the period January 1st, 2003, to December 31st, 2008. Survival analysis showed a median survival of 7 (range: 0.03-96) months and OS of 39% (95 C.I.: 31%-48%), 29% (95 C.I. 21% - 37%) and 22% (95 C.I.: 15%-29%) after one, two, and three years respectively (Figure 5.1.1). Twenty-five patients were long-term survivors (more than three years) and their primary cancer was myeloma (n=8), breast (n=7), lymphoma (n=4), prostate (n=2), kidney (n=2), lung (n=1) and sarcoma (n=1).

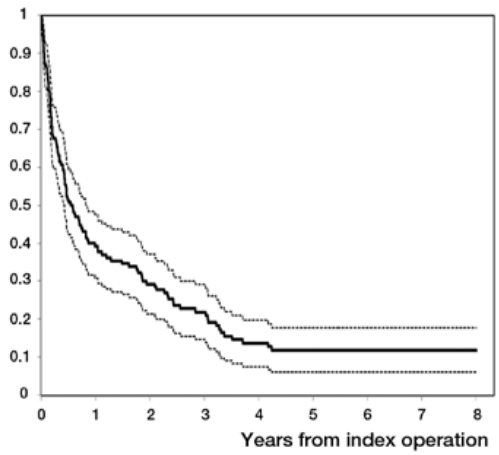

Figure 5.1.1: Kaplan-Meier analysis of OS in the early cohort with 95% C.I.

5.1.2 Revision outcome

ICD-10 output from DNPR resulted in 26,827 procedure codes performed in the cohort from the start of study to the end of study. After manually eliminating procedures representing unrelated surgery, we were able to identify 15 complications directly related to the surgical procedure or the implants inserted. Identified procedures were validated from patient records and all procedures were confirmed with the exception of two dislocations of the hip

– which were not mentioned in the patient records as the hips were treated outside CRD without later clinical follow-up at our institution.

Of the 15 complications observed, hip dislocations were observed most frequently (n= 8, one to five dislocations pr. patient) followed by deep infection (n=3). Other complications observed were peroneal palsy (n=2), implant migration with skin penetration (n=1, shoulder implant), and one disassembly of an elbow implant. In seven patients, these complications led to additional surgery (in total nine procedures) and four patients underwent revision of bone-anchored implants.

The probability of avoiding all implant related surgery (RFS) was 94% (95 C.I.: 89%-99%), 92% (95 C.I.: 85%-98%) and 84% (95 C.I.: 67%-100%) at one, two, and five years postoperatively, respectively (Figure 5.1.2.a). The cumulated probability of implant survival was 100% (95 C.I.: 100%-100%), 96% (95 C.I.: 70%-100%) and 87% (95 C.I.: 70%-100%) at one, two and five years postoperatively (Figure 5.1.2.b).

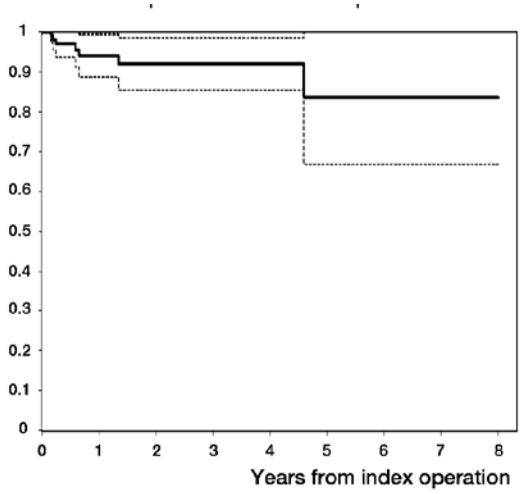

Figure 5.1.2.a: Kaplan-Meier curve estimating probablity of revision free survival with 95% C.I..

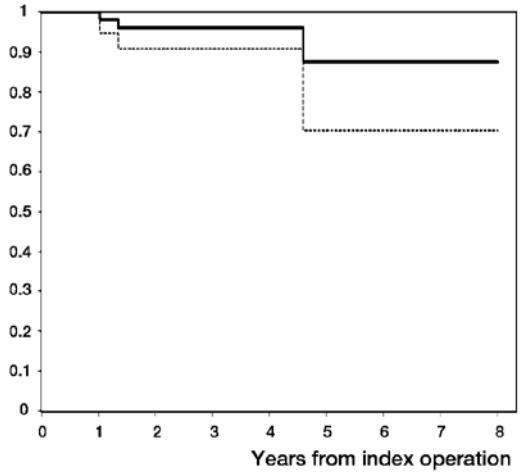

Figure 5.1.2.b: Kaplan-Meier curve estimating probablity of implant survival with 95% C.I.

5.2 Study II

5.2.1 Incidence and demographics

After initial screening of all orthopedic interventions (x-rays, trauma mechanism, and clinical evaluation) performed in the CRD, 200 potential metastatic lesions of patients living in the CRD were identified in the period May 19th, 2014 – May 18th, 2016. Two patients were

excluded after a biopsy could not confirm the suspicion of MBD. In 23 lesions, no primary cancer was known and only mechanism of trauma or ordinary x-ray raised the suspicion of a metastatic lesion by primary investigator (not the performing surgeon) and no biopsy was performed preoperatively. Of these 23 lesions, 20 lesions were excluded after multidisciplinary team evaluation (a musculoskeletal tumor radiologist expert and a senior consultant in orthopedic oncology). Three lesions were followed clinically for one year and as no progression in the lesions were observed, they were considered non-malignant and thus excluded. This resulted in 175 MBD lesions being treated in 164 patients with 168 procedures in a two-year period (Figure 5.2.1.a).

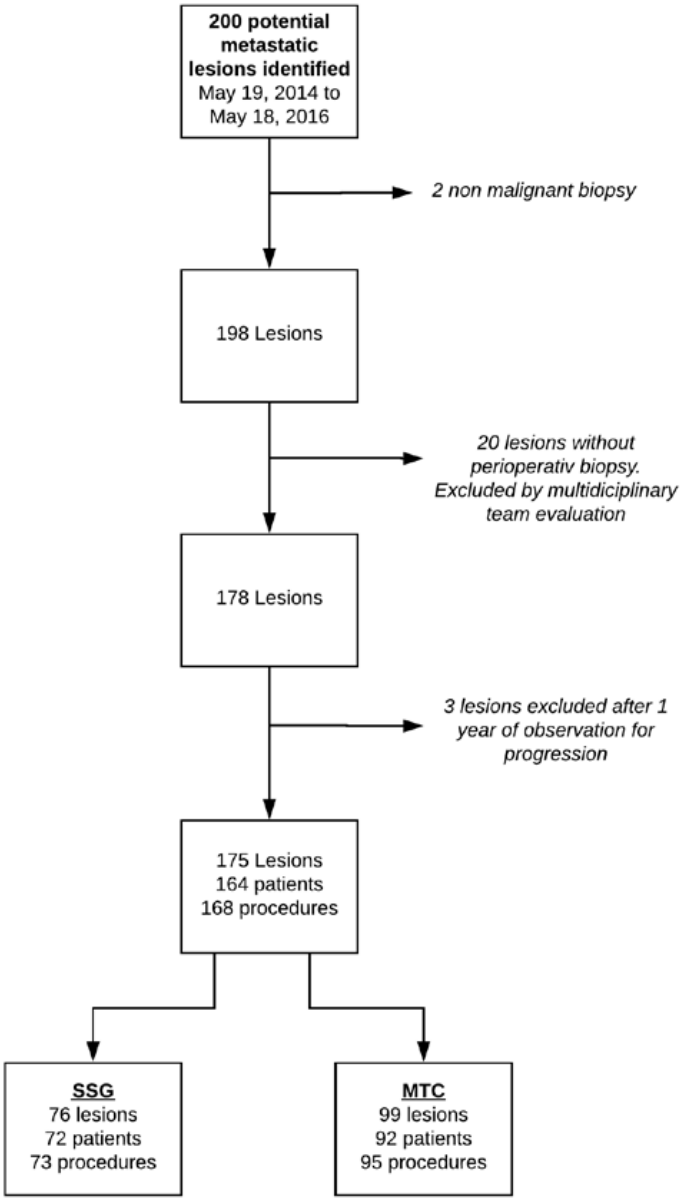

Figure 5.2.1.a: Identification of patient cohort.

SSC: Secondary Surgical Center, MTC: Musculoskeletal Tumor Center

With 1.812 million people living in the CRD, an incidence of undergoing surgery for MBDex in the general population could be estimated to 48.6 surgeries per million inhabitants per year. According to the DNPR, 5335 person years have accumulated during the study period with people living with MBD in all of Denmark (5.76 million inhabitants at the end of the study). This results in a: $\frac{164\ MBDex\ patients\ treated}{5335\ person\ years} * \frac{5.76\ million\ people}{1.81\ million\ people} * 100\%$ = 9.7 % (95% C.I.: 9.6% - 9.8%) risk of undergoing surgery for a extremity metastasis per year lived with MBD. Anatomical location of treated MBDex can be seen in Figure 5.2.1.b.

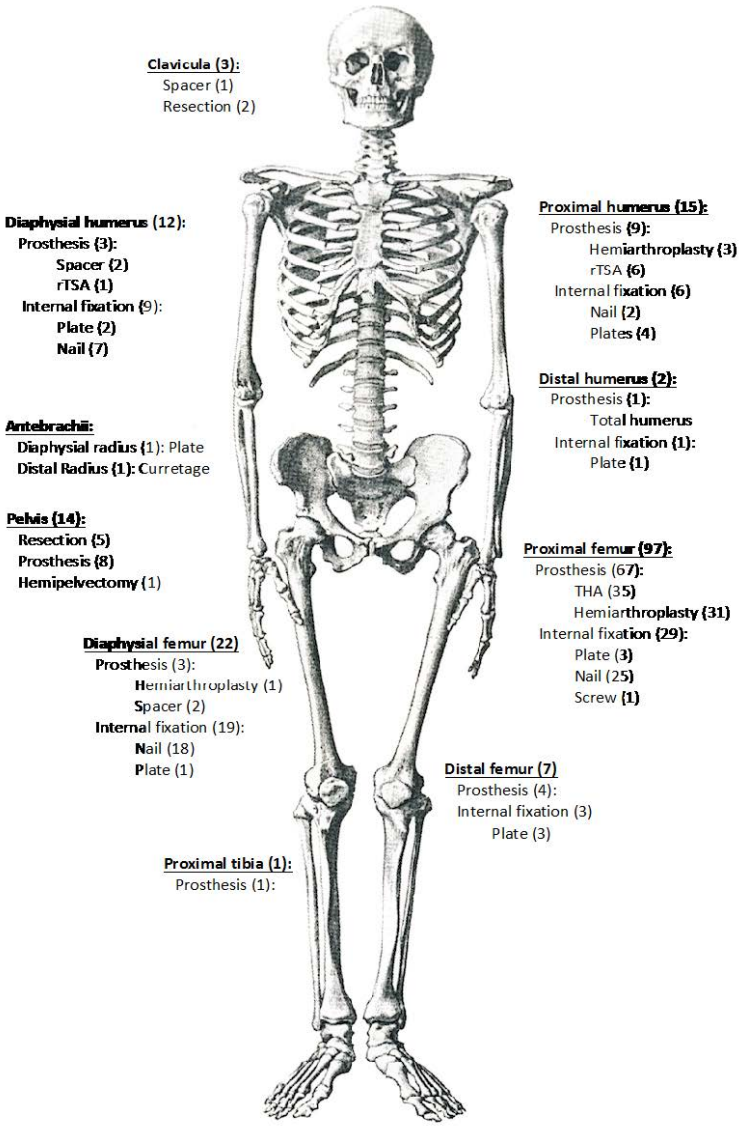

Figure 5.2.1.b: Anatomical site of surgically treated metastatic lesions (n=175) with information of implants and surgical technique used. (rTSA =reverse total shoulder arthroplasty)

In 29 patients, symptoms (pain or fracture) were the main indications that led to the diagnosis of a cancer disease. In 22 patients, the treated lesion was the main cause of diagnosing relapse of a cancer disease that was considered cured, and 8 of the 22 patients had undergone regular surveillance scans without previously identifying the lesions. The most common (85%) primary cancers causing the treated lesion were: breast (25%), lung (19%), renal (15%), prostate (15%) and myeloma (11%).

5.2.2 Referral pattern to MTC treatment

The majority of MBDex were referred for treatment at MTC (59%). Univariate analysis revealed that patients were more likely to be referred to treatment at MTC if they had a primary cancer within a good prognostic group, an impending fracture, no visceral metastases, a good performance status, a low ASA score, or were young, all variables known as good prognostic variables for survival in the literature (6, 23-26, 29, 38, 88). In this population based prospective cohort OS was 41% (95 C.I. 33%-48%) one year after surgery for MBDex. Statistically, the probability of postoperative survival was significantly improved for the subgroup of patients that were treated at the MTC (one year survival 45% (95 C.I. 35% - 55%)) compared to SSC (one year survival 34% (95 C.I. 23% - 45%)) (p=0.006)).

To test if treatment center was a risk factor for survival we performed a Cox regression analysis with known risk factors for survival. We found that treatment center was associated with increased mortality (HR 1.43 (95 C.I. 0.97-2.11, p=0.069)), although not statistical significant.

Post hoc power analysis revealed that the study was underpowered to reject the null hypothesis of equal survival between treatment center given that the true HR was 1.4 (detailed power analysis data shown in Paper II).

5.3 Study III

The early and late retrospective cohorts were included into the present study. As no imputation of missing data was performed, a total of 248 patients was included into a multivariate regression model and as none were lost to follow up in the survival analysis, all patients were available for analysis (n=270).

5.3.1 Survival

Thirty-day OS after surgery for MBDex was 88% (95 C.I.: 84%-92%) (Figure 5.3.1).

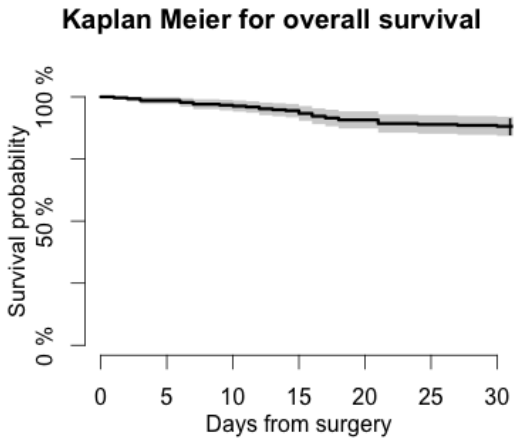

Figure 5.3.1: Kaplan-Meier curve for overall patient survival 30 days after surgery for MBDex

5.3.2 Risk factors for 30-day mortality

Multivariate logistic regression analysis identified no association between extent of the surgical trauma, expressed as the duration of surgery, major bone resection, or blood loss and increased mortality. Independent risk factors for 30-days mortality after surgery for MBDex were, in this study, factors that related to the general health status of the patient (ASA score 3 + 4 and Karnofsky score below 70), see full regression analysis in Table 5.3.2.

Logistic Regression Analysis (n=248)	Univariate analysis Odds Ratio (95 C.I.)	p-value	Multivariate analysis Odds Ratio (95 C.I.)	p-value	Reference
Demographics					
Age	1.87 (0.89 - 4.00)	0.100	n/s	n/s	<66 years
Gender	0.87 (0.41 - 1.86)	0.712	n/s	n/s	Male
Karnofsky performance status	7.34 (3.16 - 19.20)	< 0.001*	5.7 (2.39 - 15.18)	<0.001*	≥70
ASA group	4.16 (1.80 - 10.85)	0.002*	2.83 (1.69 - 7.61)	0.027*	ASA group 1 + 2
Surgery characteristics					
Bone resection	0.72 (0.35 - 1.54)	0.399	n/s	n/s	No major bone resection
Operation time	0.46 (0.20 - 1.00)	0.057	n/s	n/s	< 157 min (median)
Blood loss	1.09 (0.49 - 2.44)	0.838	n/s	n/s	> 938 min (median)
Clinical					
Primary Cancer					
Moderate growth cancer	0.53 (0.14 - 1.58)	0.282	n/s	n/s	Slow growth
Fast growth cancer	2.04 (0.91 - 4.67)	0.084	n/s	n/s	Slow growth

ASA=American Society of Anesthesiologists

* *n/s= not statically significant.*

Table 5.3.2: multivariate regression analysis of patient without missing data (n=248) showing association between risk factors and 30-day mortality after surgery for MBDex.

Interestingly, in the univariate analysis a prolonged duration of surgery seemed to have a strong association to decreased risk of death with OR 0.46 (95 C.I.: 0.20-1.00, p=0.057), but only borderline statistically significant. Subgroup analysis showed that patients who underwent prolonged surgery were more likely to have lower ASA score (ASA score 1 + 2) (and therefore decreased mortality) than patients having shorter surgical procedures (ASA score 3 + 4) with a p-value of 0.003 (chi^2 test). This was confirmed as multivariate regression diminished the effect of duration of surgery to a non-statistical significant effect.

5.4 Study IV

A multivariate logistic regression model was fitted using the early retrospective cohort - as no imputation of missing data was performed, a total of 121 patients was included in the regression analysis. Known risk factors for overall survival described in the literature were included with an adjustment of subgrouping primary cancer to accommodate our patient population (not including patients with spinal metastases).

5.4.1 Prediction model development

The overall survival in the cohort (n=130 patients) was 67% (95 C.I.: 59% – 75%), 50% (95 C.I. 41% - 59%) and 38% (95 C.I. 29%-47%) at the three end points, three, six and twelve months after surgery.

Primary cancer showed a non-statistical significant difference in survival between the three survival groups, but visually a clear tendency towards improved survival was observed in the slow growing cancer group compared to the fast and moderate growing groups in the Kaplan-Meier analysis (Figure 4.5.1.1). We therefore chose to proceed with our revised grouping of primary cancer as we concluded that the non-statistical significance was most likely due to low power in analysis rather than no association between cancer group and survival.

Multivariate regression	**3 months**		**6 months**		**12 months**		**Reference**
(n=121)	**OR (95%CI)**	**p**	**OR (95%CI)**	**p**	**OR (95%CI)**	**p**	
Variables							
Primary cancer							
Moderately growing	5.94 (1.56 to 25.73)	*0.012*	5.76 (1.63 to 22.89)	*0.009*	8.80 (2.10 to 45.09)	*0.005*	*Slow growing*
Fast growing	4.66 (1.35 to 18.01)	*0.019*	7.36 (2.27 to 26.70)	*0.001*	12.71 (3.36 to 57.49)	*< 0.001*	*Slow growing*
Fracture	1.32 (0.44 to 4.12)	*0.624*	1.90 (0.69 to 5.41)	*0.219*	0.80 (0.24 to 2.55)	*0.707*	*Impending*
Hemoglobin (mM)	0.39 (0.20 to 0.70)	*0.624*	0.53 (0.30 to 0.90)	*0.022*	0.49 (0.25 to 0.89)	*0.024*	*Continuous*
Visceral metastases	3.69 (1.40 to 10.48)	*0.010*	3.55 (1.37 to 9.81)	*0.011*	5.17 (1.73 to 17.60)	*0.005*	*None*
Multiple bone metastases	1.98 (0.60 to 7.04)	*0.270*	2.24 (0.73 to 7.17)	*0.164*	3.06 (0.87 to 11.42)	*0.086*	*None*
ASA group	2.57 (0.96 to 7.09)	*0.061*	3.19 (1.22 to 8.71)	*0.020*	4.15 (1.35 to 14.33)	*0.017*	*ASA 1 + 2*
Karnofsky score	0.23 (0.08 to 0.62)	*0.005*	0.25 (0.09 to 0.65)	*0.006*	0.18 (0.05 to 0.56)	*0.004*	*< 70*

Table 5.4.1: Logistic regression analysis of patients without missing data (n=121) showing association between risk factors and survival at the three end points.

Multivariate logistic regression analysis showed that primary cancer type, Karnofsky score < 70, hemoglobin concentration, and visceral metastases were strongly associated with the risk of death three, six and twelve months after surgery for MBDex, see Table 5.4.1. for full regression analysis. Every predictor variable's association with survival outcome was calculated and conversion from the regression coefficient to points was performed resulting in three nomograms.

The individual patient´s risk of being dead at the end point (three, six and twelve months after surgery for MBDex) is obtained by summarizing the score for each predictor variable and this sum is translated into the predicted risk of death at the bottom of each nomogram. See Figure 5.4.1. for an example of a nomogram for prediction of survival outcome 3 months after surgery for MBDex.

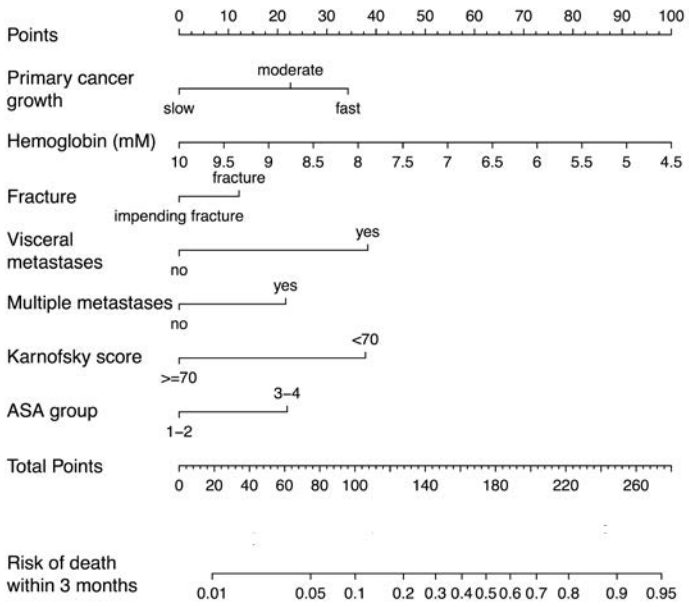

Figure 5.4.1: Illustrating nomogram for individual risk assessment after surgery for metastatic bone disease. The patient´s risk of death is evaluated by a score for each risk factor (points from the upper line) and by summarizing obtained points the risk of death can be identified by drawing a vertical line from the "total point" to "risk of death".

Example: Breast cancer patient (slow growing cancer) = 0 points + preoperative hemoglobin 8mM = 40 points + treated for an impending fracture = 0 points + with no visceral or other bone metastasis at surveillance scan = 0 + 0 points + Karnofsky score 80 = 0 points and ASA group 3 = 20 points, in total 60 points equals approx. a 2% risk of dying within 3 months postoperatively.

5.4.2 Validation

Internal 1000 bootstrap cross validations showed an accuracy, as measured by AUC, of 79% (95 C.I. 66%-90%), 81% (95 C.I. 70%-91%) and 85% (95 C.I. 74%-94%) for prediction of survival three, six and twelve months after surgery, respectively.

5.5 Study V

The model for prediction of survival after surgery for MBDex in study IV was named the SPRING model (Sørensen, PeteRsen, hINdsø, Gerds).

We used the two retrospective cohorts (n=270, 12 patients excluded in analysis due to missing data) (called the training cohort) to refit the SPRING model and externally validate it in the prospective cohort (n=164, 2 excluded in the analysis due to missing data (validation cohort)).

5.5.1 Prediction model development

Distribution of prognostic variables between the training and validation cohort only differed for ASA score (p=0.033). As with study IV, fracture was never in a statistically significant way associated with survival outcome at any end point, and the primary cancer grouping showed decreased tendency to be associated with survival status as expected when a grouping in one cohort is used in another unrelated cohort (moderate growing cancer was non-statistically significant associated with survival status after three months, OR 1.95 (95 C.I. 0.84-4.50, p=0.118)). Hemoglobin concentration (continuous variable) was consistently statistically significant associated with survival outcome with OR 0.58 (95 C.I. 0.41-0.84), OR 0.58 (95 C.I. 0.40-0.83) and OR 0.57 (95 C.I. 0.39-0.81) for three, six and twelve months respectively. See Table 5.5.1 for full analysis.

Variable	Units	3 months			6 months			12 months		
		OddsRatio	*C.I.*	*p- value*	*OddsRatio*	*C.I.*	*p-value*	*OddsRatio*	*C.I.*	*p-value*
Primary group	slow	1.00	[1.00;1.00]	1.000	1.00	[1.00;1.00]	1.000	.00	[1.00;1.00]	1.000
	moderate	1.95	[0.84;4.50]	0.118	5.69	[2.50;12.93]	<0.001	5.39	[2.41;12.06]	< 0.0001
	fast	2.75	[1.26;6.03]	0.011	7.01	[3.18;15.46]	<0.001	9.93	[4.29;22.98]	< 0.0001
Hemoglobin		0.58	[0.41;0.84]	0.004	0.58	[0.40;0.83]	0.003	0.57	[0.39;0.81]	0.002
Fracture	impending fracture	1.00	[1.00;1.00]	1.000	1.00	[1.00;1.00]	1.000	1.00	[1.00;1.00]	1.000
	fracture	1.43	[0.67;3.06]	0.354	1.60	[0.78;3.28]	0.203	0.68	[0.33;1.43]	0.313
Visceral	no	1.00	[1.00;1.00]	1.000	1.00	[1.00;1.00]	1.000	1.00	[1.00;1.00]	1.000
	yes	3.10	[1.62;5.93]	<0.001	2.40	[1.27;4.56]	0.007	2.47	[1.26;4.86]	0.009
Multiple bone metastases	no	1.00	[1.00;1.00]	1.000	1.00	[1.00;1.00]	1.000	1.00	[1.00;1.00]	1.000
	yes	1.89	[0.89;4.04]	0.099	2.19	[1.07;4.48]	0.032	2.35	[1.13;4.89]	0.022
Karnofsky	<70	1.00	[1.00;1.00]	1.000	1.00	[1.00;1.00]	1.000	1.00	[1.00;1.00]	1.000
	>=70	0.33	[0.17;0.62]	<0.001	0.26	[0.13;0.49]	<0.001	0.27	[0.13;0.54]	<0.001
ASA	1 + 2	1.00	[1.00;1.00]	1.000	1.00	[1.00;1.00]	1.000	1.00	[1.00;1.00]	1.000
	3 + 4	1.91	[0.98;3.72]	0.057	1.94	[1.03;3.68]	0.042	1.92	[0.98;3.73]	0.055

Table 5.1.1: Logistic regression analysis of patients without missing data (n=258) showing the association between risk factors and mortality three, six and twelve months after surgery for MBDex.

5.5.2 Validation

The updated model showed good calibration (Figure 5.5.2) and external validation found AUC at 82% (95 C.I.: 76% - 89%), 85% (95 C.I.: 78% - 91%) and 86% (95 C.I.: 80% - 91%) for prediction of survival at three, six and twelve months respectively. The accuracy estimated by Brier score was 0.16 (95 C.I.: 0.12-0.19), 0.16 (95 C.I.: 0.13-0.20) and 0.15 (95 C.I.: 0.12-0.19) for prediction of survival at three, six and twelve months respectively. External validation was performed for the old model, and the updated model outperformed the old model with $p<0.05$ for all three end points in both Brier score and AUC.

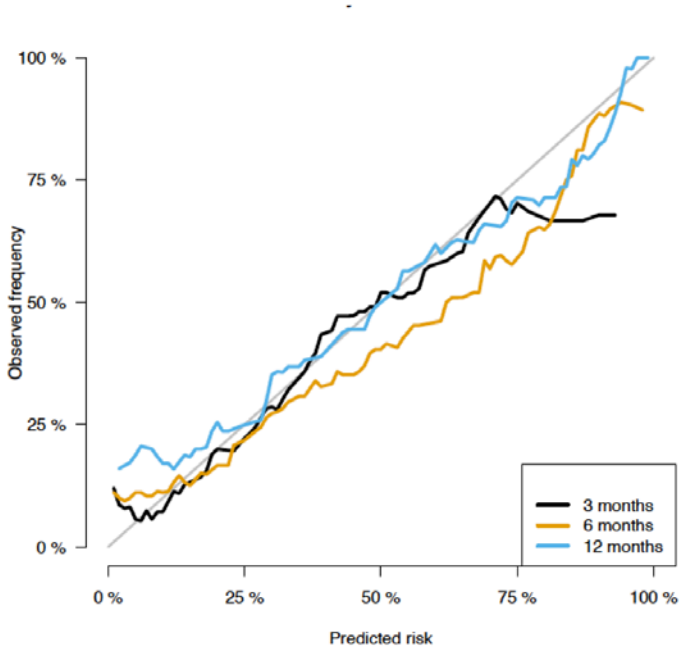

Figure 5.5.2: Calibration curve for external validation of the SPRING model for prediction of survival after surgery for MBDex

6 DISCUSSION

6.1.1 Epidemiological description and incidence

In study I, we found a one-year survival of 38% in a selected cohort of patients treated for MDB with endoprosthesis (joint replacement surgery). In comparison one-year OS for a population based cohort of patients not biased by selection was identified in study II as a 41 % after surgery for MBDex, and if surgery was performed outside a highly specialized center, one-year OS dropped to 34%. Whether this difference in survival between treatment centers is purely dependent on a selection of long term survivors to treatment at a highly specialized center or if the treatment center itself influenced survival is difficult to determine from the data available in the current thesis. However, as an association and not a statistical significant relation between survival and treatment center was found in a multivariate analysis, we speculate that a true relation could exists – although if it does, our study was underpowered to identify it.

This increased mortality if treated outside a highly specialized center could also be related to the surgical approach and implants used at secondary surgical centers, as a relation between an increased mortality if internal fixation method is used in the treatment for MBDex (71) has been suggested. However, a large study from the Scandinavian Sarcoma Group skeletal metastasis register (29) was not able to identify implant type as a risk factor for survival in a patient cohort treated solely at highly specialized centers. The relation between treatment center, implants used and postoperative mortality may confound/bias each other, as implant failure may cause increased mortality due to revision procedures mixed with selection bias in referral pattern, causing divergent results in the literature. Our one-year survival probability in studies I and II is, however, comparable to findings at other highly specialized treatment centers in Scandinavia (6).

Implant failure and revision surgery is a devastating event for any patient, but especially for patients with an expected short remaining lifetime. Kirkinis et al. (22) found that implant failure is related to implant location (upper versus lower extremities) and failure rates are reported from 3% to 70%. Janssen et al. (89) performed a review of functional outcome and revision risk after surgery for MBD in the proximal femur. In general, it was concluded that studies were relatively small, and the review was not able to identify any difference in

reoperation rate between internal fixation and endoprosthesis, but open reduction and internal fixation was more likely to fail and was not recommended in the treatment of MBD at the proximal femur. Functional outcome was comparable for all methods, but endoprosthesis had a tendency to a higher risk of infection. Based upon this, we cannot conclude that internal fixation reduces overall postoperative survival due to increased failure rate.

We found a probability of avoiding implant related revision of 94% one year after surgery with endoprosthesis (joint replacements). It is difficult to compare this to findings in other studies, as our cohort comprises both upper and lower extremity endoprostheses. Revision risks for these anatomical sites are not equal, and distribution of anatomical location in other cohorts are not equal to ours. Also, interpretation of implant failure risk depends on how long time the patient will live with the implant, e.g. an MBD patient may not survive long enough to develop wear problems or for a low virulent infection to give significant clinical symptoms.

No studies in the review by Kirkinis et al. (22), Janssen et al. (90) and our own study I, treats death as a competing risk, and therefore RFS could be strongly influenced by the low patient survival of the observed cohorts. It may be that the selection of patients with short residual life expectancy confounds the infection rate for internal fixation methods, as the patients just don't survive to experience the potential infection and we would only be able to comprehend this in a randomized controlled study, which is currently being conducted in the US as a multicenter randomized controlled trail (91).

We are, to our knowledge, the first to describe a prospective population based cohort of patients having surgery for MBDex in a general unselected population. By this, we can estimate the *true* risk of surgery for MBD and calculate the population incidence as found in study II. In addition, study II gives knowledge of the risk of an SRE in need of surgery in the extremities for patients living with a disseminated cancer disease, enabling us to improve the knowledge of what to expect in their residual lives.

6.1.2 Risk of surgery

As emphasized, from a clinical point of view it is important to ensure that the surgical trauma does not influence survival of MBD patients in a negative way. If the surgical approach is prognostic for survival, we need to consider this in further survival analyses as it may influence survival prediction and thereby confound the models. We found a 30-day OS of 88%. In the literature, mortality after surgery for MBDex is presented as in-hospital mortality and ranges for from 3% to 9% (71, 92) and as such not fully comparable to our results, as one must expect death to occur in-home as well. We choose 30-day mortality as opposed to 60 or 90 days postoperatively as has been used in other studies of early mortality (93-98) aiming to minimize the confounding of the expected mortality due to the patient's cancer disease. Lie et al. (93) advocates for only measuring mortality related to the surgical trauma of 21 days, although post hoc analysis showed no difference in the multivariate analysis using 21 days as timeline.

We know from literature that blood loss, duration of surgery and comorbidity pose a risk for early mortality in MBDex and joint replacement surgery (71, 99).
We found strong evidence that it is the performance status and general health status of the patients that is the main risk factors for mortality after MBDex surgery. Based on study III, we cannot, however, conclude how surgical treatment with internal fixation compared to bone resection and reconstruction influences 30-day mortality, and further studies investigating this issue are pending. Quinn and Drenga (92) were not able to identify a statistically significant association between early mortality and duration of surgery, blood loss, ASA score, implant type, or wide bone resection when performing surgery for MBD in a logistic regression (unknown if adjusted analysis was performed). They did, however, find an association between complete fracture and increased mortality that was not statistically significant (p=0.055). Tsuda et al. (71) found association between 30-day in hospital mortality after surgery for MBD of the proximal femur and fast-growing cancer types, visceral metastases, internal fixation and postoperative chemotherapy. They chose not to perform a multivariate analysis due to low mortality rate (3%). Intraoperative blood loss did not, in neither the studies by Tsuda et al. (71), Quinn and Drenga (92) nor in our own study

III, show any association to the risk of death as opposed to what has been seen in other studies evaluating non-MBD orthopedic surgeries (94, 97). This discrepancy between studies may be due to the different approach to estimating perioperative blood loss. In our study III, blood loss was measured by exactly weighing the drains and surgical laps, yielding an estimate of perioperative blood loss not confounded by preoperative dehydration, poorly preoperative optimization due to lack of transfusion, as seen when blood loss is calculated from postoperative transfusion, or differences in pre- and postoperative hemoglobin. As we adjust for ASA score, this may also eliminate the risk too, as several studies underline that high ASA score correlates to increased risk of perioperative blood loss (82, 99, 100).

It is well known that the cementation process poses a risk of transitory loss of systolic function (101), a clinical state that is difficult to treat in patients with heavy comorbidity. It should be emphasized that in study III, wide resection and reconstruction was performed when the multidisciplinary evaluation concluded that the lesion should not be treated in any other way, because the lesion was considered to have major bone loss which could not be mechanically stabilized by internal fixation or because the metastatic lesion was a solitary lesion.

As studies have indicated (102-104), internal fixation with intramedullary nails likewise poses a risk of cardiac arrest and pulmonary embolism as ultra sound imaging has shown a great shower of fat embolism passing through the heart in the reaming process.

We found that prolonged surgical time could be related to increased survival compared to short surgical time, opposite to the findings of Quinn and Drenga (92). We speculate that wide resection and reconstruction (which is expected to be related to prolonged surgical time) decreases the tumor load, but also removes the painful lesion, and hereby the prolonged surgical time is expected to result in a more pain free rehabilitation, decreased use of opioids and lower tumor load, which may lead to better survival. We can't, however, exclude that this finding is a result of a selection bias of patients with clinical good prognostic factors to more extensive surgery, thus leading to prolonged surgery time.

We therefore call for a careful registration of peri- or postoperative complications and early postoperative mortality in relation to implant type aiming at identifying if the surgical implant causes an increase in early mortality after surgery for MBDex, as the size of the surgical trauma as measured by blood loss and surgery time does not.

6.1.3 Predicting survival after surgery for MBDex; A step toward personalized surgical treatment

In the current thesis, we present the SPRING model for prediction of survival after surgery for MBDex. The model proved accurate in external validation and is hereby suitable to be implemented into clinical settings.

Previously, only PATHFx (76) has been externally validated in three independent cohorts from three different countries/cohorts, and in comparison, the PATHFx model performed with a slightly lower AUC than our SPRING model. This may be explained by the SPRING model being built and validated on patients having only surgery for MBDex whereas the PATHFx model includes spinal diseases as well, although a potential difference, if any, is probably not clinically relevant. The SPRING model was validated in a cohort from the same region as the cohort it was built on, which could explain the very high AUC, but readers should bear in mind that the validation cohort was a prospective population based cohort, and therefore we must conclude that the SPRING model is very robust and a clinically relevant model to use in Scandinavians settings. However, validation in other cohorts from other countries should be conducted prior to implementing it in clinical use in other countries.

In fracture settings, surgical intervention with stabilization of a metastatic lesion is considered a golden standard. This can, however, be debated as some lesions (e.g. myelomas) show some affinity for bone healing following radiation therapy (19). Some surgeons claim that anatomical location as well as the residual life expectancy should influence the decision making between conservative and surgical treatment of MBDex (49). As for impending fracture management, the gold standard for treatment is even more blurred, as no clinical prognostication can guide the clinician towards what lesions progress to complete fracture and those who will not progress to complete fracture under palliation.

Treatment of MBD should always be a multidisciplinary decision as many factors need to be addressed: will the lesion respond to radiation? Is the lesion in risk of fracture? Is it a solitary lesion? If the team advocate for surgical intervention, the anatomical location of lesion (physical strength of implant), performance status (what is the level of self-support prior to surgery?), dissemination of cancer and residual life expectancy needs to be taken into consideration in the attempt to choose an implant that will outlive the patient.

If we accept that all patients should be evaluated by a multidisciplinary team, why do we need a score system to estimate residual survival? We know that clinicians have a tendency to be overly optimistic in regards to survival (105) and it has been proposed that *"even with the knowledge that clinicians tend to overestimate residual survival by a factor 3 the combination of clinical prediction models and "best human hardware" will outperform either of these two scenarios if they were to stand alone"(106)*. To avoid overtreatment of patients we need to adjust for the clinicians´ overly optimism and the need for precise prediction model is thus pending.

Prognostication and prediction of postoperative survival after MBD has previously been addressed in literature (6, 24-26, 76, 107). So why a new attempt? Building a prediction model takes careful considerations and, most importantly, a careful selection of training cohort and external validation to ensure validity in a non-related population so the model is applicable to other treatment centers (108-111).

The methodology for prognostication used by Katagiri (25) and Tokuhashi (107) is similar to Mirel´s score (55) and as described in the background, performance in an unrelated population of the Mirel´s score is unfit for clinical usage and therefore the use of the Katagiri and Tokuhashi score is expected to be poor to predict outcome for MBDex undergoing surgical treatment.

If we aim at personalizing surgical treatment for MBDex we need to be able to select patients who will benefit from surgery, thus producing a tool that can help the clinician identify which lesions will progress to fracture. In addition, we need the clinical result of randomized controlled trials testing the durability and function of different surgical solutions thus providing information of what implant will suit the patient with long versus short life expectancy.

6.2 Methodological considerations

In this thesis, the term "prognostic study" has been used as well as "predictive study". Prognostic studies (also etiological studies) are driven by the influence of a specific risk factor on an outcome and the objective to explain an outcome, while predictive studies aim at predicting an outcome based on known or suspected risk factors at a specific timeline (110, 111).

As of such, in predictive studies, it is important to use a cohort that fulfills these specifications if one wishes to produce a valid prediction model for a specific outcome. When mixing patients having surgery for MBD of the spine with patients having surgery in the extremities and more so by including MBD patients not treated surgically at all into the same prediction models, one makes the mistake of trying to predict survival of patients who are not at the same point in their illness course. This will make the models less fit for clinical use due to introduction of lead time bias. It is debatable whether patients undergoing surgery for spine or extremity MBD share the same baseline.

Although there is no consensus on how to build the best model for prediction (underlying statistical method) though, it is commonly considered that a model should undergo validation in new patients to conclude on the predictive performance of the models (108). As no current studies today fulfill the criteria of including patients at the same timeline of their cancer disease *and* proper validation, a need for studies IV and V were pending to supply the clinician with a valid tool for predicting the future course of MBDex patients. In the future, we must aim to perform an impact study quantifying if the use of the SPRING model truly improves the decision making for orthopedic oncologists.

Study III is purely driven by the wish to explain if survival outcome depends on the surgical trauma – hereby it is not a prognostic study but instead an example of an etiological study providing causal factors related to outcome. If the surgical trauma did influence survival, this should be taken into consideration in prediction models, as the surgical trauma would modify the individual patient's outcome, thus introducing bias.

6.2.1 Strength and limitations of cohorts

The strength of the reported studies is the completeness of included patients who meet the inclusion criteria but also, due to the DCRS, the completeness of follow-up. The strength of the prospective cohort is the population based inclusion method, which creates a consecutive cohort of MBDex patients undergoing surgery not biased by selection.
The limitation of all studies is the low sample size. Although a randomized, large study would be preferable due to low incidence, such a study would need either multicenter settings or a long inclusion period. Long inclusion periods lead to risk of time period bias and multicenter settings demands a consensus on treatment indication so patients enter the study at the same baseline.

6.2.2 Bias

In the retrospective studies of the current thesis, bias by selection of patient to highly specialized surgery is present. We have tried to minimize the systematic errors that may lead to a falsely increased RFS by excluding patients receiving internal fixation as we would probably be more likely to include patients who are readmitted due to implant failure as no consecutive list of internal fixation devises is kept at our institution.
Selection bias in the prospective cohort may be present as Lange et al. (112) finds that only 50% of metastases can be identified on plain x-rays – we most certainly missed a few patients to include in our screening methods in study II. We endeavored to minimize this selection bias by including fractures from suspicious trauma mechanisms and followed them for progression prospectively.
Lead time bias is probably current in the survival observations between fractured patients and impending fractures. We've sought to adjust for this by including fracture as a risk factor in studies IV and V even though fracture status is not an independent risk factor – it does influence, however, the time from exposure to outcome.
Lastly, as we do not take death into consideration in our reporting of failure of implants in study I, this results in bias of our outcome which must be expected to be falsely increased. We suggest, in coherence to Ranstam and Robertsson (113) and the NARA group(114), that future studies also report competing risk analysis of implant failure rates, thus enabling a

true comparison between treatment modalities to be performed, as done in a recent publication by Hovgaard et al. (115). Another appeal (in studies of patients with high mortality, such as MBD patients) is to be careful in reporting loss to clinical and survival follow up as this potentially strongly bias outcome. Is it a possibility that patients lost to follow up are in such bad physical conditions due to malfunction of surgical implant that they are not able to attend clinical follow-up?

6.2.3 Confounding

In current studies a confounder was a factor associated with both exposure and outcome without influencing the exposure. In study III (etiology studies) we included confounders in a multivariate analysis based on literature and clinical knowledge.

We therefore chose not to include age and gender in the analysis, as these factors are so strongly related to the primary cancer (e.g. only men having prostate cancer and women breast cancer).

As the threshold for surgical intervention for MBDex varies between countries, our survival rate is probably not applicable to other cohorts. We found a high percent of complete fractures, and one would expect longer survival for patients treated at institutions, where the threshold for surgery of impending fracture is lower as patients with impending fractures are included in the analysis at an earlier timeline than our population. Therefore, fracture is on the cause from primary cancer and survival outcome, but fracture does not influence the exposure (cancer). We therefore chose to include fracture into multivariate models in studies III, IV and V even though literature is not consistent about this being a true risk factor for survival outcome, thus aiming to adjust for a potential confounding effect of this variable.

6.2.4 Statistical considerations

In general, all studies suffer from wide confidence intervals, which is a result of low sample size. In studies III, IV and V, logistic regression is used. Overfitting in these studies may explain the very wide confidence intervals, although the “one in ten-rule” (ten observations per variable for regression analysis (116)) is not violated.

7 CONCLUSION

Overall, we were able to identify risk factors for survival after surgery for MBDex and, by using these, produce and validate the SPRING model for prediction of survival after surgery for MBDex.

OS was identified for patients having surgery at a highly specialized center, and this was comparable to descriptions in the literature. Also, incidence and risk of surgery for MBDex were found in a population based cohort, providing information for cancer patients with dissemination of disease to bone of what to expect in their residual lives. We were also able to identify that patients with good prognostic factors were more likely to be referred to specialized treatment, thus underlining the selection bias of OS estimates in studies of selected cohorts. Lastly, we found that early mortality after surgery for MBDex was attributed to the general health status of the patient.

7.1 Perspective

In the future, researchers should aim at providing and making conclusion on representative cohorts of patients, ensuring the inclusion also of the most vulnerable patients that might not be referred to highly specialized treatment in order to prevent the selection bias that currently dominate literature. We need to report implant failures as “crudes”, eliminating the contamination of competing risk, which is a substantially contaminating the RFS in this patient cohort.

We need to focus on how the surgical trauma impacts the patient, perioperative and in the early postoperative period. We hypothesize that internal fixation of weight bearing limbs results in decreased ambulatory function and hereby poses a risk of a thromboembolic event that increases mortality.

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PAPER I

Patient and implant survival following joint replacement because of metastatic bone disease

A cross-sectional study of 130 patients with 140 joint replacements

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Background **Patients suffering from a pathological fracture or painful bony lesion because of metastatic bone disease often benefit from a total joint replacement. However, these are large operations in patients who are often weak. We examined the patient survival and complication rates after total joint replacement as the treatment for bone metastasis or hematological diseases of the extremities.**

Patients and methods **130 patients (mean age 64 (30–85) years, 76 females) received 140 joint replacements due to skeletal metastases (n = 114) or hematological disease (n = 16) during the period 2003–2008. 21 replaced joints were located in the upper extremities and 119 in the lower extremities. Clinical and survival data were extracted from patient files and various registers.**

Results **The probability of patient survival was 51% (95% CI: 42–59) after 6 months, 39% (CI: 31–48) after 12 months, and 29% (CI: 21–37) after 24 months. The following surgical complications were seen (8 of which led to additional surgery): 2–5 hip dislocations (n = 8), deep infection (n = 3), peroneal palsy (n = 2), a shoulder prosthesis penetrating the skin (n = 1), and disassembly of an elbow prosthesis (n = 1). The probability of avoiding all kinds of surgery related to the implanted prosthesis was 94% (CI: 89–99) after 1 year and 92% (CI: 85–98) after 2 years.**

Conclusion **Joint replacement operations because of metastatic bone disease do not appear to have given a poorer rate of patient survival than other types of surgical treatment, and the reoperation rate was low.**

Since the beginning of the 1990s, advances in the diagnosis and treatment of various types of cancer have led to a gradually increased survival in patients, and combined with the increase in the elderly population the number of patients suffering from metastatic bone disease has increased. Most of these patients can be treated without surgery, for example with radiotherapy, chemotherapy, bisphosphonates, or analgesic treatment. However, surgical treatment is a good treatment option for this group of patients in cases with a pathological fracture or impending fracture, and in patients with a solitary metastatic lesion (Rougraff 2000, Bauer 2005). Previous studies (Wedin et al. 1999, Harvey et al. 2012) have compared the failure rate after treatment of metastatic bone disease with a joint replacement to conventional osteosynthetic devices and shown a lower risk of failure of the bony reconstruction when a joint replacement was used. Patients suffering from bone metastases or hematological disease of bone often have relatively poor health, and in previous studies that have evaluated the probability of survival in this group of patients treated surgically for long bone or pelvic metastases, a 1-year survival of 16–70% was found (Wedin et al. 1999, Hansen et al. 2004, Camnasio et al. 2008, Harvey et al. 2012).

The aim of this study was 2-fold. Firstly, we wanted to determine the oncological outcome (survival) of patients who received an artificial joint replacement due to bone metastases or malignant hematological disease of the extremities, and secondly we wanted to determine what kinds of complications are seen in this group of patients (including an estimation of implant survival).

Patients and methods

Patients

In a cross-sectional study, we included all 130 patients (76 females) who received a joint replacement operation due to skeletal metastases (n = 114) or hematological disease (n = 16) from January 2003 through December 2008 at the Section for Tumor Surgery, Department of Orthopedic Surgery, Rigshospitalet, Copenhagen, Denmark (Table). The Section for Tumor Surgery is a tertiary referral center for orthopedic

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Descriptive data for 130 patients who had 140 joint replacements because of metastatic bone disease during the period 2003–2008

No. of patients	130
Female/male	76/54
Age at surgery, years	
mean (range)	64 (30–85)
Primary tumor site	
breast	31
lung	20
kidney	16
prostate	15
myeloma	12
unknown	9
lymphoma	5
malignant melanoma	4
bladder	4
sarcoma	4
other	10
No. of operations	140
Major bone resection	
yes/no	103/37
Joints replaced	
hip	105
shoulder	16
knee (distal femur)	14
elbow	5
Type of bone lesion	
pathological fracture	101
osteolytic lesion	38
sclerotic lesion	1

oncology surgery, which specializes in bone and soft tissue sarcomas and metastatic bone disease with major bone loss. Throughout the study period, it was departmental policy to prefer a joint replacement for treatment of an extremity metastatic lesion in proximity to a joint and to attempt a wide margin in solitary lesions. When hip replacement surgery was done, total hip replacement was preferred instead of a hemiarthroplasty. The patients received 140 joint replacements in total, and the mean age at the first operation was 64 (30–85) years (Table). Patients who received other orthopedic implants (e.g. diaphyseal spacers, arthodeses, nails etc.), even if it was a large implant used for treatment of a metastatic lesion close to a joint, were not included in the study.

Breast cancer (n = 31), lung cancer (n = 20), and kidney cancer (n = 16) were the predominant causes of the skeletal metastases leading to joint replacement (Table). 36 patients had only 1 bony metastasis, 21 patients had 2 or 3 metastases, 70 patients had multiple metastases, and in 3 patients the data regarding the number of metastases were missing.

The study was approved by the Danish Data Protection Agency (no. 2008-41-2819) and the Danish Health and Medicines Authority (no. 7-505-29-1642/1). The study was evaluated by the Regional Scientific Ethical Committee of the Capital Region of Denmark (no. H-3-2010-130) and it was not considered to be a notifiable study.

Operation

The bony lesions were located in the lower extremities in 119 cases (proximal femur: 105; distal femur: 14) and in the upper extremities in 21 cases (distal humerus: 5; shoulder: 16). The indication for surgery of the individual joints was: a pathological fracture (n = 101), an osteolytic lesion (n = 38), or a sclerotic lesion (n = 1) (Table). 3 patients had 2 joint replacements performed in different anatomical locations as a 1-stage procedure and 1 patient had 3 such joint replacements. 5 patients had more than 1 joint replacement performed on different days during the study period. Major bone resection—defined as resection through or below the lesser trochanter at the hip, above the femoral condyles at the knee, below the humeral head, and above the humeral condyles at the elbow—was performed in 103 operations.

The following types of implants were used for reconstruction of the hip joint and surrounding bone defects: Bimetric stems for primary total hip replacement (n = 5), medium or long stem revision prostheses (n = 97) (i.e. Bimetric revision stems (n = 55), MP reconstruction hip stems (n = 22) (Figure 1), RX 90 prostheses (n = 14), long Kent hip stems (n = 5), and long Lubinus revision stem (n = 1)), and modular tumor prostheses (n = 3) (HMRS, GMRS, Mega C). With the exception of 3 hips that received bipolar heads, all hips (with very few exceptions) received a cemented Lubinus cup. At the knee, the following prostheses were used: GMRS tumor prostheses (n = 7) (Figure 1), Endorotational knee (n = 6), and Mega C (n = 1). For shoulder and elbow replacements, the following prostheses were used: Bigliani/Flatow (n = 15), HMRS tumor prosthesis (n = 1), and Coonrad/Moorey (n = 5).

Average blood loss during surgery ((n = 134), missing data in 4 patients (6 operations)) was 1.3 (0.1–7) L.

Data and statistics

Clinical data on complications and reoperations after the joint replacement operation were extracted from the patient files. To supplement these data and to compensate for a lack of data in patients with short follow-up in our hospital or missing patient files (n = 4), data were also extracted from the Danish National Registry of Patients on March 29, 2011. Survival data were extracted from the Danish Central Civil Register on March 29, 2011. Thus, the follow-up for both survival and clinical data was at least 28 months or until death, giving a mean follow-up time of 17 (0–96) months from the operation.

Kaplan-Meier survival analysis was used for estimation of the probability of patient survival, the probability of surgical removal or replacement of 1 or all of the prosthetic components anchored to the bone, and the probability of avoiding all kinds of surgery related to the implanted prosthesis. If a patient was treated for more than 1 metastasis during the study period, patient survival was calculated from the time of the first joint replacement only. To be able to compare survival to a wide range of previous studies, we also calculated a median value for survival.

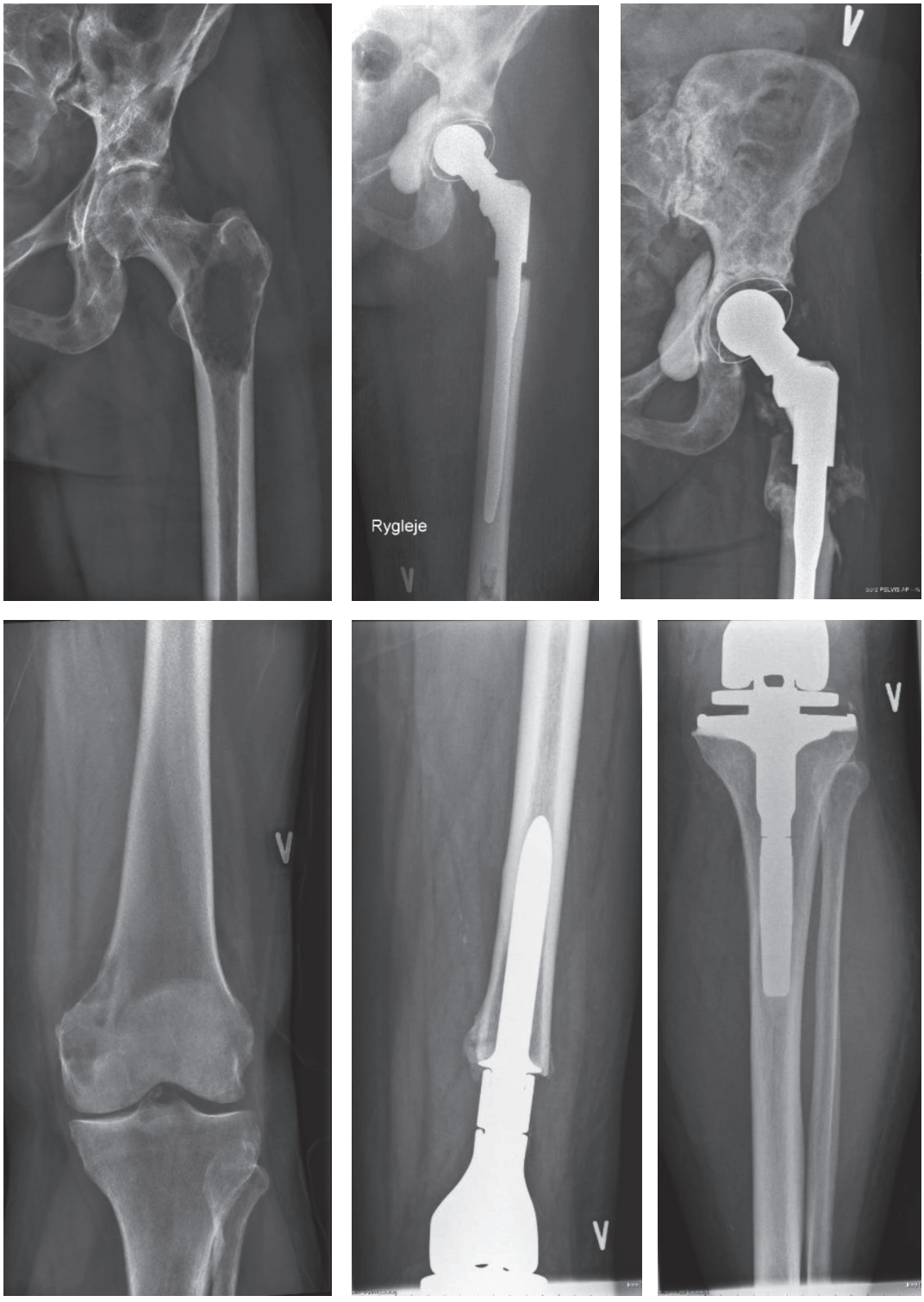

Figure 1. Upper panels. A patient suffering from breast cancer and left hip pain because of multiple osteolytic metastases of the left hip and acetabular region (left panel); postoperatively, after resection of the proximal femur and insertion of a total hip replacement using an MP reconstruction hip stem (middle panel) and status 4 years later (right panel).
Lower panels. A patient with previous cancer of the bladder, suffering from knee pain because of a solitary metastasis of the medial femoral condyle (left panel); status 4 months postoperatively after resection of the distal femur and reconstruction with a GMRS prosthesis (middle and right panels).

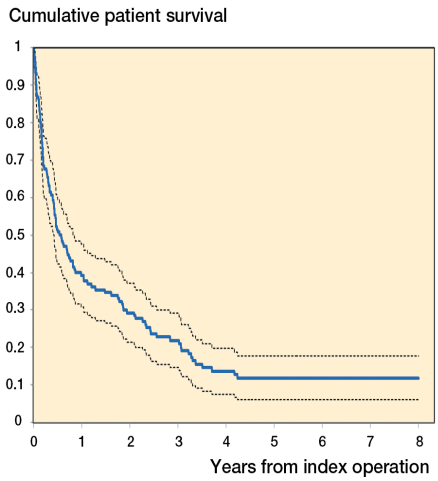

Figure 2. Cumulative survival rate (solid line) and 95% confidence interval (dotted lines) for 130 patients who had 1 or more joint replacements because of metastatic bone disease during the period 2003–2008.

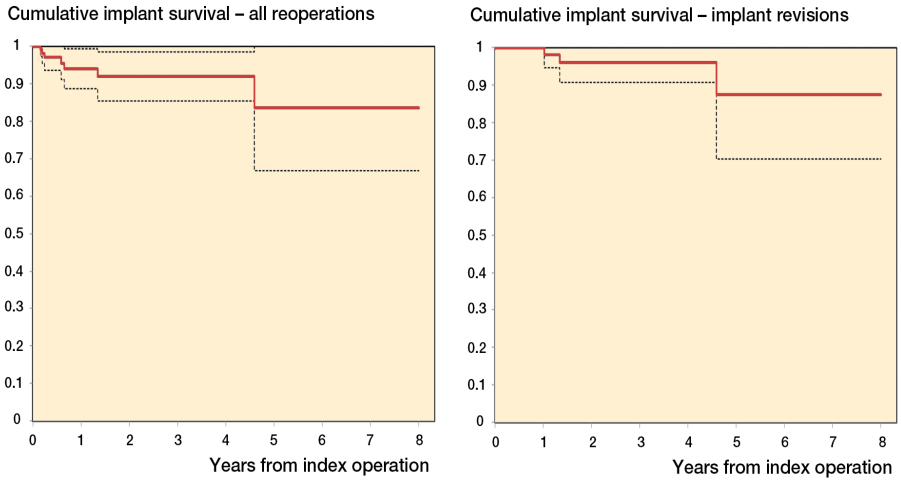

Figure 3. Cumulative survival rate (solid line) and 95% confidence limits (dotted line) for all 140 joint replacements inserted because of metastatic bone disease during the period 2003–2008. The probability of survival was calculated with either all kinds of surgery of the affected joint (left panel) or removal of at least 1 prosthetic component anchored to bone (right panel) as endpoint in the Kaplan-Meier analysis.

We used IBM SPSS software (version 19) for most of the statistical calculations. Calculation of 95% confidence intervals (CIs) for the survival data was done in Microsoft Excel 2010 using Greenwood's formula for calculation of standard error.

Results

The calculated probability of patient survival was 51% (CI: 42–59), 39% (CI: 31–48), 29% (CI: 21–37), and 22% (CI: 15–29) at 6 months and 1, 2, and 3 years of follow-up (Figure 2), and the median survival time was 7 (0.03–96) months. 17 patients died in the early postoperative period (within 30 days after operation) and 4 of these patients died of an illness that could be traced directly to the operation or to the period of time under general anesthesia: cardiac arrest (n = 2), pulmonary embolism (n = 1), and severe hypotension (n = 1). 25 patients were long-term survivors beyond 3 years, and the underlying disease in these patients was: hematological disease (n = 12: 8 myelomatosis and 4 lymphoma), breast cancer (n = 7), prostate cancer (n = 2), kidney cancer (n = 2), lung cancer (n = 1), and uterine leiomyosarcoma (n = 1).

The following 15 complications directly related to the joint replacement operations were seen: hip dislocations 2–5 times (n = 8), deep infection (n = 3), peroneal palsy (n = 2), a shoulder prosthesis penetrating the skin more than 4 and a half years after implantation (n = 1), and an early disassembly of an elbow joint prosthesis (n = 1). The complications led to additional surgery in 7 of the patients (9 operations). The patient with disassembly of an elbow joint prosthesis had a mechanical component replaced 2 months after surgery, and the same patient later developed deep infection leading to removal of the prosthesis 1 year after the initial operation. Because of early recurrent hip dislocation 2 hip replacement patients were reoperated on 2–3 months after the index operation with implantation of a device that made the cup constraint. Another hip patient had the cup revised 7 months after implantation of the prosthesis due to early recurrent dislocation of the hip (5 times within 6 months after the initial operation). 1 patient had soft tissue revision due to deep infection 8 months and 2.3 years after implantation of an MP hip prosthesis. The patient had long-term antibiotic treatment and the prosthesis was never removed. 1 knee patient had 1-stage revision surgery with replacement of a Mega C distal femur tumor prosthesis due to deep infection 1.3 years after implantation. Finally, the patient who had a shoulder replacement penetrating the skin had the prosthesis removed.

The probability of avoiding all kinds of surgery related to the implanted prosthesis was 94% (CI: 89–99) after 1 year, 92% (CI: 85–98) after 2 years, and 84% (CI: 67–100) after 5 years (Figure 3 left). When only removal or replacement of components anchored to the bone was considered an event in the survival analysis, the probability of prosthesis survival was 100%, 96% (CI: 91–100), and 87% (CI: 70–100) after 1, 2, and 5 years (Figure 3 right).

Discussion

Several studies have evaluated patient survival following operative treatment of metastatic bone disease, but few have involved 100 or more patients with precise information of patient survival data (Bauer and Wedin 1995, Wedin et al. 1999, Hansen et al. 2004, Camnasio et al. 2008, Chandrasekar et al. 2008, Sarahrudi et al. 2009, Harvey et al. 2012, Wedin et

al. 2012). With the exception of one of them (Chandrasekar et al. 2008) where it was not obvious if patients with malignant hematological diseases were included, these studies all had an almost identical distribution of the various primary tumors to what was seen in the present study (Bauer and Wedin 1995, Wedin et al. 1999, Hansen et al. 2004, Camnasio et al. 2008, Sarahrudi et al. 2009, Harvey et al. 2012, Wedin et al. 2012). Some of the largest studies were registry studies from the Scandinavian Sarcoma Group (Hansen et al. 2004, Wedin et al. 2012) and in the study by Hansen et al., patient survival after operative treatment of metastases of the extremities and pelvis in 460 patients was evaluated. These authors found a 1-year survival of 39% in a material consisting of an almost equal number of osteosyntheses and joint replacements, and operation method was not related to survival. Wedin et al. (2012) presented survival data from 208 patients who were treated operatively for bone metastases of the upper extremities and they found a 1-year survival of 40% in a material dominated by lesions treated by osteosythesis (mainly intramedullar nails (n = 148)) and with only 35 joint replacements of the shoulder joint.

Bauer and Wedin (1995) evaluated the survival in 153 patients who were treated surgically (with no information regarding the type of treatment) for an extremity metastasis, and they found a 1-year survival of 31%. Wedin et al. (1999) reviewed 192 patients who underwent 228 operations for metastatic lesions of a long bone (54 joint replacements and 162 ostesynthesis), and they found a 1-year survival of 30%. Harvey et al. (2012) retrospectively evaluated the survival of 158 patients treated with either an intramedullar nail (n = 46) or a joint replacement (n = 113) because of a metastatic lesion of the proximal third of the femur, and a 1-year survival of 51% was found. Camnesio et al. (2008) evaluated patient survival in 154 patients treated with bone resection and joint replacement because of bone metastases over a 13-year period, and they found a 1-year survival of 70%. Chandrasekar et al. (2008) evaluated patient survival following operation with bone resection and reconstruction of the proximal femur with a modular tumor prosthesis in 100 consecutive patients who were operated on during a period of 6 years, and these authors found a 1 year survival of 35%.

The 1-year survival of 39% that we found is similar to that (30–40%) found in previous Scandinavian studies reporting data from patients treated with a joint replacement or various types of osteosynthetic device (Bauer and Wedin 1995, Wedin et al. 1999, 2012, Hansen et al. 2004). 1-year survival rates ranging from 17% to 70% have been found in various studies (Bauer and Wedin 1995, Wedin et al. 1999, 2012, Hansen et al. 2004, Camnasio et al. 2008, Chandrasekar et al. 2008, Sarahrudi et al. 2009, Harvey et al. 2012). In studies evaluating survival in patients treated solely with joint replacement, the 1-year survival was 35–70% (Camnasio et al. 2008, Chandrasekar et al. 2008). Thus, no data from our study or from previous studies indicate a higher mortality rate in patients treated with joint replacements than in those treated with osteosynthetic devices, and the very different survival rates between the studies are probably more an expression of different criteria for selecting patients for surgical treatment than an effect of the treatment itself. Furthermore, when comparing survival of the patients in the present study to that in patients treated with radiotherapy alone (Steenland et al. 1999), the median survival is the same, thus indicating that undergoing surgery for treatment of metastatic bony lesions does not reduce life length compared to nonoperative treatment such as radiotherapy.

In patients with metastatic bone disease, it is also important that the surgical treatment is uncomplicated with only minor risk of reoperation, especially when taking the short expected patient survival into consideration. In our material, the infection rate after the index operation was 2% (2/140 joint replacements), which is just slightly above the rate in primary joint replacements. However, the real infection rate in our patients was probably underestimated because we cannot rule out the possibility that a few patients with very poor health could have been given long-term antibiotic treatment in a local hospital because of a suspected deep infection, without our knowledge. Furthermore, the high mortality of the patients also reduces the probability that a late infection with low virulent bacteria would become a clinical problem.

Recurrent hip dislocation was seen in 8% (8/105 hips) and peroneal palsy in 2% (2/105 hips). The rates of peroneal palsy and of hip dislocation were higher than that in primary total hip replacement, and were closer to the level in revision total hip replacement (Garcia-Cimbrelo and Munuera 1992, Schmalzried et al. 1997). This is not surprising, because the operations in our patients were often similar to revision joint replacements regarding duration and magnitude of the surgery. Furthermore, in several of the operations we performed a major bone resection sometimes combined with removal of a soft tissue tumor component. It was policy in our department to use total hip replacement, while in many clinics a hemiarthroplasty is preferred when treating metastatic bone disease at the hip. The use of hemiarthroplasty in our study population could most likely have reduced the risk of hip dislocation and the risk of early reoperation in some patients. However, later acetabular cartilage degeneration may necessitate later conversion to total hip arthroplaty in long-term survivors if hemiarthroplasty is used (Kim et al. 2012).

Due to poor survival of the patients, the implant survival in our study was difficult to compare with the level seen in primary joint replacements, but not surprisingly it was far below the implant survival found in registry studies evaluating implant survival after primary knee replacement or hip replacement (Hailer et al. 2010, Paxton et al. 2011). However, in studies comparing implant survival in patients operated with osteosynthesis and in those operated with joint replacement, the joint replacement group has shown a lower mechanical failure rate and a higher rate of implant survivorship (Wedin et al. 1999, Harvey et al. 2012).

The design of our study allowed more than 1 observation in each patient when evaluating implant complications and survival, which could have introduced bias (Bryant et al. 2006). However, it happened in only 8 patients, who either had 2 or 3 joint replacements as a 1-stage procedure or had 2 or 3 joint replacements on different days during the study period. However, in the patient survival analysis this bias was not allowed, since each patient could only be entered into the survival analysis at the time of the first joint replacement operation in the study period.

In conclusion, joint replacement operations because of metastatic bone disease did not appear to give a poorer patient survival rate than other types of surgical treatment. However, this conclusion relies only on a comparison between the results of various descriptive studies that have obviously had different criteria for allocation of the patients to joint replacement or osteosynthesis; no prospective randomized studies dealing with this problem have been published. The reoperation and complication rate was low, but it was higher than in primary joint replacement and closer to what is seen after revision joint replacement surgery.

MSS collected and analyzed data, and wrote the article. KGG collected data and reviewed the article. TG-S reviewed the protocol, performed surgery, and reviewed the article. DH reviewed the protocol, performed surgery, and reviewed the article. MMP wrote the protocol, performed surgery, collected data, analyzed data, and wrote the article.

No competing interests declared.

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PAPER II

INCIDENCE OF SURGICAL INTERVENTIONS FOR METASTATIC BONE DISEASE IN THE EXTREMITIES: A POPULATION BASED COHORT STUDY

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Lastly a great thanks to all the staff at Musculoskeletal Tumor Section, Department of Orthopedics, Rigshospitalet, Copenhagen University Hospital for support to this study – it has been more than one could expect!

Level of evidence

Level I, Diagnostic Study.

ABSTRACT

Aims: To identify incidence, demographic and survival of a population based cohort of patients having surgery for metastatic bone disease in the extremities (MBDex) and the rate of referrals/referral pattern to a musculoskeletal tumour centre (MTC).

Patients and method: A prospective study of a consecutive population based cohort of patients having surgery for MBDex from 2014 to 2016. Patient demographics, indication for surgery, oncological status, and postoperative survival was obtained from patient interviews, surveillance scans and patient records.

Results: We identified 164 patients treated for 175 bone lesions in 168 procedures, resulting in an incidence of MBDex surgery of 48.6 lesions/million inhabitants/year. The most common primary cancers were breast, lung, renal, prostate and myeloma. Patients referred to MTC (59%) had better prognostic preoperative parameters for survival compared to patient treated at a local secondary specialised centre (SSC). Twenty-nine lesions represented the debut of cancer and 22 lesions the debut of relapse. Patient referred for treatment at MTC had better prognostic baseline characteristic than patients treated at SSC (lower ASA score ($p<0.001$), less patients with visceral metastasis ($p<0.001$), lower age ($p>0.001$) and better prognostic group of primary cancer ($p<0.001$) and Overall one-year postoperative survival was 41% (95% C.I.: 33%-48%). One-year overall survival was higher for MTC patients compared to SSC patients ($p=0.006$). Multivariate regression analysis of risk factors for overall survival showed that patient treated at SSC had an HR 1.43 (95% C.I.: 0.97-2.11), but present study was underpowered to identify a statistical significant risk ($p=0.069$).

Conclusion: Present study is, to our knowledge, the first to describe a prospective population based cohort of patient having surgery for MBDex. We find increased survival in patients treated at a MTC and proves selection bias of referral although improved survival due to treatment centre cannot be excluded.

Introduction

Dissemination of cancer to the skeleton is common for patients living with cancer with reported rates from 30 %(1) to 50 %(2) in autopsy studies. Phase III studies of bone targeted therapy trials show a decreasing incidence of skeletal related events (SRE) as new generations of targeted therapies are introduced(3). Surgical treatment of metastatic bone disease in the extremities (MBDex) should optimally result in reconstructions or surgical stabilisation that will outlive the patient.

Literature reports very diverse patient survivals after surgery for MBDex in the extremities. Kirkinis et al. found in a review one-year overall survival rates ranging from 17 % to 69.5% after surgery for MBDex (4). Different mechanisms of confounding are inherent to the published literature and could in part explain the variation: reports from selected populations only reflect the outcome of selected patients treated at specialised MTC's (survival confounded by indication for referral); different institutional policies on indication for surgery in impending lesions may cause time bias of reported survival, because patients will live longer if treated primarily for an impending fracture, instead of waiting until fracture occurs 8introducing lead time bias). Finally, survival estimates from patients operated prior to introduction of targeted oncologic treatment might not capture the expected gain in survival from this.

Hitherto no population based study of surgery due to MBDex has been performed. Therefore, the incidence of MBDex related surgical interventions, postoperative survival, and demographic composition of this patient group remains unknown. Also, it is unclear to what extend there is a selection in referral of MBDex patients to undergo surgery at a highly specialised centre, and how this impacts the reported patient survival.

Aim of study was to investigate the incidence of surgical interventions for MBDex, the postoperative patient survival, and the epidemiological composition of surgical intervention in a population based prospective cohort. Secondly, we investigated if there is a selection bias in referral patterns between patients treated in a highly specialised musculoskeletal tumour centre (MTC) and a secondary specialised centre (SSC).

We hypothesised that survival reporting in literature is confounded by selection bias of patients treated at specialised centres representing selected cohorts and as such does not provide the clinician with a valid reference in the treatment of MBDex.

Material and Methods:

We conducted a prospective observational study of all patients having surgery due to MBDex in a two year period from May 19, 2014 to May 18, 2016 in the Capital Region of Denmark (CRD) (inhabits 31.35 % of the Danish population (1.8 million people), which is a reliable cross section of the entire population(5)).

Ethical approval was obtained from the regional ethical committee (ID.nb.: H-4-2014-005) and the Danish Data Protection agency (ID.nb.: 30-1222).

Patients were identified if preoperative imaging showed signs of malignant disease in the bone or if malignant disease was suspected by the history of fracture mechanism. Every treatment centre in the CRD had an appointed study investigator to identify the patients and report back to primary investigator (MS). To insure complete inclusion, all preoperative imaging from all patients having orthopaedic intervention in the CRD was systematically screened by one investigator (MS) in the inclusion period.

The five CRD hospitals are licensed to treat orthopaedic patients, and no patients can be expected to be treated outside these centres due to the social healthcare system in Denmark. If a patient experienced an acute fracture during e.g. a holiday outside the CRD and hereby needed surgery outside the CRD, the patient would always be transferred back to a regional hospital for rehabilitation. Hence, all patients having surgery due to MBDex can be expected to be included in this study, thus providing a true population based cohort.

Treatments was purely based upon decisions by the local orthopaedic department and sometimes solely on the local on-call surgeon, and the present study had no influence on the local treatment strategy.

Patients were excluded from the study if histopathology showed no signs of malignant disease. If histopathology was not ensured during surgery, or if material was not suitable for histopathology analysis, the patient/lesion was followed for 1 year. If no progression of the lesion was observed, the lesion was considered non-malignant. If the patient died in close relation to surgery and therefore no progression of a lesion could be expected, the case was evaluated by a multidisciplinary team including a senior consultant musculoskeletal tumour surgeon and a musculoskeletal radiologist and they decided if the lesion was highly likeable to be malignant or not.

All patients were included prior to surgery or, in case of acute surgical intervention, in immediate coherence to surgery. Data of prevalence of metastatic bone disease in the Danish population was obtained from the Danish National Patient Registry (DNPR)(6) and was used to calculate the risk of undergoing surgery for MBDex for patients diagnosed and living with metastatic bone disease. DNPR was founded in 1976 and include all data (ICD-coding) on every hospital admissions (1977) and outpatient clinics (since 1995).

Preoperative variables:

Karnofsky performance status score (KPS)(7) was estimated retrospectively 1 month prior to surgery in case of acute fracture by patient interview at inclusion.

From the Danish National Pathology Registry(8), we identified histopathological diagnosis and date for debut of primary cancer causing the lesion. If primary cancer was unknown and no previous cancer was diagnosed, the date of diagnosis was considered the same as the date of surgery. If primary cancer was diagnosed outside Denmark and the precise date was unknown to the patient, it was set to the first calendar day of the month of diagnosis.
From patient interviews and the oncologist records, the following variables were obtained: presence of visceral metastases (in case of no prior screening for disseminated disease, imaging performed up to 3 months after surgery was used to estimate this variable at baseline), number of bone metastases (same approach as visceral metastases), age, gender, anatomical site of lesion, and it was recorded if the treated lesion represented the debut of cancer or relapse of primary cancer.

Perioperative variables:

From the surgical notes and implant lists, we identified surgical technique (bone resection or stabilisation), implants used (devises for internal fixation, prostheses), and if representative histopathology material was obtained.

Follow-up:

Patients were followed until the end of study (May 18, 2017) or death. No patients were lost to follow-up due to the Danish Civil Registration System that ensures accurate account for emigration and/or death(9).

Missing data:

Residual disease (bone metastases and visceral metastases): whole body scans were evaluated if they were performed within the last three months before or three months after surgery. If no scans were performed during this period, the variable was considered missing.

ASA score: Was considered missing if the anaesthesiologist did not include this information in the preoperative evaluation prior to the surgery.

Statistical analysis:

All statistical calculations were performed using R (R Foundation, Vienna, Austria)(10). Confidence interval (C.I.) was considered as 95 % of normal distribution and statistical significance level was set at $p < 0.05$. Subgroups were analysed by treatment centre (MTC vs. SSC) and tested for statistical significance using Mann-Whitney-Wilcoxon test for continuous variables and Chi^2 for categorical variables. Patient survival was addressed using Kaplan Meier estimate for cumulated survival and difference between survivals in patients related to treatment centre was evaluated by log rank test. Censoring was always right censoring and patients was included into survival analysis only at index surgery.

Power analysis was performed using PS(11).

Results:

Two-hundred lesions were suspected of being malignant by initial screening of x-rays and patient history. Two lesions were without findings of malignant disease in histopathological specimens. Twenty-three lesions had no per-operative biopsy performed. After evaluation of history, x-rays, CT and/or MRI scan in a multidisciplinary setting, 20 lesions were considered not malignant and thus excluded. Three lesions were suspected malignant after multidisciplinary evaluation but showed no signs of progression of the suspected lesion after one year, and MBDex was ruled out (all three received internal fixation with no removal of lesion or local/systemic therapy). We therefore identified 164 patients with 175 metastatic bone lesions (see figure 1 for anatomical location) in168 procedures treated surgically during the two-year period resulting in an incidence of 48.6 MBDex surgically treated lesions per million inhabitants per year. See figure 2 for flowchart for selection of patients and lesions.

During the inclusion period of two years 5,335 person years for patients living with bone metastases were accumulated in the Danish population (ICD-10 code DC79.5) with a point prevalence of 2,690 persons at May 18th, 2016. Based on these numbers we estimated a median survival of approximately one year for persons diagnosed with bone metastases.

Currently the Danish population counts 5.76 million people with 1.81 million living in the capital region(12). With 164 patients surgically treated in the capital region we found that approximately 10% of patients with bone metastases needed surgical treatment: $\frac{164\ MBDex\ lesions\ treated}{5335\ person\ years} * \frac{5.71\ million\ people}{1.81\ million\ people} *$ 100%= 9.7 % (95% C.I.: 9.6% - 9.8%).

Ninety-nine lesions (59%) were referred and treated at MTC. Twenty-nine lesions (17%) represented the debut of cancer and 22 lesions (13%) debut of relapse (of whom 14 had no regular surveillance scan performed and 8 had regularly scans performed, but the lesion was not identified due to insufficient scanning area of extremities) see figure 3.

Of the 29 lesions that represented the debut of a cancer disease, sufficient biopsy material was obtained in 19 of the cases. In three cases the biopsy was insufficient, and in the remaining seven cases no biopsy was taken. In these cases, suspicion of metastatic lesion was withheld based on imagining, and primary tumour was identified by PET scans. In three lesions, no biopsy was performed and primary tumour was never identified. All three patients were treated at SSC (see figure 3).

Breast, lung, kidney, prostate and myeloma was the most common type of primary cancer causing MBDex (see table 1). One-hundred and forty-one lesions (81%) were located in the lower extremities/pelvis and 34 lesions (19%) were located in the upper extremities. Ninety-six lesions (55%) were treated with a prosthesis, 10 lesions (6%) were resected without reconstruction and 69 lesions (39%) were stabilised with an internal fixation (see figure 1).

Patients treated at MTC had a statistically significant better preoperative status with regard to known prognostic variables compared to patients treated at SSC. We found that a patient referred to a MTC were characterised by lower ASA score ($p<0.001$), younger age ($p<0.001$), a less aggressive cancer disease ($p<0.001$), impending fracture ($p<0.001$), no visceral metastases or a longer interval from diagnose of primary disease to surgery for the metastatic lesion ($p<0.001$). (see table 1).

There was no difference between SSC and MTC related to presence of multiple bone metastases, spinal metastases, if the lesion was debut of cancer or relapse, or preoperative irradiated (see table 1).

Mean difference in KPS for MTC patients (mean 76 range 20-100) versus SSC patients (mean 73 range 20-100) showed no statistical significant difference in distribution ($p=0.324$).

The estimated cumulated probability of overall survival for this population based cohort was 41 % (95% C.I.: 33%-48%) at one year, 27 % (95% C.I.: 20%-34%) at two years and 21 % (95% C.I.: 13%-28%) at three years (see table 2 and figure 4). We found a statically significant difference in survival between patient having surgery at MTC vs. SSC $p = 0.006$ (see table 2 and figure 5). Mean time to death for the entire cohort was 211 days (range 0-930), 225 days (range 4-930) for MTC, and 197 days (range 0-871) for SSC patients.

To test if the better survival observed in the MTC group was a result of selection bias of patients with good survival prognosis, we performed at Cox regression analysis to adjust for known risk factors for survival. Univariate analysis showed an increased mortality in the SSC group with a Hazard Ratio of 1.63 (95% C.I.: 1.15-2.32, p=0.007). When adjusted for known risk factors for mortality (presence of visceral metastasis, ASA-score, cancer group, Karnofsky score) we found a Hazard Ratio of 1.43 (95% C.I.: 0.97-2.11, p=0.069). So, after correction for confounders, there was no significant difference in mortality between MTC and SSC. However, posthoc power calculation showed our study is under powered (55%) and therefore if there was a statistical significant better survival for patient treated at MTC our study would not be able to detect it due to lack of power in analysis (see appendix).

Discussion:

A great variety in postoperative survival after surgery for MBDex has been reported in literature, and this is probably a reflection of selection bias, but could also reflect improvement in oncologic treatment though time. We need a better understanding of how a population of MBDex patients is composed in order to recognise and stratify patients to surgery.

We found an incidence of 48.6 MBDex lesions surgically treated /million inhabitants/year with a one year survival rate of 41% - an approximate median of what literature reports(4). We also found a selection bias of patients with good performance status to be referred to highly specialised centres and a concomitant better survival compared to patients treated at SSC. These findings are important to bear in mind in interpretation of studies from selected cohorts of patients being treated only at highly specialized centres and especially in case of statistical analysis of patients from highly specialised centres.

In the present study, 13 % of the lesions represented relapse of cancer and in 17% the debut of cancer. This is coherent with findings in database studies, where the Scandinavian Sarcoma Group Skeletal Metastasis Registry report 14% of treated lesions to represent debut of cancer and 12% to represent relapse of cancer. Our findings are increased in comparison, and as a substantially proportion of relapse patients are treated at SSC without prober preoperatively biopsy in present cohort, our study

underline Cummings et al's(13) conclusion, that even with decades of guidelines for surgical treatment for MBD, there remains a low awareness in SSC for treatment principle/options as these patients should have been referred for MDT evaluation and preoperative biopsy to out rule primary/new malignancy.

Very few studies report MBDex surgery incidence from population based studies and to our knowledge only Tsuda et al.(14) has performed a similar study in 2016. They identify 1,497 patients undergoing surgery for metastatic bone disease of the femur during a 4-year period. Patients were identified from a database coding and according to the authors the database represented 50% of the Japanese population (distributed on 1,000 hospitals). Based on a population of 127.6 million inhabitants this equals an incidence of 2.9 metastatic femur lesions/million inhabitants/year compared to 35 lesions/million inhabitants/year in our study. In our opinion, it is important to match the expectation of the patients, and as such we find important to calculate the actual risk of undergoing surgery for MBDex in case of disseminated cancer disease which this study has identified as 10.4%. Compression of our study with the Japanese underlines the importance of caution in interpretation of studies conducted on databases without national coverages as one cannot expect them to represent the entire population due to selection bias.

The prevalence/incidence of MBDex is difficult to quantify partly due to the sensitivity of the diagnostic tools(15) and the extent of surveillance scans after primary diagnosis. The authors feel that the findings of the present study contribute to a better understanding of the number of patients suffering from these complications to cancer.

Several risk factors related to survival has been identified for patients undergoing surgery for MBDex where visceral metastatases(16-21), primary cancer (16, 18-21), ASA(22) and KPS (16, 18, 19) represents the most important. Present study finds a tendency for referral of patients with good medical status to treatment at the MTC and a concomitant improved survival, that is probably due to the health status of the patients and not the treatment centre (as shown in the Cox regression analysis). However, our analysis shows a borderline statistical significant influence between treatment centre and survival (p=0.069) and weather this relation is due to confounders not adjusted for

remains unknown. We do however know that our study is not suitable to identify if there is a relation between treatment centre and survival outcome due to type 2 error (lack of power).

Also, this study highlights the need for preoperative considerations when dealing with malignant lesions as 30% of the treated lesions in our study were in patients considered cancer free and hereby the origin of lesion remains undetermined, underlining the importance in ensuring representative biopsy of lesion.

Because of the prospective design and collected population based data, this study has few limitations although this is a population representing a Scandinavian population, where treatment of MBDex is anchored in government financed hospitals. Thus, the treatment strategy in the present study might not reflect other populations in countries with different healthcare system/ policies on operation indication. The strength of present study is that no patient was lost to inclusion. The authors emphasise that every surgery was based on a case by case decision from attending physician and no interference from study investigators was present, hereby minimalizing confounding.

As the risk of undergoing surgery for MBDex is based on ICD-10 coding for bone metastasis, it might be underestimated, hence the code does not differentiate between patients having only spinal metastasis (and therefore not in risk of having surgery for MBDex) and patients having metastasis in the extremities. As no code to differentiate these two patient categories exists, calculating by this manner was the only way of means. Bearing this in mind, the risk of undergoing surgery for MBDex is probably higher than 10%.

In conclusion, the estimated survival after surgery for MBDex can be expected to be approximately 41% one year after surgery in a general unselected patient population with a 10% risk of undergoing surgery for MBDex in case of dissemination of cancer to the bone. Increased survival was found in patient referred for specialised treatment at a MTC which can be explained by selection bias by referral pattern. Surely, as literature describes, there is a great variance of individual patient survival and caution should be made in generalising this percentage to the individual patient. Several models for prediction of survival after surgery for MBDex has been published and are better suited for this

purpose (21-23). However, this study provides for the first time a cohort that can validate these systems and contribute to investigate how the models perform in an unselected patient cohort and hereby aid to test their calibration and robustness.

Orthopaedic surgeons should address and further investigate a suspected malignant lesion prior to treatment with histopathological material to diagnose cancer and surveillance scan bearing in mind that even though a patient is not known with malignant disease 17% of metastatic lesions in the population represents debut of cancer and 13% represents relapse of cancer.

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Legends

Table 1: Table describing and comparing the cohort preoperatively.

Preoperative variables	**All patients (data/missing)**	**Musculoskeletal tumour centre**	**Secondary specialized centre**	**p value between cohorts**
No. of patients/lesions	168	95	73	
Female/Male	84/84	43/52	41/32	**p =0.213**
Age at surgery mean				
(range)	68 (32 - 90)	64 (32-89)	71 (49-90)	**p < 0.001**
Primary Cancer	**175**			
Breast	43	23	20	
Lung	33	15	18	
Renal	26	12	14	
Prostate	26	19	7	
Myeloma	20	14	6	
Unknown	3	0	3	
Fracture	**(n=168/0)**	**(n=95/0)**	**(n=73/0)**	**p < 0.001**
Complete	125	60	65	
Impending	43	35	8	
Karnofsky score	**(n=168/0)**	**(n=95/0)**	**(n=73/0)**	**p = 0.324**
Mean (range)	74 (20-100)	76 (20-100)	73 (20-100)	
>= 70	108	63	45	**p = 0.643**
<70	60	32	28	
ASA group	**(n=166/2)**	**(n=95/0)**	**(n=71/2)**	
Mean (range)	3 (1-4)	2.45 (1-4)	2.83 (1-4)	**p <0.001**
Group 1	7	5	2	**p <0.001**
Group 2	66	43	20	
Group 3	86	46	37	
Group 4	14	1	12	
Group 1+2	*70*	*48*	*22*	**p = 0.018**
Group 3+4	*96*	*47*	*49*	
Bone Metastases	**(n=168/0)**	**(n=95/0)**	**(n=73/0)**	**p = 0.220**
Single bone	44	28	16	
Multiple in extremities	15	11	4	

	All patients (data/missing)	**Musculoskeletal tumour centre**	**Secondary specialized centre**	**p value between cohorts**
Multiple incl. spinal w/o neuro. deficit	103	52	51	
Multiple incl. spinal w neuro. deficit	6	4	2	
Solitary lesion	*44*	*28*	*16*	**p = 0.353**
Multiple bone	*124*	*67*	*57*	
Visceral	**(n=168/0)**	**(n=95/0)**	**(n=73/0)**	**p <0.001**
Yes	68	26	42	
No	100	69	31	
Days from diagnose to surgery	**(n=168/0)**	**(n=95/0)**	**(n=73/0)**	
Mean (Days)	1554 (0 - 14040)	1644 (0-14040)	1437 (0-8301)	**p = 0.272**
Debut of cancer	**(n=168/0)**	**(n=95/0)**	**(n=73/0)**	**p =0.889**
Yes	28	15	13	
No	140	80	60	
Debut of cancer relaps	**(n=141/27)**	**(n=82/13)**	**(n=59/14)**	**p = 0.891**
Yes	21	13	8	
No	120	69	51	
Irradiation of metastasis prior to surgery	**(n=168/0)**	**(n=95/0)**	**(n=73/0)**	**p = 0.416**
Yes	36	23	13	
No	132	72	60	

Table 2*:* Table summarises the estimates of survival rates for the population based cohort and for patients treated at a musculoskeletal tumour centre (MTC) and secondary specialised centre (SSC) (p=0.006)

	Mean time to death (range) - days	1 year		2 years		3 years	
		Survival	95% C.I	Survival	95% C.I	Survival	95% C.I
Overall	211 (0-930)	41%	33 % - 48%	27%	20 % - 34%	21%	13% - 28%
MTC	225 (4-930)	46%	36 % - 56%	33%	23 % - 43%	29%	19 % - 39%
SSC	197 (0-871)	35%	24 % - 46%	17%	8 % - 27%	N/A	N/A

Figure 1: Figure illustrating the anatomical site of treated metastatic lesions and method of surgical management. rTSA: reverse total shoulder arthroplasty, THA: Total Hip Arthroplasty.

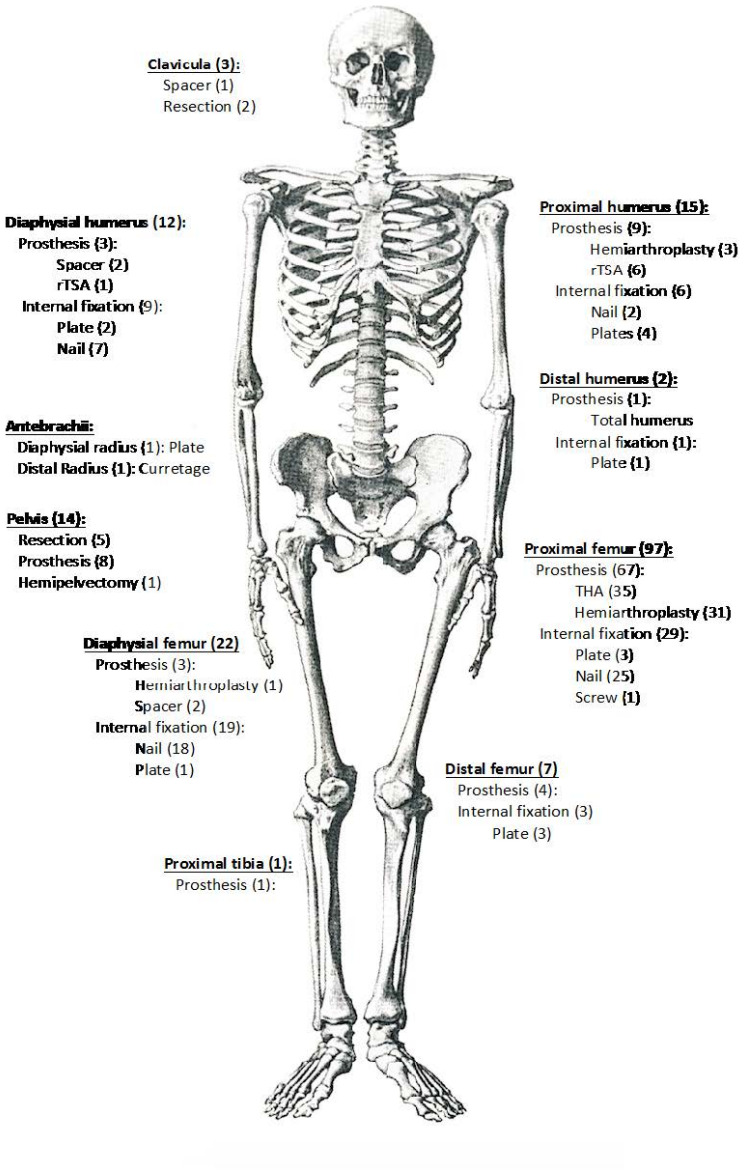


Figure 2*:* flow diagram illustrating identification of cohort of patients having surgery for metastatic bone disease in the extremities.

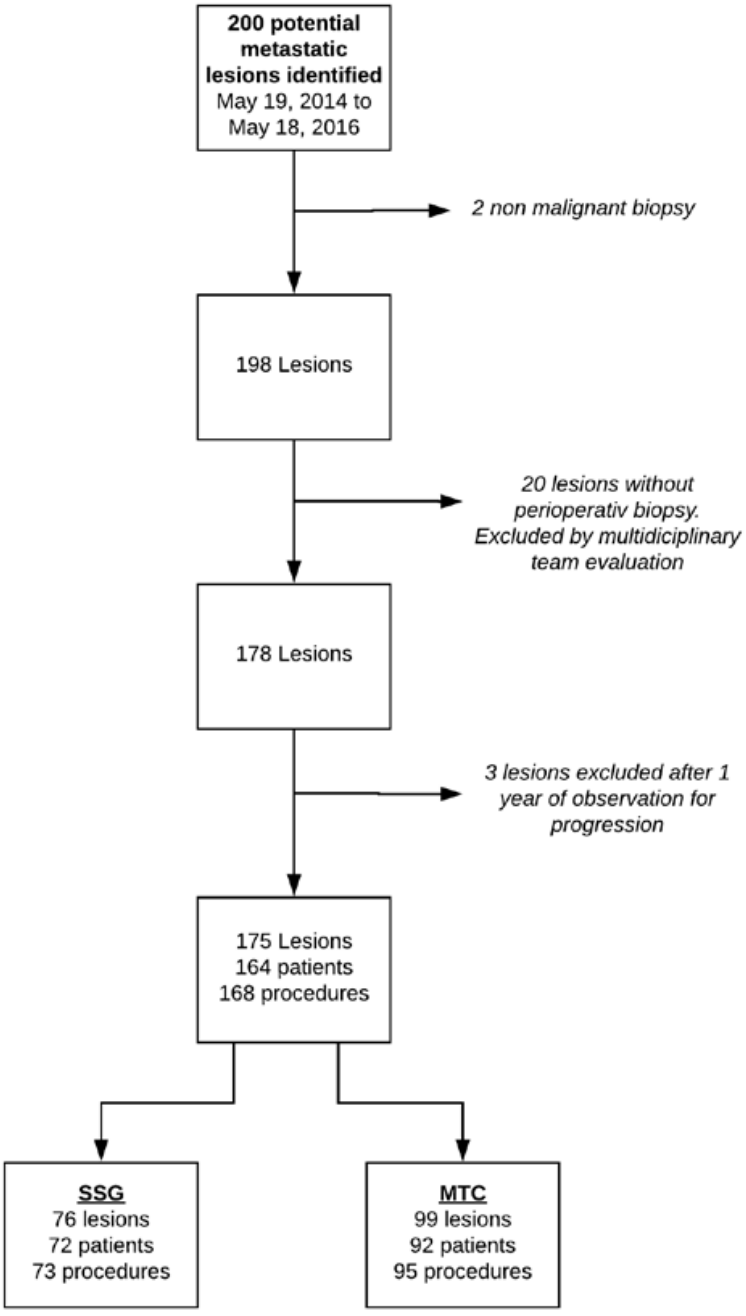


Figure 3: flow diagram illustrating how the metastatic lesion debuted and if it represented debut or relapse of primary cancer disease.

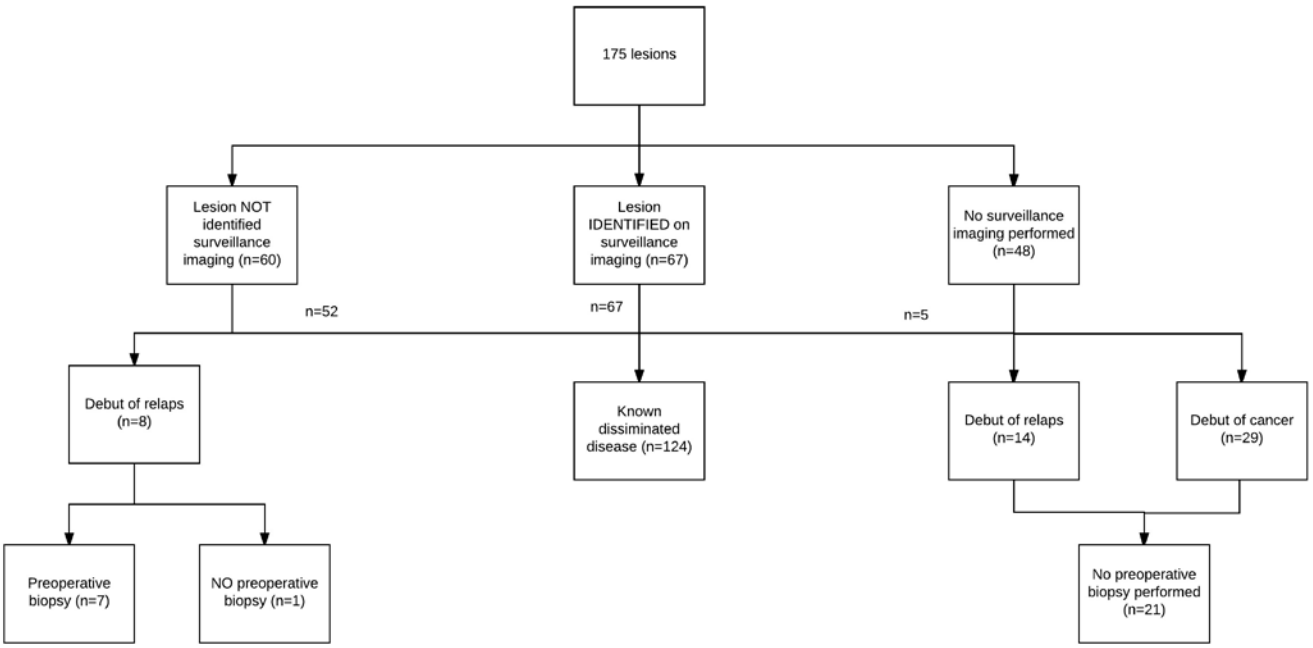


Figure 4: Kaplan Meier survival analysis showing cumulated overall survival for a population based cohort of patients having surgery for metastatic bone disease in the extremities. Patients was only included into analysis at index surgery during study (n=164).

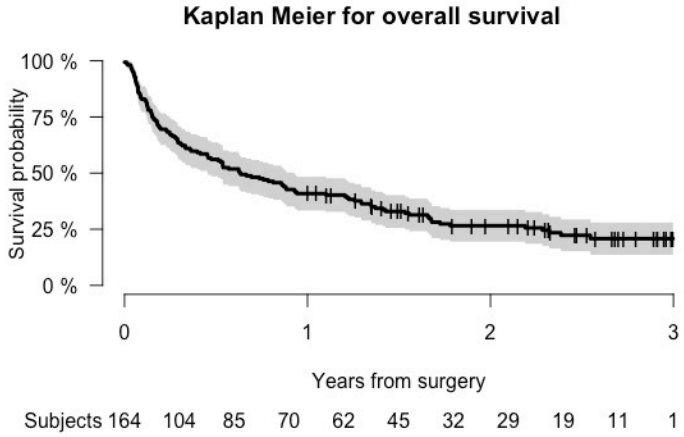
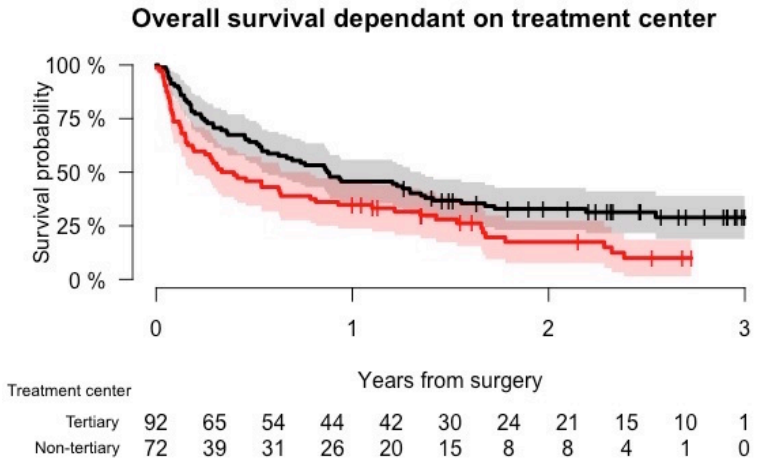


Figure 5*:* Kaplan Meier survival analysis showing cumulated overall survival stratified for treatment centre (p=0.006). Patients was only included into analysis at index surgery during study (n=164).



Appendix:

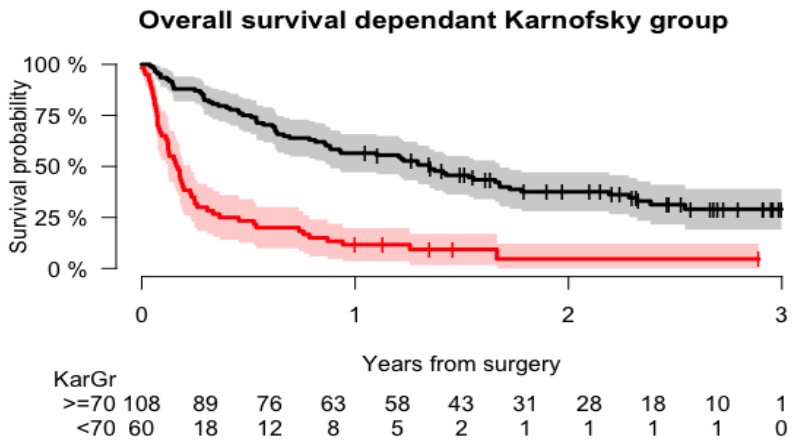
Survival analysis showed better survival for patients treated at MTC compared to SSC. In order to determine if this difference was an expression of confounding, we performed a survival analysis adjusted for known confounders (visceral metastasis, ASA-group, primary cancer[1] and Karnofsky score) as shown in table below.

Test of the proportional hazards assumption for a Cox regression model fit revealed that Karnofsky score grouped <70 or >= 70 violated this assumption (see Kaplan Meier curve for survival stratified for Karnofsky group and res.zhp1 test in R resulted in Karnofsky group p value = 0.016) and therefor the adjusted analysis was stratified for Karnosky score grouping and presented as such in the adjusted analysis.

We can hereby not reject the null hypothesis that treatment centre does not influence the survival probabilities when known risk factors for survival is taken into consideration. Posthoc power analysis show that this study is however underpowered (55%) to detect a true difference in survival between treatment centre and the authors therefor call for future studies to clarify the hypothesis that treatment at SSC is a risk factor for mortality.

	Univariate Cox regression		Adjusted Cox regression		Baseline
	HR (95% C.I.)	p	HR (95% C.I.)	p	
Treatment centre	1.63 (1.15-2.32)	0.007	1.43 (0.97-2.11)	0.069	MTC centre
Cancer group					
Moderate growing			1.93 (1.20 – 3.14)	0.007	Slow growing
Fast growing			5.07 (3.06-8.41)	<0.001	Slow growing
ASA group 3 + 4			1.46 (0.95-2.25)	0.087	ASA group 1 + 2
Visceral metastasis			1.71 (1.11-2.64)	0.015	No visceral metastasis
Haemoglobin < 7 mM			1.18 (0.82-1.70)	0.368	Haemoglobin > 7 mM

[1] Grouped as suggested by Sorensen MS, Gerds TA, Hindso K, Petersen MM. Prediction of survival after surgery due to skeletal metastases in the extremities. *The bone & joint journal.* Feb 2016;98-b(2):271-277.



Sorensen MS, Gerds TA, Hindso K, Petersen MM. Prediction of survival after surgery due to skeletal metastases in the extremities. *The bone & joint journal.* Feb 2016;98-b(2):271-277.

PAPER III

Medicine®

OBSERVATIONAL STUDY

OPEN

Extent of Surgery Does Not Influence 30-Day Mortality in Surgery for Metastatic Bone Disease

An Observational Study of a Historical Cohort

Michala Skovlund Sørensen, MD, Klaus Hindsø, MD, PhD, Thea Bechmann Hovgaard, Bach. Med., and Michael Mørk Petersen, MD, DMSc

Abstract: Estimating patient survival has hitherto been the main focus when treating metastatic bone disease (MBD) in the appendicular skeleton. This has been done in an attempt to allocate the patient to a surgical procedure that outlives them. No questions have been addressed as to whether the extent of the surgery and thus the surgical trauma reduces survival in this patient group.

We wanted to evaluate if perioperative parameters such as blood loss, extent of bone resection, and duration of surgery were risk factors for 30-day mortality in patients having surgery due to MBD in the appendicular skeleton.

We retrospectively identified 270 consecutive patients who underwent joint replacement surgery or intercalary spacing for skeletal metastases in the appendicular skeleton from January 1, 2003 to December 31, 2013. We collected intraoperative (duration of surgery, extent of bone resection, and blood loss), demographic (age, gender, American Society of Anesthesiologist score [ASA score], and Karnofsky score), and disease-specific (primary cancer) variables. An association with 30-day mortality was addressed using univariate and multivariable analyses and calculation of odds ratio (OR).

All patients were included in the analysis. ASA score 3 + 4 (OR 4.16 [95% confidence interval, CI, 1.80–10.85], $P = 0.002$) and Karnofsky performance status below 70 (OR 7.34 [95% CI 3.16–19.20], $P < 0.001$) were associated with increased 30-day mortality in univariate analysis. This did not change in multivariable analysis. No parameters describing the extent of the surgical trauma were found to be associated with 30-day mortality.

The 30-day mortality in patients undergoing surgery for MBD is highly dependent on the general health status of the patients as measured by the ASA score and the Karnofsky performance status. The extent of surgery, measured as duration of surgery, blood loss, and degree of bone resection were not associated with 30-day mortality.

(*Medicine* 95(15):e3354)

Abbreviations: 95% CI = 95% confidence interval, ASA score = American Society of Anesthesiologist score, MBD = metastatic bone disease, OR = odds ratio.

INTRODUCTION

In the acute setting, patients with metastatic bone disease (MBD) in the appendicular skeleton often pose an extraordinary perioperative challenge. This is mainly caused by the comorbidity of patients with MBD compared with other types of orthopedic patients. Recent work evaluating a large, diverse orthopedic patient population identified MBD as a strong, independent risk factor for in-hospital mortality.[1] Furthermore, a previous study showed an increased embolic shower in patients treated with intramedullary fixation or joint replacement surgery in MBD patients compared with patients suffering from nonpathological fractures.[2]

It is well known that patient survival after surgical treatment of pathologic fractures or painful bony lesions due to MBD is relatively poor.[3–7] As such, surgical procedures are almost always considered palliative in nature, and the extent of surgery and choice of implant should be adapted to expected postoperative survival for the individual patient.[8–10] For these patients, postoperative survival is considered to depend on their general health and functional status and not the surgical trauma, as described in previous studies.[11–13] However, these studies did not consider the relative impact on mortality from various pre and perioperative factors. Since the American Society of Anesthesiologists (ASA) Physical Status classification system,[14–16] duration of surgery,[16] and blood loss[17–22] have been associated with short-term survival in other settings such as surgery of the spine and joint replacement surgery, we hypothesize that these and similar perioperative variables could be important for MBD patients as well.

We aimed to evaluate if perioperative parameters such as blood loss, extent of bone resection, and duration of surgery

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The study was approved by the Danish Data Protection Agency (no. 2008-41-2819) and the Danish Health and Medicines Authority (no. 3.3013-880/1).
This work was performed at Musculoskeletal Tumor Section, Department of Orthopedic Surgery, Rigshospitalet, University of Copenhagen, Denmark.
MSS: contributed to idea of concept, study design, data collection, statistical analysis and interpretation, manuscript development, and revision (principal investigator of study). KH: contributed to study design, statistical supervision, interpretation of data, and manuscript revision. TBH: data collection and manuscript revision. MMP: contributed to idea of concept, study design, data collection, statistical supervision, data interpretation, and manuscript revision (supervisor of study).
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TABLE 1. Patient Demographics

Number of patients	270
Female/male	110/160
Age at surgery, y; median, range	64 (21–90)
ASA group (n = 259)	
Group 1	14
Group 2	121
Group 3	115
Group 4	9
Major bone resection (n = 273)	
Yes/no	165/108
Duration of surgery, min (n = 264)	
Median (range)	156.5 (60–494)
Blood loss, mL (n = 248)	
Median (range)	937.5 (100–7000)
Karnofsky score (n = 266)	
Mean (range)	70% (30–100%)
Patients ≥70%	170
Patients <70%	96
Fracture/impending (n = 270)	
Fracture	198
Impending	72

ASA = American Society of Anesthesiologist.

were risk factors for 30-day mortality in patients having surgery due to MBD in the appendicular skeleton.

METHODS

Study Population and Design

We retrospectively identified a consecutive cohort of 270 patients who underwent joint replacement surgery (n = 270) and intercalary spacing (n = 3) for MBD at our facility, a tertiary referral center for orthopedic oncology, from 2003 to 2013 (Table 1). Three patients had 2 or 3 skeletal sites treated as a 1-stage procedure. Joints replaced were the hip (n = 210), the knee (n = 25), the shoulder (n = 29), or the elbow (n = 6), and intercalary spacers were inserted in the femur (n = 2) or the humerus (n = 1). Examples of surgical implants used are shown in Figure 1. The patients who underwent surgery in 2003 to 2008 have previously been described in Sørensen et al,[6,23] and patient demographics of the complete study cohort are shown in Table 1. All patients had adequate follow-up to establish survival at 30 days postsurgery. In case of multiple operations during the inclusion period, patients were included in the study at the time of the first operation only.

Variables

We collected intraoperative variables including duration of surgery, blood loss (counted from blood in the drains and weight of the surgical laps), and the degree of bone resection. This was chosen as parameters for describing the magnitude of the surgical trauma. The degree of bone resection was classified as major, if resection was done below the lesser trochanter at the hip, above the femoral condyles at the knee, below the surgical neck of the proximal humerus, or above the condyles of the distal humerus. In addition, age, gender, ASA score[24] from the preoperative evaluation by the anesthesiologist, and data for estimating the Karnofsky performance score[25] were collected from the patient files.

We grouped the parameters as follows: blood loss above or below the median (938 mL), duration of surgery above or below the median (157 min), ASA scores were pooled into 2 groups (1 + 2 and 3 + 4), and age as described by Bauer and Wedin[26] (below/equal to or above 65 years of age). Karnofsky performance score[25] was grouped as above/equal to or below 70%. This grouping was selected because a Karnofsky score above/equal to 70% equals patients able to care for themselves in daily activities. Primary cancers were divided into 3 different

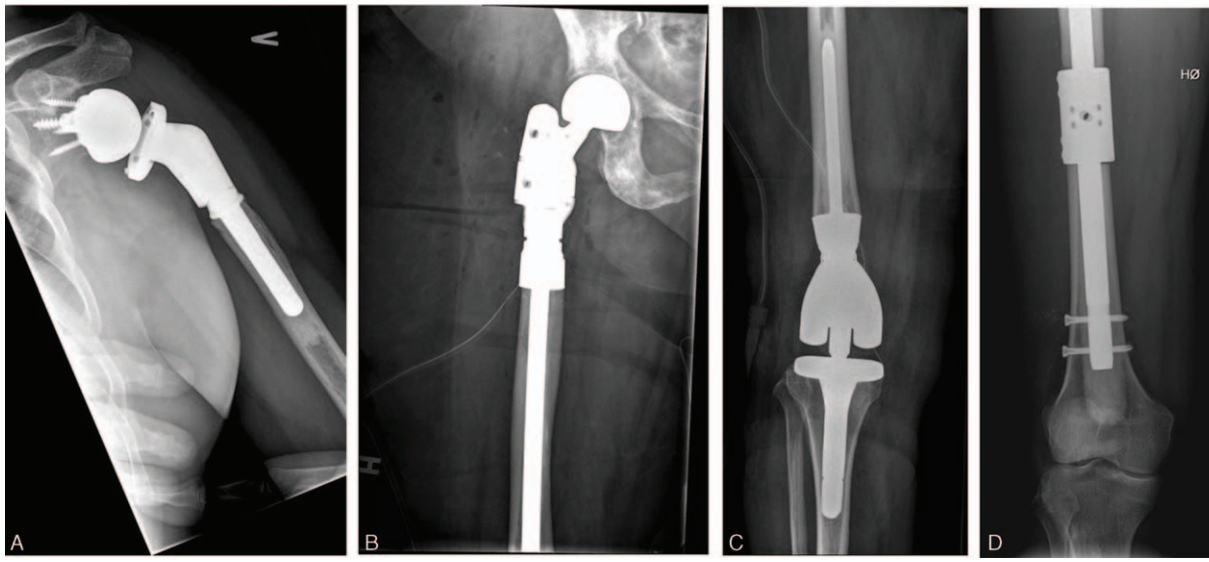

FIGURE 1. Examples of surgical implant used. (A) Proximal humerus resection and reconstruction with a tumor prosthesis (Mutars, Implantcast GmbH, Buxtehude, Germany) with a reverse shoulder joint. (B) Proximal femur resection and reconstruction with a tumor prosthesis (Segmental System, Zimmer, Warsaw, IN, USA). (C) Distal femur resection and reconstruction with a tumor prosthesis (Segmental System, Zimmer, Warsaw, IN, USA). (D) Resection of the femoral shaft and reconstruction with an intercalary spacer (Osteobridge, Merete Medical GmbH, Berlin, Germany).

TABLE 2. Type of Primary Cancer Type

	n
Slow growth	
Breast	78
Lymphoma	13
Myeloma	25
Moderate growth	
Kidney	34
Uterus	3
Prostate	27
Sarcoma	2
Fast growth	
Malignant melanoma	5
Cervix	1
Lung	39
Head and neck	4
Hepatocellular	2
Gastro intestinal	2
Pheochromocytoma	2
Colorectal	3
Bladder	7
Mediastinal	2
Angiosarcoma	2
Cancer of unknown primary site	19

Categorized into groups depending on growth rate of primary cancer. A modification of grouping proposed by Sørensen et al.[23]

prognostic groups as described by Sørensen et al[23] (Table 2). Two patients had surgery due an osteosarcoma metastasis (a primary cancer that was not described by Sørensen et al[23]) and they were grouped into the moderate growth group as proposed by Forsberg et al.[12]

Follow-Up

The follow-up on survival was until death or a minimum of 30 days postoperatively; no patients were excluded or lost to follow-up. Survival time data were collected from the Danish Civil Register on August 1, 2015 giving a complete follow-up.[27]

Statistics

Kaplan–Meier survival analysis was used for calculation of the 30-day overall survival presented with the 95% confidence interval (95% CI). Logistic regression with dichotomized variables was used, and a stepwise backward elimination multivariable logistic regression was used to identify independent risk factors for mortality, expressed as odds ratio (OR) with the 95% CI. P values < 0.05 were considered statistically significant. We used R[28] for the statistical calculations.

Ethics

The study was approved by the Danish Data Protection Agency and the Danish Health and Medicines Authority.

RESULTS

We found a 30-day overall survival of 88% (95% CI 84–92) (Figure 2). Unadjusted univariate logistic regression analyses showed a significant increased 30-day mortality with ASA score 3 + 4 (OR 4.16 [95% CI 1.80–10.85], $P = 0.002$) and Karnofsky performance status below 70 (OR 7.34 [95% CI 3.16–19.20], $P < 0.001$; Table 3). We found no significant association between age, gender, blood loss, duration of surgery, primary cancer type, or major bony resection and the 30-day mortality in the univariate analysis (Table 3). Duration of surgery seemed to influence mortality in the univariate analysis with an OR for prolonged duration of surgery (over 157 min) of 0.46 (95% CI 0.20–1.00); however, this was not statistically significant ($P = 0.057$).

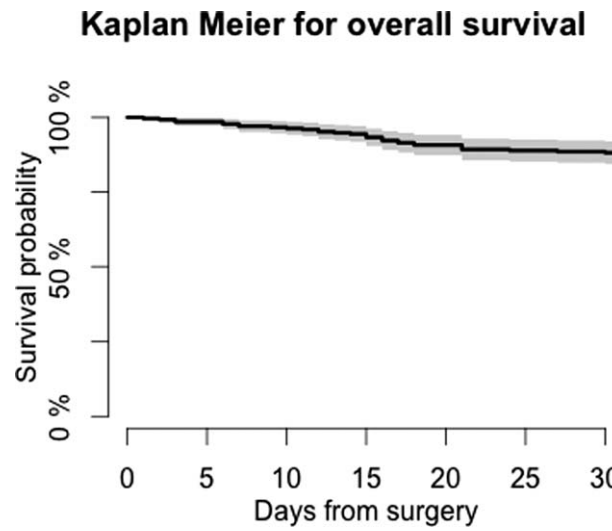

FIGURE 2. Kaplan–Meier survival curves. Thirty-day overall survival with 95% confidence interval.

The multivariable regression analysis showed that only high ASA score and low Karnofsky score was independent risk factors for 30-day mortality with an OR for ASA score of 2.83 (95% CI 1.69–7.61), $P = 0.027$ and for Karnofsky score 5.70 (95% CI 2.39–15.18), $P < 0.001$, respectively (Table 3).

Further evaluation of the distribution of the duration of surgery in relation to ASA score revealed that confounding of low ASA score patients to prolonged surgery was present in this study (Figure 3).

DISCUSSION

We know from the literature that in general some perioperative factors such as blood loss, duration of surgery, and comorbidity poses a risk for increased mortality when performing spinal surgery or joint replacement surgery.[14–22] However, whether the extent of surgery in patients treated for MBD in the appendicular skeleton poses a risk for early mortality remains unknown. We identified a statistically significant association between 30-day mortality and the general health status of the patients expressed as the ASA score and the Karnofsky score, but we failed to demonstrate an association with intraoperative variables such as blood loss, major bone resection, and duration of surgery. We therefore conclude that the extent of surgery does not influence a patient's risk of dying within the first 30 days after surgical treatment of MBD.

The present study has limitations. Although we aimed to include patients exposed to both small and extended surgery by including patients who had regular arthroplasties as well as larger tumor-prostheses and intercalary spacers inserted, we did not have any data from patients having their MBD treated with less invasive methods such as intramedullary nailing or plating. It is also possible that other intraoperative metrics not captured by this study could add prognostic information in this patient

TABLE 3. Regression Analysis

Logistic Regression Analysis (n = 248)	Univariate Analysis Odds Ratio (95% CI)	*P* Value	Multivariable Analysis Odds Ratio (95% CI)	*P* Value	Reference
Demographics					
Age at operation	1.87 (0.89–4.00)	0.100	n/s	n/s	<66 y
Gender	0.87 (0.41–1.86)	0.712	n/s	n/s	Male
Karnofsky group	7.34 (3.16–19.20)	<0.001*	5.7 (2.39–15.18)	<0.001*	≥70
ASA group	4.16 (1.80–10.85)	0.002*	2.83 (1.69–7.61)	0.027*	ASA group 1 + 2
Surgery characteristics					
Bone resection	0.72 (0.35–1.54)	0.399	n/s	n/s	No major bone resection
Duration of surgery	0.46 (0.20–1.00)	0.057	n/s	n/s	<157 min (median)
Blood loss	1.09 (0.49–2.44)	0.838	n/s	n/s	>938 mL (median)
Clinical					
Primary cancer					
Moderate growth cancer	0.53 (0.14–1.58)	0.282	n/s	n/s	Slow growth
Fast growth cancer	2.04 (0.91–4.67)	0.084	n/s	n/s	Slow growth

ASA = American Society of Anesthesiologist, CI = confidence interval, n/s = not significant.
*Statistically significant.

population. However, the authors find this unlikely since we attempted to capture the most objective and widely used variables, by including, for example, ASA score, primary tumor location, extent of bone resection, duration of surgery, and blood loss; each of which has been shown to be prognostic factors in other areas of orthopedic surgery.[1,9,11,15,17–22,24,29–38]

Of all variables collected, only ASA score and Karnofsky score were independently associated with 30-day mortality in the present study. Several studies have been published describing parameters that relates to peri or postoperative mortality in patients having surgery due to other pathologies than MBD. Only 1 study[32] has investigated if any perioperative variables were associated with early mortality after surgery due to MBD in the proximal femur and acetabulum. Quinn and Drenga[32] were not able to identify any association between early mortality and blood loss, duration of surgery, ASA score, type of implant, or extent of resection. However, they found a marginally significant association between the presence of a pathological fracture and early mortality with an OR 8.37 (95% CI 0.96–73.30). ASA score has been verified as a predictor for early mortality in the literature, when performing orthopedic procedures in the spine or joint replacement surgery[15,19,20,29,30,34,35] so it is plausible that the ASA score is of great importance, also when performing surgery due to MBD in the appendicular skeleton as shown in our study.

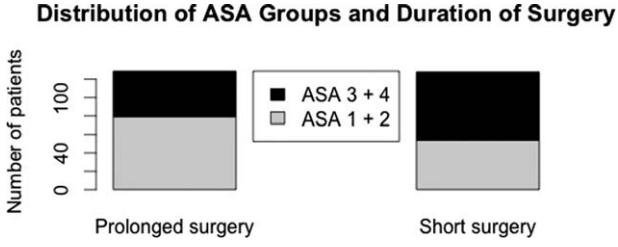

FIGURE 3. Histogram showing the distribution of ASA groups in patients with short and long surgery duration. This shows a selection of low ASA score patients to long surgical time. ASA = American Society of Anesthesiologist.

A study from the Institutional Joint Registry, Mayo Clinic, included a historical cohort of 12,727 patients undergoing surgery with total hip arthroplasty and 12,484 patients with total knee replacement.[31] They identified high ASA score (groups 3–4) and high Deyo-Charlson comorbidity index to be associated with increased 90-day mortality. Although this study only included patients suffering from a nonmalignant disease, we feel that similarities of the surgical procedures allow this study to be compared with our study to support the evidence that the general health status of the patient is the main risk factor for postoperative mortality. Wolters et al[29] found an association between increasing ASA score and increased risk of perioperative blood loss and duration of surgery, though these variables were not found to be independent predictors for postoperative mortality in our study.

Other studies have investigated if blood loss and duration of surgery pose a risk for postoperative mortality[15,33,38] and there seems to be lacking evidence as to whether or not these parameters are true predictors or just strongly related to the ASA score as indicated in 2 previously published studies.[17,18] The literature is contradictory when it comes to the relation between blood transfusions and postoperative mortality.[19,20,22] In our institution, the amount of blood loss is well documented with weighing of surgical laps and measurement of drains. Evidence of blood transfusions relation to postoperative mortality seems very weak. This might be due to the fact that using units of blood transfusion as exposure, 1 does not know whether 1 measures the effect a low preoperative hemoglobin level has on mortality, perioperative blood loss, or the true systemic reactions to transfusion and the relations to peri and postoperative morbidity as indicated by Glance et al.[21] In theory, tumors with known high blood supply (e.g., kidney tumors) might pose a risk of peri and postoperative mortality due to the risk of major bleeding. However, our study was not powered to detect such a relation with only 16 patients having kidney tumor as primary cancer (average bleeding 1712 mL;

range 250–7000 mL). With this in mind, the authors feel confident that perioperative blood loss within nonextreme bleeding situations does not pose a risk for increased postoperative mortality in patients having surgery due to MBD in the appendicular skeleton.

Prolonged surgery seemed, in the univariate analysis, to be a protective factor against high 30-day mortality rate. However, this is most likely to be the result of the bias introduced into the study by the institutional treatment philosophy: to reserve an extended surgical approach for those patients who are estimated to have a long postoperative survival. By extension, this indicates a propensity toward less invasive or palliative surgery in patients with high ASA scores, further emphasizing the importance of patient selection and survival estimates. We have shown an inverse relationship between ASA groups and duration of surgery, as shown in Figure 3, which supports this theory.

We did not find that the type of primary tumor poses a risk for 30-day mortality. Still, the authors expect that type of primary cancer poses a risk for mortality on a longer timeline. Our choice of 30-day mortality to measure early postoperative mortality was based upon the literature[15,19–21,38,39] but can be debated. Lie et al[36] propose the use of a 21-day postoperative period for measuring early postoperative mortality and argue that 60 to 90 days might be a wrong timeline. Timeline of 21- or 30-day did not make a difference in our study.

In conclusion, our findings showed that the surgical trauma does not pose an increased risk for death within the first 30 days postoperatively. Early mortality in patients undergoing joint replacement and intercalary replacement surgery for MBD is dependent on the general health status of the patients, as measured by the ASA score and Karnofsky performance score. The extent of surgery, measured as duration of surgery, blood loss, and extent of bone resection are not associated with 30-day mortality. We therefore advise that surgeons decide a surgical approach upon residual life expectancy and choose an implant that will outlive the patient, as opposed to fear that the extent of surgery and the surgical trauma poses a risk of increased mortality in this patient group. Nevertheless, further research is necessary to determine whether intraoperative or other variables are associated with very short postoperative survival in patients with MBD.

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PAPER IV

■ ONCOLOGY

Prediction of survival after surgery due to skeletal metastases in the extremities

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Aims

The purpose of this study was to develop a prognostic model for predicting survival of patients undergoing surgery owing to metastatic bone disease (MBD) in the appendicular skeleton.

Methods

We included a historical cohort of 130 consecutive patients (mean age 64 years, 30 to 85; 76 females/54 males) who underwent joint arthroplasty surgery (140 procedures) owing to MBD in the appendicular skeleton during the period between January 2003 and December 2008. Primary cancer, pre-operative haemoglobin, fracture *versus* impending fracture, Karnofsky score, visceral metastases, multiple bony metastases and American Society of Anaesthesiologist's score were included into a series of logistic regression models. The outcome was the survival status at three, six and 12 months respectively. Results were internally validated based on 1000 cross-validations and reported as time-dependent area under the receiver-operating characteristic curves (AUC) for predictions of outcome.

Results

The predictive scores obtained showed AUC values of 79.1% (95% confidence intervals (CI) 65.6 to 89.6), 80.9% (95% CI 70.3 to 90.84) and 85.1% (95% CI 73.5 to 93.9) at three, six and 12 months.

Discussion

In conclusion, we have presented and internally validated a model for predicting survival after surgery owing to MBD in the appendicular skeleton. The model is the first, to our knowledge, built solely on material from patients who only had surgery in the appendicular skeleton.

Take home message: Applying this prognostic model will help determine whether the patients' anticipated survival makes it reasonable to subject them to extensive reconstructive surgery for which there may be an extended period of rehabilitation.

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In treating metastatic bone disease (MBD) in the appendicular skeleton two problems have to be faced, firstly, whether surgery is the best solution and secondly, if surgery is indicated, how best to stabilise the affected bone in order to give the patient acceptable pain relief and the best quality of life.

In order to be able to answer these questions a pre-operative estimation of the survival of the individual patient is often warranted.

Predicting residual survival of the individual patient is important as various techniques for osteosynthesis seem to be less durable compared with prosthetic reconstruction. Osteosynthesis has a high failure rate, especially if the patients are surviving for a longer period after surgery.[1-3]

As treatment is palliative we must aim to provide the surgical solution that imposes the least surgical trauma but adequate the post-operative demands with sufficient durability of the implant inserted. Re-operation for implant failure decreases the quality of life for the patient.

The five-year relative survival of cancer patients is increasing.[4] In turn this means there is an increased risk of dissemination and thereby an increase in cancer-related complications such as MBD. However, it is uncertain

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how long can we expect these patients in need of surgical intervention to live.

Several attempts have been made to develop and describe survival of cancer patients after surgery owing to metastases in the appendicular skeleton.[2,5-13] Only one model for prediction of residual survival (based on a Bayesian Belief Network) has been externally validated,[6] and has demonstrated its worth in the clinical setting. Development of a prediction model for survival of the individual patient is profoundly different than identifying predictors for survival.[14] A prediction model combines multiple prognostic parameters, but the quality of the prediction model depends on how well the model performs in a population. The quality of a prediction model obviously depends on the quality of data on which it is based. Within the limitations of a single cohort the performance of the model can be tested with an internal validation approach. A useful criterion is the model's ability to discriminate and order individual patients correctly according to their survival chances.

To our knowledge no model for prediction of survival in patients having surgery owing to MBD in only the appendicular skeleton has been developed. The aim of this study was to develop a simple, practical model with good predictive capacity of survival for individual patients having surgery because of MBD in the appendicular skeleton using a historic cohort from our institution.

Patients and Methods

We included a historical cohort of 130 consecutive patients (mean age of 64 years, 30 to 85), 76 females/54 males) suffering from skeletal metastases (n = 114) or haematological disease (n = 16) who underwent 140 joint arthroplasties owing to MBD in the appendicular skeleton between January 2003 and December 2008, at our department. All patients had the diagnosis confirmed by histopathological analysis of the resected bone, and no patients were excluded in this study. A detailed description of the cohort (n = 130) regarding the surgery type, implants inserted, implant survival and surgical complications has previously been published.[15] A total of 105 hip, 16 shoulders, 14 distal femurs and five elbows were replaced. In all, 101 procedures were undertaken because of pathological fracture and 39 owing to impending fractures. No relation was found between joint replaced (upper extremity *vs* lower) and residual survival in multivariate analysis.[15]

Our department is a tertiary referral centre for musculoskeletal tumour surgery. It is our policy to prefer a joint arthroplasty, when treating appendicular metastatic lesions in proximity to a joint. When possible we do wide resections in the bone, thus anchoring the implant in healthy bone or protect the whole bone with a long stem in cases of wide-spread lesions within the affected bone. Survival status of every patient was extracted from the Danish Civil Registry on 29 March 2011. This resulted in complete follow-up of the population, owing to the completeness of the Danish Civil Registry.[16] In the event of multiple operations during the inclusion period, survival from the first operation until death or end of study was used in the prediction model.

Clinical variables included were primary cancer diagnosis and American Society of Anaesthesiologists score (ASA score).[17] Age was not included into the model, owing to the fact that it was not a parameter that had an impact on the surgeons' estimate for survival in clinical settings. Gender was also excluded as a variable, because of the close clinical relation to the type of primary cancer.

The primary cancer group was subdivided according to Katagiri et al[9,10] with the following adjustment: owing to lack of information about subtypes, lung cancer was grouped into the fast growing group, prostate cancer into the moderate and breast cancer into the slow growing group. This was decided after plotting Kaplan–Meier estimates, where we found good correlation between these primary cancer types and estimated survival. All metastases were diagnosed with histopathological examination, and if dedifferentiated carcinoma was found but no primary tumour could be identified after additional diagnostics, the bone metastases were considered to arise from an unknown type of primary cancer.

Biochemical variables included only haemoglobin measured in mmol/L. The dataset originally included C-reactive protein and sedimentation rate, but these variables were left out of the analysis because of a high proportion of missing data.

Assessment of visceral metastases status (liver, lung, cerebrum, adrenal glands) was based on the radiological assessment pre-operatively. If knowledge of visceral metastases was gained after surgery, it was the knowledge preoperatively that determined the status, with the aim of mimicking the actual parameters available at the time of decision-making before surgery in the clinical settings and minimise the risk of overestimating the number of patients with visceral metastasis at surgery time. The same approach was used in regards to number of bone metastases. We decided to subdivide into solitary or multiple metastases (pooling axial and appendicular metastases into the same group).

Fracture *versus* impending fracture status was based on radiological findings, where breakage of the cortex was the definition of fracture according to Mirels.[18]

We also included pre-operative Karnofsky score.[19,20] The Karnofsky score is a performance score often used by oncologists. It is scaled from 0% (dead) to 100% (completely healthy without any sign of illness).

The choice of timeframe with risk of death at three, six and 12 months was based on clinicians' reflections in the pre-operative planning phase, where especially three and 12 month survival is widely accepted as critical time points for discriminating between surgical treatment options.[7-11] In patients with very short survival expectancy (under three months) the rehabilitation period might be longer than the expected residual survival and non-surgical management

Table I. Type of primary cancer type categorised into groups depending on growth rate of primary cancer. A modification of grouping proposed by Katagiri et al[9,10] (n = 121)

Growth rate of primary cancer	Type of primary cancer
Slow growth	Breast (n = 28)
	Lymphoma (n = 4)
	Myeloma (n = 10)
Moderate growth	Kidney (n = 15)
	Uterus (n = 4)
	Prostate (n = 15)
Fast growth	Malignant melanoma (n = 4)
	Cervix (n = 1)
	Lung (n = 18)
	Head and neck (n =1)
	Mediastinal (n = 2)
	Hepatocellulaer (n = 2)
	Gastro intestinal (n = 1)
	Faeocomatoma (n = 1)
	Colon cancer (n = 1)
	Bladder (n = 4)
	Angiosarcoma (n = 1)
	Cancer of unkown primary site (n = 9)

(especially with impending fractures of the upper extremities) might be in the best interest of the patient.

Estimation of survival within six or 12 months will give a surgeon a tool for selecting patients expected to live for a longer period, and therefore might be eligible for prosthetic implantation. As previously stated, a prosthesis is more likely to outlive the patient, compared with an osteosythetic device[1-3] if residual life expectancy is long. Also, if the patient is more likely to live less than six months, the rehabilitation period, if treated with a prosthesis, might be too long for the patient to gain acceptable quality of life in the residual survival time.

Ethics. The study was approved by the Danish Data Protection Agency (no. 2008-41-2819) and the Danish Health and Medicine Authority (no. 7-505-29-1642/1). The study was evaluated by the Regional Scientific Ethical Committee of the Capital Region of Denmark (no. H-3-2010-130) and it was not considered to be a notifiable study.

Statistical analysis. All patients were followed regarding survival status for a minimum of two years or until death. Kaplan–Meier curves with 95% confidence intervals (CI) were used to describe long-term survival. Multiple logistic regression was used to describe the associations between risk factors and vital status (alive/dead) at three, six and 12 months, respectively. The following variables were used as predictors: haemoglobin (mmol/L) (continuous variable), visceral metastases (yes/no), multiple bone metastases (yes/no), fracture status (impending fracture/fracture), Karnofsky score (< 70% *vs* ≥ 70%), ASA score (1 to 2/3 to 4) and primary cancer grouped according to Katagiri et al[9,10] (slow growth/moderate growth/rapid growth) (Table I). The statistical analysis included data of 121 patients. Data of nine patients were removed owing to missing predictor values.

The models were internally validated based on 1000 cross validations.[21] Briefly, this was done as follows: in each step the logistic regression model was fitted in a bootstrap sample (n = 121) obtained by drawing with replacement from the data of the 121 patients. The risk of death was predicted based on the patients who were not drawn into the respective bootstrap sample. Reported were mean areas under the receiver operating characteristic curves (AUC) with corresponding 2.5% and 97.5% quantiles of the 1000 cross validations. At three months (same for six and 12 months) AUC is the probability that in a randomly selected pair of patients the model predicts lower three months survival chances to the patient who did not survive the first three months post-operatively. Nomograms were obtained to illustrate the risk scores at three, six and 12 months. The level of significance was set at 5%. All analyses were carried out using software R (R Foundation, Vienna, Austria).

Results

The probability of overall survival was 66.9% (95% CI 58.6 to 75.3), 49.6% (95% CI 40.7 to 58.5) and 38.0% (95% CI 29.4 to 46.7), respectively at three, six and 12 months after surgery. Median overall survival time was 180 days (95% CI 144 to 294) (Fig. 1). The overall survival curves in the three prognostic subgroups of cancer growth are shown in Figure 2. We notice that the CI of the three groups intersect, but they seem to be a trend of different survival between the three groups.

The multiple logistic regression analyses showed that primary cancer type, Karnofsky score at least 70, haemoglobin pre-operatively and presence of visceral metastases had a strong influence on the risk of death at three, six and 12 months (Table II).

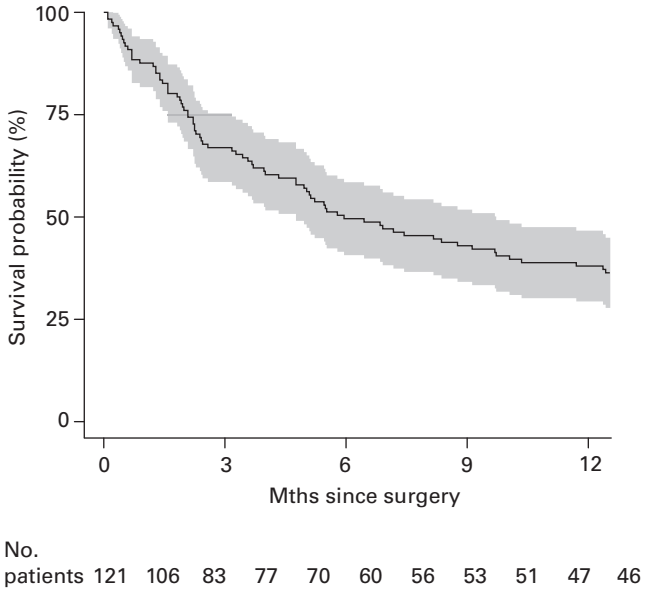

Fig. 1

Kaplan–Meier estimate with 95% confidence intervals of overall all-cause mortality for the population included in the model (patients n = 121).

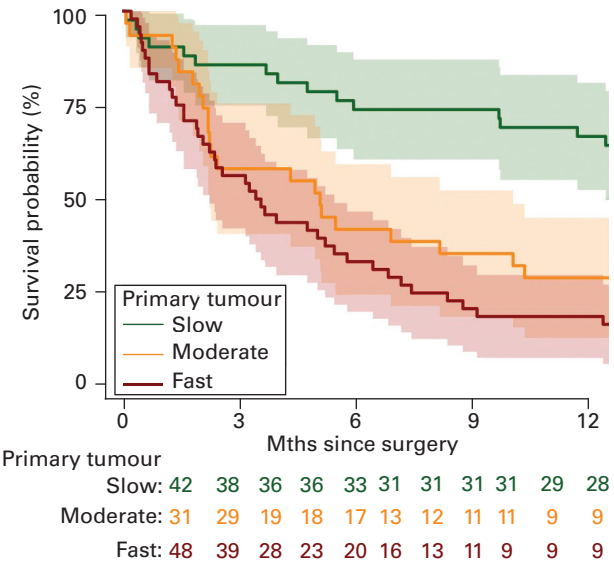

Fig. 2

Kaplan–Meier estimate with 95% confidence interval of survival for the three growth groups of primary cancer type.

Table II. Multiple regression analysis of all parameters included as predictors for survival

Multiple regression (n = 121)	3 month survival OR (95% CI)	p-value	6 month survival OR (95% CI)	p-value	12 month survival OR (95% CI)	p-value	Reference
Variables							
Primary cancer							Slow growing cancer
Moderate growing cancer	5.94 (1.56 to 25.73)	0.012	5.76 (1.63 to 22.89)	0.009	8.80 (2.10 to 45.09)	0.005	Slow growing cancer
Fast growing cancer	4.66 (1.35 to 18.01)	0.019	7.36 (2.27 to 26.70)	0.001	12.71 (3.36 to 57.49)	< 0.001	Slow growing cancer
Fracture	1.32 (0.44 to 4.12)	0.624	1.90 (0.69 to 5.41)	0.219	0.80 (0.24 to 2.55)	0.707	Impending fracture
Haemoglobin (mM)	0.39 (0.20 to 0.70)	0.624	0.53 (0.30 to 0.90)	0.022	0.49 (0.25 to 0.89)	0.024	Continuous varibles
Visceral metastases	3.69 (1.40 to 10.48)	0.010	3.55 (1.37 to 9.81)	0.011	5.17 (1.73 to 17.60)	0.005	None
Multiple bone metastases	1.98 (0.60 to 7.04)	0.270	2.24 (0.73 to 7.17)	0.164	3.06 (0.87 to 11.42)	0.086	None
ASA group	2.57 (0.96 to 7.09)	0.061	3.19 (1.22 to 8.71)	0.020	4.15 (1.35 to 14.33)	0.017	ASA 1 + 2
Karnofsky score	0.23 (0.08 to 0.62)	0.005	0.25 (0.09 to 0.65)	0.006	0.18 (0.05 to 0.56)	0.004	< 70

OR, odds ratio; CI, confidence interval; ASA, American Society of Anesthesiologists

Figures 3 to 5 show the nomograms for chance of survival within three, six and 12 months, respectively. For every predictor variable the surgeon reads off the corresponding points and calculates the sum score. The scales at the bottom of the nomogram can then be used to translate the sum score into the predicted risk of death at the respective time point.

The accuracy of the nomogram in predicting risk of death after surgery at the three time points were determined as AUC (mean and CI based on 1000 cross validations) 79.1% (95% CI 65.6 to 89.6), 80.9% (95% CI 70.3 to 90.8) and 85.1% (95% CI 73.5 to 94.0) at three, six and 12 months, respectively (Fig. 6).

Discussion

Deciding on which parameters to include into a prediction model for survival in this patient group has shown to be difficult, as many predictors for survival have previously been identified and published.[5-13,22]

In summary authors seems to agree that primary cancer type, presence of multiple bone metastases and visceral metastases are of interest. Forsberg et al[7] included biochemical parameters, and also Katagiri et al[10] pooled abnormal biochemical parameters in his prediction model, but in contrast with Forsberg et al,[7] Katagiri et al[10]did not include pre-operative haemoglobin. Hansen et al[8] found haemoglobin to be an independent predictor for survival in a

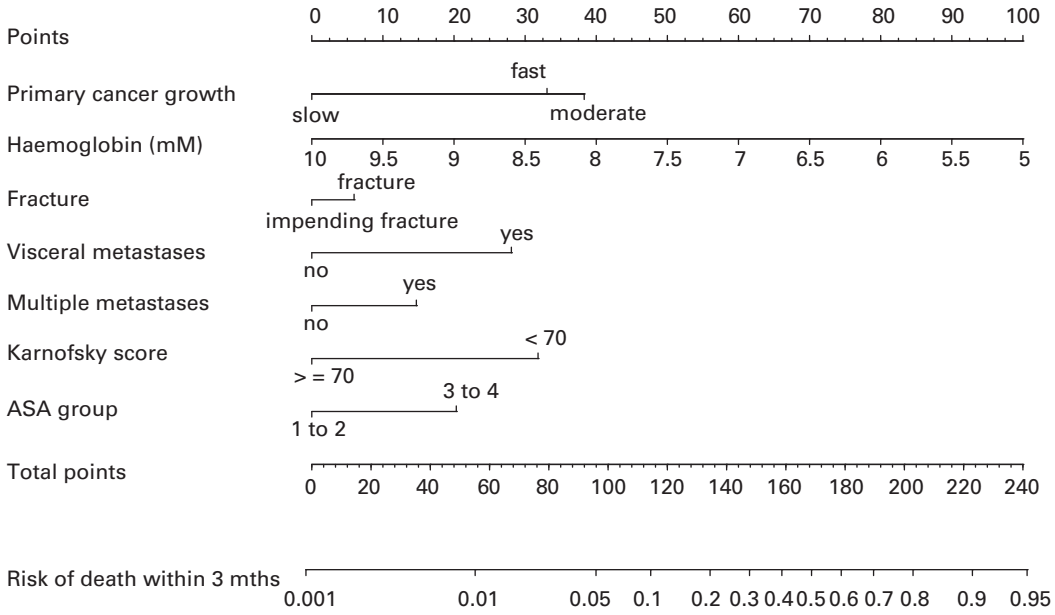

Fig. 3

Nomogram for prediction of survival at three months after surgery. ASA, American Society of Anesthesiologists.

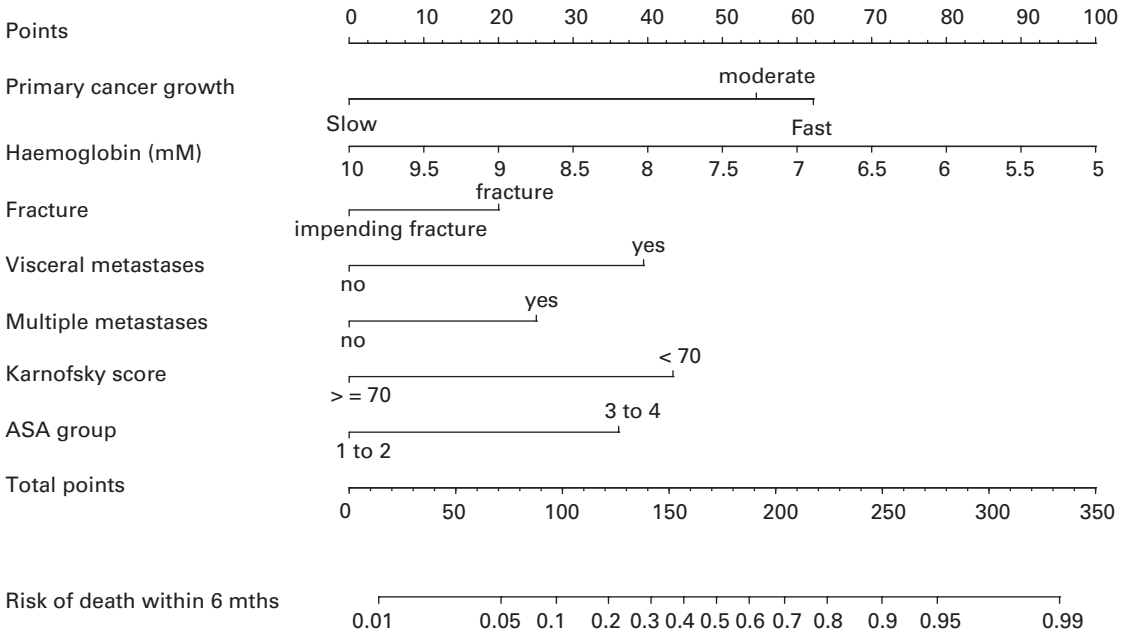

Fig. 4

Nomogram for prediction of survival at six months after surgery. ASA, American Society of Anesthesiologists.

multivariate analysis. Katagiri et al[10] and Ratasvuori et al[11] did not include haemoglobin in their analysis, in contrast, Bauer and Wedin[13] and Hansen et al[8] identified pathological fracture as an independent risk factor for survival compared with impending fracture.

All mentioned studies,[7,8,10,11] except Bauer and Wedin,[13] investigated the influence of performance status (measured either as Karnofsky performance score[20] or Eastern Cooperative Oncology Group (ECOG) performance status[23]) on post-operative mortality. Forsberg et al,[7] Nathan et al,[12] Ratasvouri et al[11] and Katagiri et al[10] either found the performance status to be an independent predictor for survival or included it into their prediction of survival model. However, Hansen et al[8] were not able to identify the performance status as a prognostic factor for survival.

These contradictory findings of predictors for survival for this patient group might be owing to the heterogeneity in patients having surgery because of MBD in the appendic-

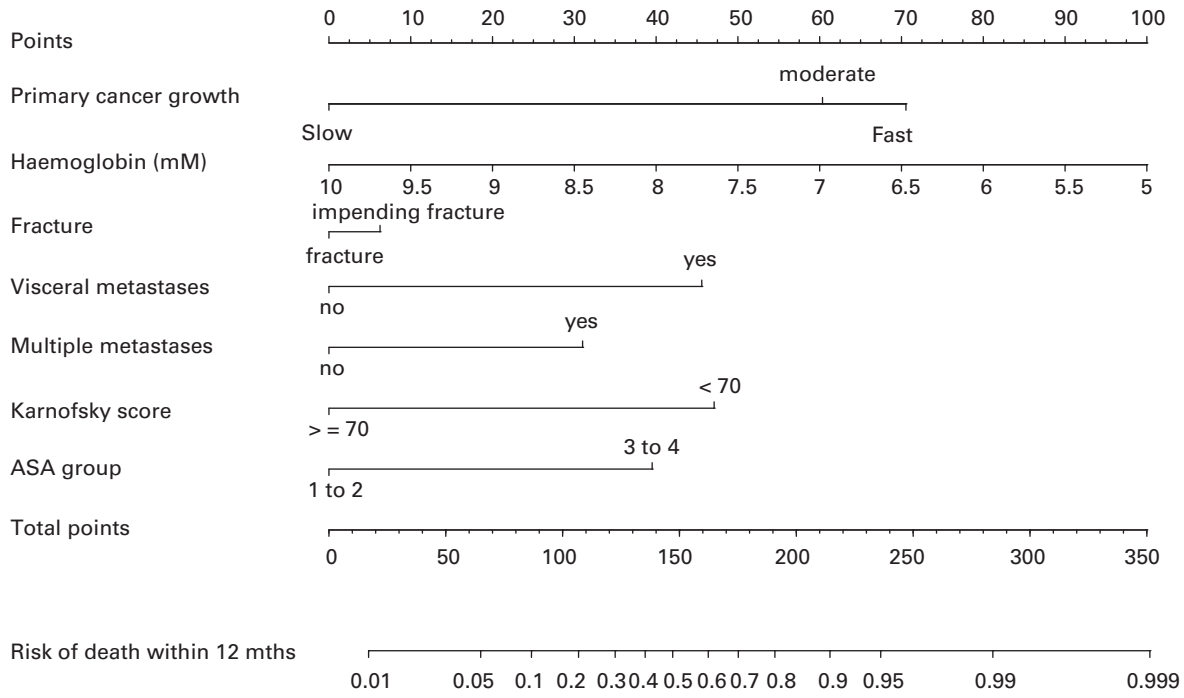

Fig. 5

Nomogram for prediction of survival at 12 months after surgery. ASA, American Society of Anesthesiologists.

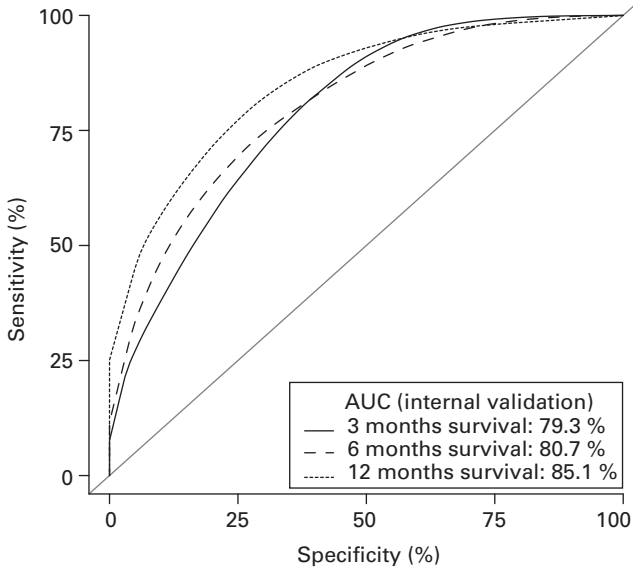

Fig. 6

Receiver-operator characteristic curve analysis giving an area under the curve (AUC) for predicting survival after surgery owing to metastatic bone disease in the appendicular skeleton at three, six and 12 months.

ular skeleton. This is partly because a great variety of primary cancers are found in this population, and no reference standard exists for grouping the primary types of cancer with regards to survival prognosis at the time of surgical treatment of MBD in the appendicular skeleton. We have chosen a revised graduation according to Katagiri et al[9,10] based on its previous use in prediction models proposed by Forsberg et al.[7] A limitation to this grouping is that it was developed on a population of 350 subjects that consists of 71% patients not having surgery at all, and 11% having surgery owing to axial metastases, thus, leaving only 18% with surgery because of skeletal metastases in the appendicular skeleton.[9] We have chosen to include parameters in our prediction model that are easily accessible in the daily clinical work and reflect what a clinician already considers preoperatively.

Four prediction models have been proposed earlier for related cohorts. Nathan et al[12] proposed a model for predicting survival in patients having surgery owing to MBD (18% because of axial lesions) based on 191 patients prospectively registered into a database at Memorial Sloan-Kettering Cancer Centre during the period 22 September 1999 to 13 March 2003. A logistic regression model for prediction of survival was based on six parameters (primary cancer, haemoglobin, ECOG performance status, number of bone metastases, presence of visceral metastases and surgeons' estimate of survival), chosen for their independent significance in prediction of survival in a Cox-regression analysis. Internal analysis showed that this prediction system was able to predict the minimal survival time for 61% of the patients.

Forsberg et al[7] extended Nathan et al's[12] model by including more predictor variables and was able to show AUC of 84% (95% CI 77 to 90) at three months survival and 83% (95% CI 78 to 89) using a logistic regression model including 14 variables (age, gender, primary cancer (based on modified Katagiri growth group), number of bone metastases, visceral metastases, fracture/impending fracture, ECOG performance status, lymph node metasta-

ses, albumin level, absolute lymphocyte count, calcium, glomerular filtration rate, haemoglobin and surgeons' estimate of survival).

It is difficult to discuss the use of other published models[9-11] for predicting survival in patients having surgery because of MBD, since none other than the mentioned studies (to our knowledge) have been validated, and therefore the quality and performance of these models are unknown.

Colleagues who treat axial metastasis routinely use survival prediction models as part of their pre-operative planning and in making a decision regarding surgical treatment *versus* conservative treatment of spinal cord compression[24] with the use of Tomita and Tokuhashi scores,[25,26] and our research group is confident that this also could become a routine part of pre-operative planning when treating MBD in the appendicular skeleton.

We have selected predictor variables based on clinical knowledge and results of previous studies and grouped according to clinical reference intervals. This was primarily done to stabilise the results and hence to increase their generalisability to future patients. Another criterion for selecting predictor values was that they had to be accessible from patient records. In Denmark, treatment of MBD in the appendicular skeleton is not allocated exclusively to highly specialised treatment centres, and therefore including parameters that depend on highly specialised trained personnel (e.g. surgeons' estimate of patient survival) is not suitable for our country.

In conclusion, we have created a model for predicting survival in patients having surgery because of MBD in the appendicular skeleton that seems easy to use in clinical settings and performs well in an internal validation model. Our model is based solely on patients having surgery owing to MDB in the appendicular skeleton. This might make it more robust in predicting survival compared with existing prediction models, which are developed on a mixture of patients having surgery in both the axial and appendicular skeleton. On the other hand patients treated with osteosynthesis are not included into our model, and it might not be usable for this population. Our model should be validated with external data to prove this. Also, a larger prospective study would be desirable to improve our model and preferably a population consisting of MBD patients undergoing all possible types of surgery including osteosynthesis in order to reduce selection bias.

Author contributions:

M. S. Sørensen: Lead contributor in manuscript development, study design, data collection, data analysis and data interpretation.
T. A. Gerds: Statistical analysis, data interpretation and manuscript revision.
K Hindsø: Contributor to study design and data interpretation and manuscript revision.
M. M. Petersen: Senior advisor for the project, initiator for study and hereby: contributor to study design, supervision for data collection, data analysis, data interpretation and revision of manuscript.

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PAPER V

External validation and optimization of the SPRING model: a model for prediction of patient survival after surgical treatment of bone metastases of the extremities.

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Publication

Manuscript ready for publication

Abstract

Background

Prediction of survival prior to surgery for metastatic bone disease in the extremities (MBDex) based on statistical models and data of previous patients is important in the attempt to choose an implant that will outlive the patient. However, maintaining and updating the patient database and the prediction models is necessary. The 2008-SPRING model (Sørensen, PeteRsen, hINdsø, Gerds) presented in 2016 enables the clinician to predict expected survival prior to surgery for MBDex.

Questions / Purposes

1. Update the 2008-SPRING model for prediction of survival prior to surgery for MBDex with more modern cohort
2. Evaluate the performance of the updated SPRING model in a population based cohort of patients having surgery for MBDex

Methods

The 2008-SPRING model was updated by adding data from patients having surgery between 2009-2013 at a tertiary referral center. This yielded the 2013-SPRING model based on 270 patients. We externally validated the 2008-SPRING and the 2013-SPRING models on a prospective cohort (n=164) which included 162 patients with complete data who underwent stabilization for MBDex in the period May 2014 to May 2016 identified from a cross section of the Danish population. No patients were lost to follow-up. Variables in the model included hemoglobin, complete fracture contra impending lesion, visceral metastasis, multiple bone metastasis, Karnofsky Performance Score (KPS) (≥70 or <70) and American Society of Anesthesiologists score (ASA) (1 + 2 or 3 + 4). Primary cancer was categorized in slow, moderate and fast-growing cancer types depending on observed survival as described by Sørensen et al. with the alteration of adding “other cancers” to the fast-growing group and hereby enable clinicians to score cancers that rarely present with bone metastasis.

We performed AUC ROC (area under receiver operator characteristic curve) analysis, Brier score and calibrations plots 3, 6 and 12 months after stabilization to evaluate the SPRING model's predictive performance in the external validation data.

Results

The 2013-SPRING model showed significantly better performance compared to the 2008-SPRING model ($p<0.05$). AUC ROC of the 2013-SPRING model was 82% (C.I.: 76% - 89%), 85% (C.I.: 78% - 91%) and 86% (C.I.: 80% - 91%) for prediction of survival at 3, 6 and 12 months respectively. For the Brier score, the prediction of survival was 0.155 (95% CI, 0.121–0.188) at 3 months, 0.162 (95% CI, 0.127–0.198) at 6 months, and 0.152 (95% CI, 0.117–0.187) at 12 months.

Conclusions

We were able to improve the SPRING model for prediction of survival prior to surgery for MBDex, and external validation showed better performance for survival prediction for the 2013 model than the 2008.

Level of Evidence:

Level I diagnostic study

Introduction

Estimating survival after surgical treatment of metastatic bone disease in the extremities (MBDex) is a corner stone in orthopedic oncology. It is well established that the main goal is that patients should outlive their implant and that patients with long expected survival after surgery need more durable implants like e.g. tumor prostheses to minimize the risk of implant failure [5, 11, 18].

A survey investigating Musculoskeletal Tumor Society Members[20] reviled that 6 months postoperative survival was considered an indication for using of a more durable implant in treatment of metastatic bone disease of the proximal femur. If patients are expected to live more or less one should evaluate the gain of fast recovery and risk of implant failure for the individual patients. On the other hand a study showed that a metastatic lesion cannot be expected to heal, even under treatment with radiotherapy and chemotherapy within the first 6 months after surgery [7].

With this in mind, surgeons need to evaluate if a MBDex lesion should be resected, and the bone reconstructed with an artificial joint or a tumor-prosthesis as part of a palliative pain control in patients with shorter life expectancy than 6 months or they should simply just stabilize the lesion. Considering this, a model for prediction of survival should, preferably, be able to estimate survival for multiple endpoints and not just 6 months.

Surgeon's subjective estimate of residual live expectancy have a tendency to be overly optimistic [9]. This strengthens the importance of a clinical tool to predict life expectancy after surgery for MBDex.

Chen et al.[3] found small amounts of morden data to be more effective than large amounts of "old" data when producing prediction models for various clinical outcomes. We proposed the 2008-SPRING (Sørensen, PeteRsen, hINdsø, Gerds) model [19] for prediction of survival prior to surgery for MBDex in 2016, and we find it important to improve and test the model for its performance as a clinical tool when treating MBDex. We wanted to improve the model with

more modern data added to the population the model initially was built on. The purpose of this study was therefore:

1. Update the 2008-SPRING model for prediction of survival prior to surgery for MBDex with a more modern cohort
2. Evaluate the performance of the updated SPRING model in a population based cohort of patients having surgery for MBDex

Methods and material

The SPRING model

Proposed by this research group in 2016 [19], the 2008-SPRING model predicts survival 3, 6, and 12 months after surgery for metastatic bone disease in the extremities. We used a logistic regression model to build the model with data from a cohort of 130 patients who had joint replacement surgery from 2003 to 2008 (patients who is included in the early cohort of the COBOM database[10]). We presented the model as a nomogram.

Experimental Overview

Initially the statistical analysis forming the 2008-SPRING model was run using the early cohort of the COBOM database. In current study, we combined the early and late cohort of the COBOM database (n=270) to produce the nomograms that forms the 2013-model for prediction of survival after surgery for metastatic lesions in the extremities. The 2013-SPRING's performance was tested in an independent external cohort (called the validation cohort), see Fig. 1.

Before study initiation, we obtained ethical approval from the regional ethic committee (ID.nb.: H-4-2014-005) and institutional data protection agency (ID.nb.: 30-1222).

Training Cohort (COBOM cohort)

The COBOM cohort[10] is an institutional database containing prospectively collected data of patients having bone resection and reconstruction for metastatic bone disease of the extremities at the Musculoskeletal Tumor Section, Rigshospitalet. The cohort consists of an early treatment period (prior to electronic patient record, 2003-2008) and a late (after implementation of electronic patient records, 2009-2013).

Institutional policy is bone resection and reconstruction using endoprosthesis/tumor prosthesis or intercalary spacers after multidisciplinary evaluation and only rarely internal fixation method is used (as we find a high failure rate due to implant wear out). It was chosen not to include patients treated for metastatic lesion using internal fixation method as consecutive registration of these patients has not been kept, and including them would increase the risk of selection bias of patients who were treated due to failed devices (selection of long term survivors).

In general, patients are found candidate for surgical treatment in case of pathological fracture, impending fracture or intractable painful lesions that cannot be managed by palliative matters (medication or radiation).

Validation Cohort

The goal of this prospective, population-based cohort study[22] was to identify the incidence and epidemiological composition of patients undergoing surgical intervention for metastatic bone disease in the extremities. The study identified 175 lesions treated in 164 patients from May 19, 2014 to May 18, 2016 at one of six centers in the Capital Region of Denmark. This region is a representable cross section of the Danish population. Due to government paid health care setting, all patient treated for metastatic bone disease will be treated at one of these six centers, and therefor no patient is lost to inclusion. All surgical treatment modality was used on the cohort, and the study was purely observational and therefor no influence on treatment was present. In the validation cohort, 162 participants had a complete dataset and were included in further analysis (as no imputation of missing data was performed, patients with missing data was excluded from analysis).

Follow-up

All patients had 12 months follow up and none was lost to follow-up due to the Danish Civil Registration System[18]. No patients died from other reasons than the primary malignancy ensuring no competing risk. In the training cohort 150 patients (out of 270, 56%) and in the validation cohort 97 patients (out of 164, 59%)) succumbed to disease within one year after surgery.

Variables:

Variables included in the 2013-SPRING model did not differ from the original 2008-SPRING model and included: Hemoglobin, impending/or complete fracture of lesion, visceral metastases (if no preoperative scans were performed, status of surveillance scans performed up to three months postoperatively was considered as baseline scans), multiple bone metastases (same approach as visceral metastasis), Karnofsky Performance Score (KPS) (≥70 or <70) and American Society of Anesthesiologists score (ASA) (1 + 2 or 3 + 4). Primary cancer was categorized in slow, moderate and fast-growing types depending on observed survival as described by Sørensen et al. [19] with the correction of adding the "other cancers" to the fast-growing type enabling clinicians to score cancers that rarely presents with bone metastasis (see table 1). For description of baseline variables for the validation and training cohort see table 2.

Statistics:

The survival chances were predicted for individual patients at 3, 6 and 12 months after surgery using separate logistic regression models for the three prediction horizons. All models included the following predictors: location of primary cancer, pre-operative hemoglobin, fracture versus impending fracture, Karnofsky score, visceral metastases, multiple bony metastases and ASA score. The models were presented as nomograms. We evaluated the predictive performance of the models in the validation cohort using Brier score[2], area under curves (AUC) of receiver operating characteristic (ROC) curves and calibration plots.

The Brier score is the quadratic distance between the predicted survival probability (a value between 0 and 1) and the vital status at the prediction horizon (0 when the patient has died and 1 when the patient has survived). Reported is the average Brier score in the validation cohort, the lower the better. The AUC ROC is the probability that a randomly chosen patient who died before the prediction horizon has received a lower survival chance by SPRING model than a randomly chosen patient who survived until the prediction horizon. Furthermore, we present calibration plots. No imputation of missing data was performed.

The level of statistical significance was set at 95%.

Results

The model was successfully updated using all data from 2003-2013 (training cohort) and presented in nomograms for the three predictions horizons (survival 3, 6 and 12 months after surgery yes/no) in figure 2 a-c. In the training cohort, all variables showed statistically significant associations with the odds of survival at all three endpoints except for moderate growing cancer group (p=0.118), multiple bone metastasis (p=0.099) and ASA (p=0.057) at the 3-month endpoint. Fracture was not significantly associated with changes in odds of survival outcome at any endpoint (3 months p=0.354, 6 months p=0.203 and 12 months p=0.313). OR for survival status at 3 months was highest for presence of visceral metastasis OR 3.10 (C.I.: 1.62-5.93, p<0.001) followed by fast growing cancer OR 2.75 (C.I.: 1.26-6.03, p<0.001). At 6 months fast growing cancer had the highest OR (7.01 (C.I.: 3.18-15.46, p<0.001)) followed by presence of visceral metastasis (OR 2.40 (C.I.: 1.27-4.56, p=0.007)). At 12 months, fast growing cancer and presence of visceral metastasis has likewise the highest OR with OR of 9.93 (C.I.: 4.29-22.98, p<0.001) and 2.47 (C.I.: 1.26-4.86, p=0.008) respectively. See table 3 for full regression analysis.

The training cohort was compared to the validation cohort and no difference in distribution of variables was observed (see table 2).

AUC ROC in the external validation was 82% (C.I.: 76% - 89%), 85% (C.I.: 78% - 91%) and 86% (C.I.: 80% - 91%) for prediction of survival at 3, 6 and 12 months respectively (see figure 3). The accuracy estimated by Brier score was 0.155 (95% CI, 0.121–0.188), 0.162 (95% CI, 0.127–0.198), and 0.152 (95% CI, 0.117–0.187) for prediction of survival at 3, 6, and 12 months, respectively. The null model (prediction of prevalence of mortality between the cohort without using the variables, the so-called “insanity test”) yielded a Brier score of 0.220 (95% CI, 0.195–0.245) at 3 months, 0.246 (95% CI, 0.237–0.256) at 6 months, and 0.240 (95% CI, 0.225–0.255) at 12 months, resulting in p values of < 0.001 at all three endpoints.

In comparison, the 2008-SPRING model preformed an AUC ROC of 79% (C.I.: 70% - 88%), 82 % (C.I.: 74%-91%) and 85% (C.I.: 76% - 94%) at 3, 6 and 12 months in external validation using the

same validation cohort and a Brier score of 0.17 (C.I.: 0.14-0.21), 0.19 (C.I.: 0.15-0.24) and 0.17 (C.I.: 0.12-0.19), respectively. Comparison of AUC ROC and Brier score between the 2008-SPRING model and 2013-SPRING model showed better performance at all three endpoints (all $p < 0.05$).

The model seemed well calibrated at all three endpoints (figure 4)

Discussion

Prediction of survival in patients undergoing surgery for MBDex is important in an attempt to provide a surgical treatment that will outlive the patient.

As Chen and Asch [4] underline; even with the knowledge that a clinician tends to overestimate residual survival by a factor 3 the combination of clinical prediction model and the "best human "hardware" will outperform either of these two scenarios if they were to stand alone. This taken into consideration authors are also obliged to constantly update and improve such models for predictions [3]. As such, we successfully updated our SPRING model for prediction of survival in patients having surgery for MBDex with a more modern cohort and found that the 2013-SPRING model performance in an external cohort was sufficient to use in clinical setting at all three endpoints (survival 3, 6 and 12 months after surgery) and better than the 2008-model.

Limitations in the present study are limited as all three cohorts were consecutively enrolled into the study and validation was performed on a population based prospective cohort. The SPRING model is, however, been built on a cohort solely from a Scandinavian population and as such discrepancies in indication for surgical treatment of MBDex throughout the world may not be captured by this study and validation of the 2013-SPRING model is pending in a non-Scandinavian population.

Previously several risk factors for survival in patients having surgery for MBDex have been identified. In coherence to literature our study showed no statistical significant influence of complete fracture compared to impending [12-14, 16] on survival at any endpoint. Fracture

does, however, seem to influence residual survival in data from randomized controlled trials of Zoledronic acid [22]. We therefore still advocate that this variable should be taken into consideration when estimating residual life expectancy in MBDex patients.

We choose to include performance status into our prediction model both measured as ASA-score and KPS. We feel that the two variables capture different aspects of performance. The ASA-score is evaluated by the anesthesiologist preoperatively, and the score is strongly influenced by comorbidity and the anesthesiologists subjective evaluation of risk of death [1], whereas the KPS evaluates a patients ability to care for himself. The KPS is comparable to the Eastern Cooperative Oncology Group ECOG [15]. ECOG level has previously been shown to be predictive for residual survival after surgery for metastatic bone disease [13, 14, 16]. The present study indicates that both performance systems are important factors for predicting survival in MBDex patients although KPS seems to outperform in short term survival. Lastly, we chose to include hemoglobin as a continuous factor rather than dichotomized [6, 8, 12, 14]. This seemed relevant, as no consensus of a clinical relevant cut has been established. Also, dichotomizing a variable can result in loss of power and residual confounding of outcome [17].

Our analysis showed improvement of the SPRING model after refitting the model with a more modern cohort from 2009-2013 added to the original cohort from 2003-2008. This is expected, as it has been established that a more modern material will outperform a large quantity in model performance as shown by Chen et al. [3]. This could explain why the 2013-SPRING model seems to outperform other prediction models for survival built on large data sets. Another explanation is that other models tends to be built on populations identified from billing codes and as such is inherent to selection bias whereas our cohort is consecutive.

Conclusion:

In conclusion, we were able to update and optimize the SPRING model for prediction of survival in patients having surgery for MBDex and hereby provide the clinician with an improved tool to assist in the decision making of a surgical approached that will outlive the patient and provide the best quality of life in their residual life. Also, the SPRING model was found to be suitable to

use in an unrelated Scandinavian population for prediction of survival outcome prior to surgery for MBDex.

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Figures

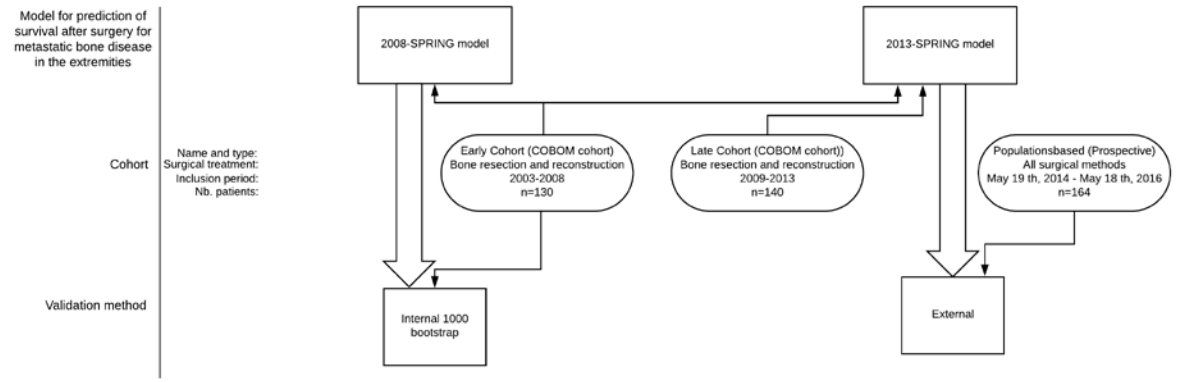

Figure 1: Experimental overview illustrating cohorts used to develop and validate the 2008 and 2013-SPRING model for prediction of survival after surgery for MBDex.

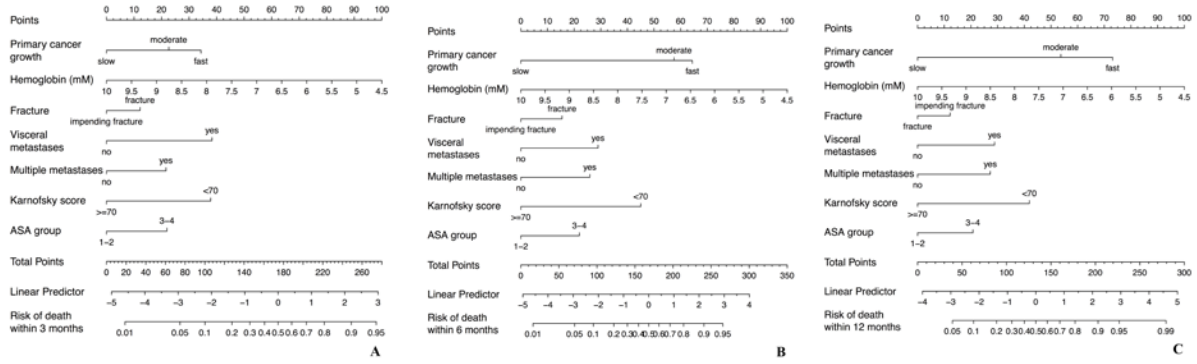

Figure 2A-C: Figure showing the nomograms for prediction of survival 3 (A), 6 (B) and 12 (C) months after surgery for MBDex. A patient is scored preoperatively on all variables. The sum of variables correlates with the risk of death at the specific nomograms endpoint (3, 6 or 12 months postoperatively.

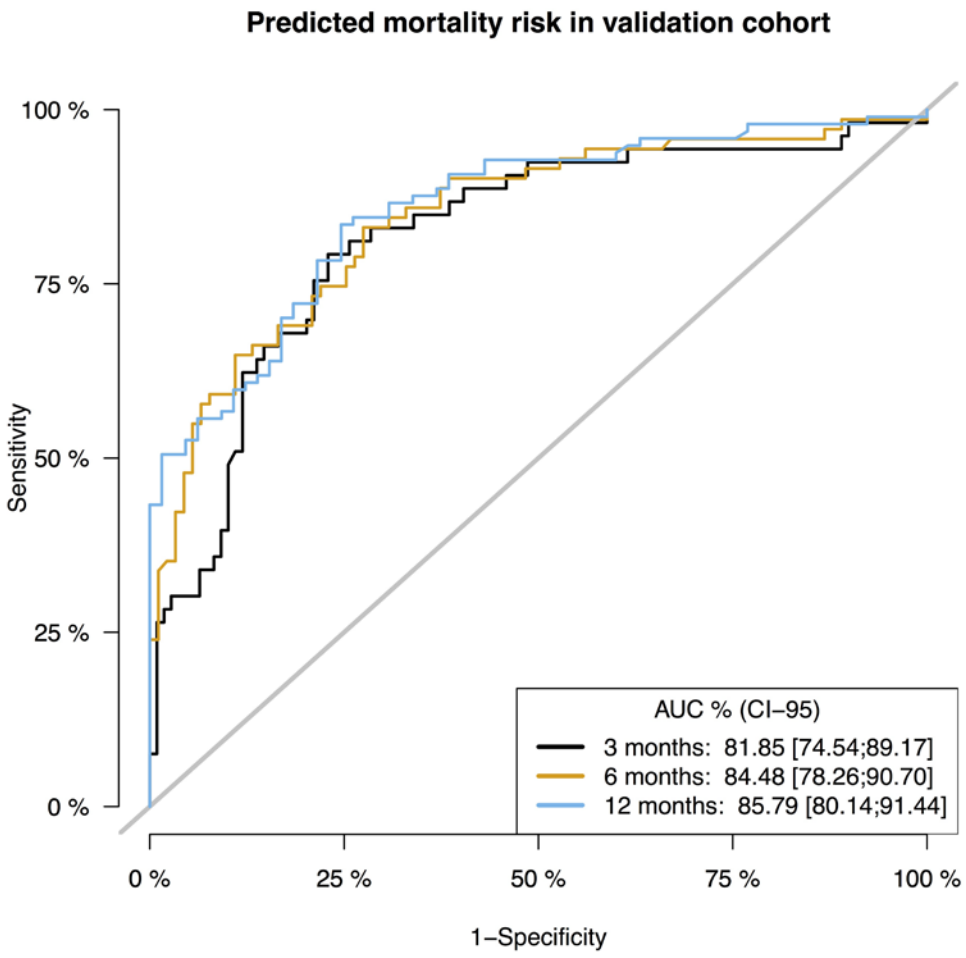

Figure 3: Curves showing the ROC curves of the 2013 SPRING model at each endpoint (survival status 3 (black), 6 (yellow) or 12 (blue) months after surgery for MBDex). AUC ROC of the refitted 2013- SPRING model was 82% (C.I.: 76% - 89%), 85% (C.I.: 78% - 91%) and 86% (C.I.: 80% - 91%) respectively.

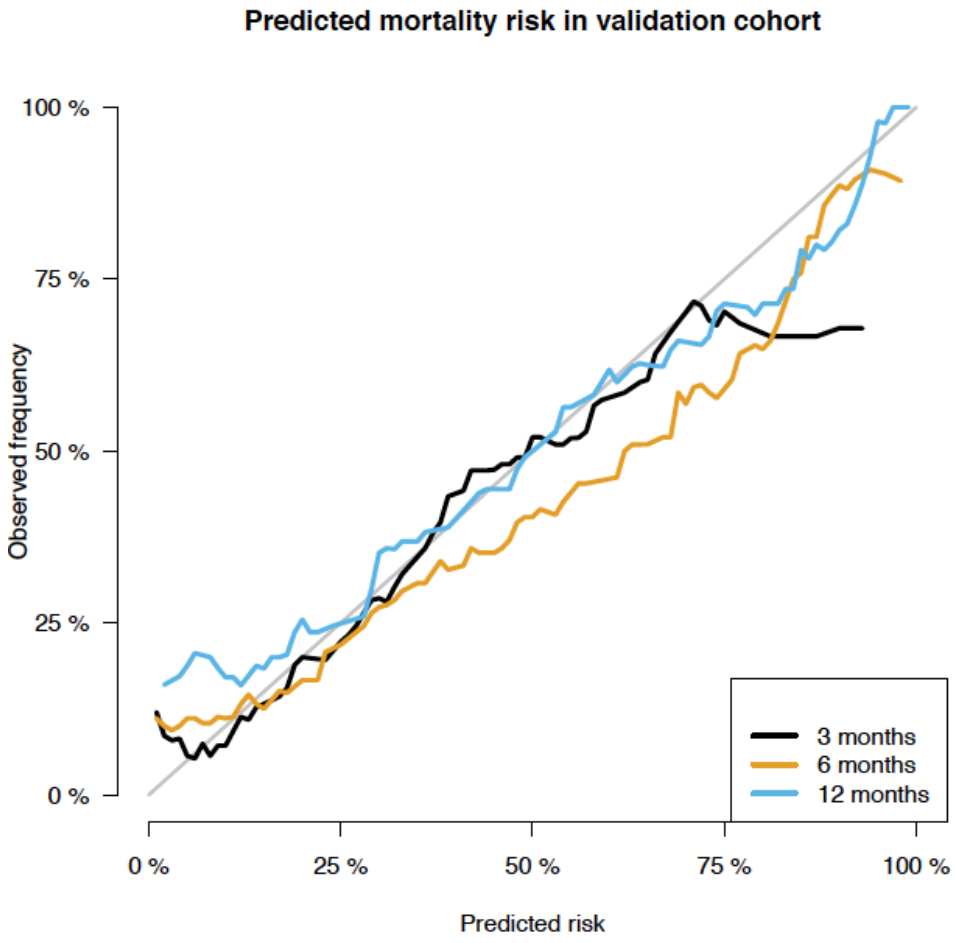

Figure 3: Plots showing the calibration of the model at each endpoint (survival 3 (black), 6 (yellow) or 12 (blue) months after surgery for MBDex.

Tables

Prognostic group	**Primary cancers**
Fast growing	Bladder, colorectal, hepatocellular, lung, malignant melanoma, unknown, others
Moderate growing	Prostate, renal, sarcoma
Slow growing	Breast, lymphoma, myeloma

Table 1: Categorization of primary cancers as described by Sørensen et. al. 2016 into slow, moderate and fast-growing cancers depending upon survival observations.

Variable	Level	Training (n=270)	Validation (n=164)	Total (n=434)	p-value
Primary cancer growth	slow	116 (43.0)	61 (37.2)	177 (40.8)	
	moderate	70 (25.9)	51 (31.1)	121 (27.9)	
	fast	84 (31.1)	52 (31.7)	136 (31.3)	0.402
Hemoglobin (mM)	mean (sd)	7.3 (1.0)	7.2 (1.4)	7.2 (1.1)	0.367
	missing	1	0	1	
Fracture	impending fracture	72 (26.7)	41 (25.0)	113 (26.0)	
	fracture	198 (73.3)	123 (75.0)	321 (74.0)	0.787
Visceral metastases	no	165 (61.1)	97 (59.1)	262 (60.4)	
	yes	105 (38.9)	67 (40.9)	172 (39.6)	0.761
Multible bone metastases	no	91 (33.7)	43 (26.2)	134 (30.9)	
	yes	179 (66.3)	121 (73.8)	300 (69.1)	0.126
Karnofsky score	<70	97 (36.2)	60 (36.6)	157 (36.3)	
	>=70	171 (63.8)	104 (63.4)	275 (63.7)	1.000
	missing	2	0	2	
ASA group	1+2	137 (52.5)	67 (41.4)	204 (48.2)	
	3+4	124 (47.5)	95 (58.6)	219 (51.8)	0.033
	missing	9	2	11	

Table 2: The distribution of variables between the training and validation cohort and tested for difference in distribution by Chi2 for categorical variables and t-test for continues variables.

Variable	Units	3 months survival			6 months survival			12 months survival		
		OddsRatio	***C.I.***	***p-value***	***OddsRatio***	***C.I.***	***p-value***	***OddsRatio***	***C.I.***	***p-value***
primarygroup	slow	1.00	[1.00;1.00]	1.000	1.00	[1.00;1.00]	1.000	1.00	[1.00;1.00]	1.000
	moderate	1.95	[0.84;4.50]	0.118	5.69	[2.50;12.93]	<0.001	5.39	[2.41;12.06]	< 0.001
	fast	2.75	[1.26;6.03]	0.011	7.01	[3.18;15.46]	<0.001	9.93	[4.29;22.98]	< 0.001
hemoglobin		0.58	[0.41;0.84]	0.004	0.58	[0.40;0.83]	0.003	0.57	[0.39;0.81]	0.002
fraktur	impending fracture	1.00	[1.00;1.00]	1.000	1.00	[1.00;1.00]	1.000	1.00	[1.00;1.00]	1.00
	fracture	1.43	[0.67;3.06]	0.354	1.60	[0.78;3.28]	0.203	0.68	[0.33;1.43]	0.313
visceral	no	1.00	[1.00;1.00]	1.000	1.00	[1.00;1.00]	1.000	1.00	[1.00;1.00]	1.000
	yes	3.10	[1.62;5.93]	<0.001	2.40	[1.27;4.56]	0.007	2.47	[1.26;4.86]	0.009
Multible bone metastases	no	1.00	[1.00;1.00]	1.000	1.00	[1.00;1.00]	1.000	1.00	[1.00;1.00]	1.000
	yes	1.89	[0.89;4.04]	0.099	2.19	[1.07;4.48]	0.032	2.35	[1.13;4.89]	0.022
karnofsky	<70	1.00	[1.00;1.00]	1.000	1.00	[1.00;1.00]	1.000	1.00	[1.00;1.00]	1.000
	>=70	0.33	[0.17;0.62]	<0.001	0.26	[0.13;0.49]	<0.001	0.27	[0.13;0.54]	<0.001
asa	1 + 2	1.00	[1.00;1.00]	1.000	1.00	[1.00;1.00]	1.000	1.00	[1.00;1.00]	1.000
	3 + 4	1.91	[0.98;3.72]	0.057	1.94	[1.03;3.68]	0.042	1.92	[0.98;3.73]	0.055

Table 3: Table showing the variables explanatory relation to survival outcome at 3, 6 and 12 months after surgery as expressed by a multivariate logistic regression.

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Survival after treatment of metastatic bone disease in the extremities, factors influencing survival followed by development and validation of a prediction model for postoperative survival

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STUDY 1: Patient and implant survival following joint replacement surgery because of metastatic bone disease. A cross sectional study of 130 patients with 140 joint replacements published in Acta Orthop 2013; 84 (3): 301-306

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1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	A
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4. Presentation, interpretation and discussion in a journal article format of obtained data	B

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A. refers to:	*Has contributed to the co-operation*	*0-33 %*
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STUDY 4: Prediction of survival after surgery due to skeletal metastases in the extremities Bone and Joint Journal. Feb 2016;98-B(2):271-277

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**Benchmark scale of the PhD student's contribution to the article*		
A. refers to:	*Has contributed to the co-operation*	*0-33 %*
B. refers to:	*Has contributed considerably to the co-operation*	*34-66 %*
C. refers to:	*Has predominantly executed the work independently*	*67-100 %*

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