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Optimising the treatment of patients with long bone metastases

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OPTIMISING THE TREATMENT OF PATIENTS WITH LONG BONE METASTASES

Julie Willeumier

Optimising the treatment of patients with long bone metastases J. J. Willeumier

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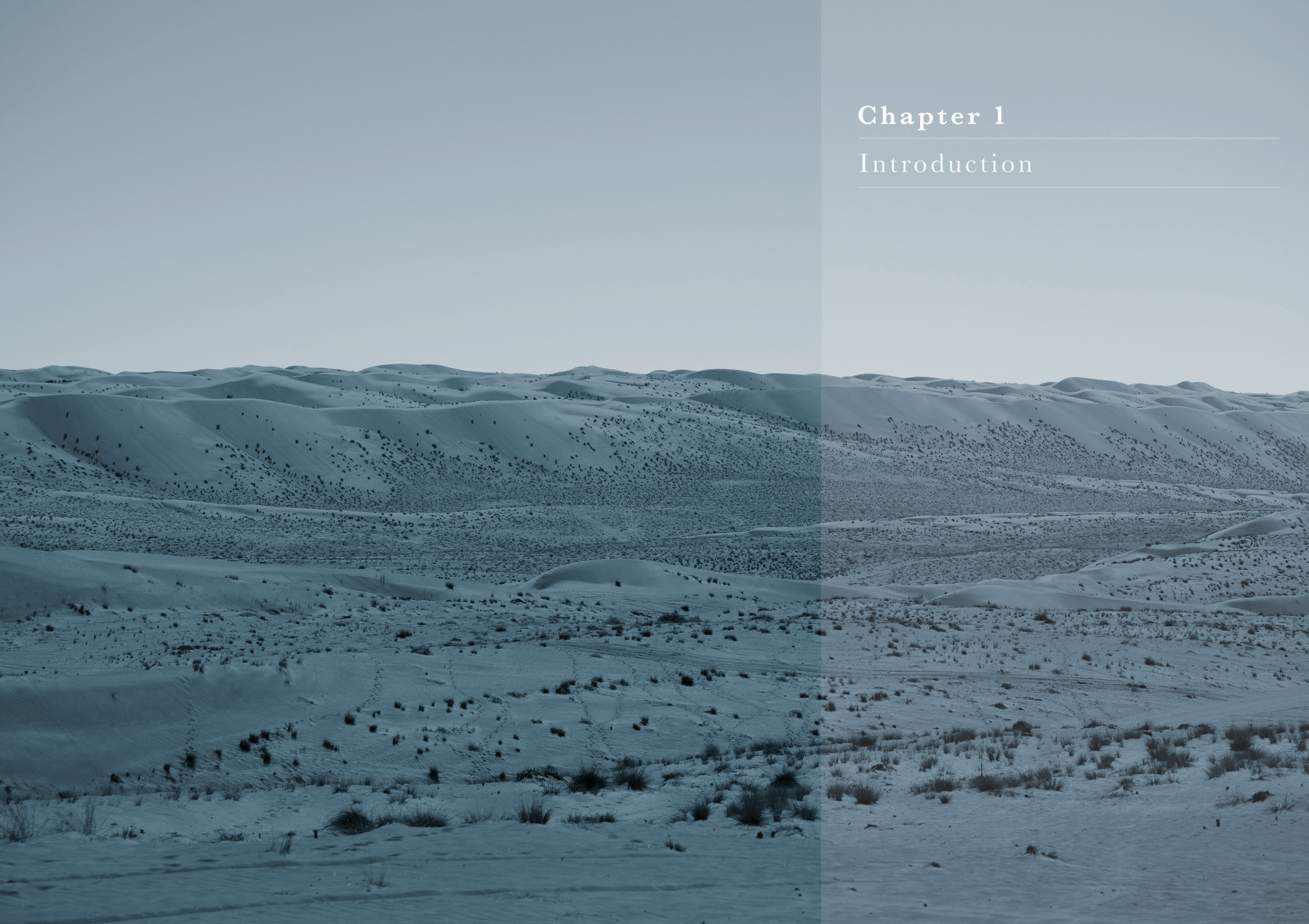

Chapter 1

Introduction

Background

In 2009, a total of 91.400 new patients with cancer were diagnosed in the Netherlands. In 2012, this had already increased to 101.800 new cases.[1] It is expected that in 2020, 123.000 new patients will be diagnosed with cancer.[2] This increase is primarily due to the phenomenon of *double-aging*: the number of aging people is increasing, and they live longer, leading to a larger (elderly) population at risk of developing cancer.[2] Conversely, the risk of dying of cancer is decreasing as an effect of the improving efficacy and growing possibilities of both local and systemic cancer treatments, including radiotherapy, surgery, hormonal treatment, chemotherapy and immunotherapy. Furthermore, treatments for patients with disseminated disease are also improving leading to longer survival.[3,4] All in all, an increasing number of patients and during a longer period of time are at risk of developing metastases which will lead to an absolute increase of the number of metastases and subsequent symptoms.

Bone is the third most common site of metastasis, after lung and liver. Bone metastases arise in approximately 50-70% of all patients diagnosed with cancer, most commonly in patients suffering from breast, prostate, kidney or lung cancer.[5] A post-mortem study has shown skeletal involvement in up to 70% of patients with metastasised breast or prostate carcinoma, and in 30% of patients with thyroid, kidney or bronchus carcinoma.[6] This study was performed in 1981 and it is questionable whether these commonly referred to incidence rates hold in the current era of improved and widespread use of systemic treatments on one hand, and improved diagnostic imaging on the other, with an increasing use of whole body imaging, such as PET-CT.

The majority of bone metastases are located in the spinal column and the femur, followed by the pelvis and the humerus.[7-9] Metastases of the long bones are the subject of interest in this thesis and future references to bone metastases generally refer to those located in the long bones. The femur is the most affected of the long bones, followed by the humerus.[10] Especially the metaphyseal region is a common site for tumour cells due to the high vascularization and easy access into the marrow.[11]

Metastases are caused by tumour cells that disturb and imbalance the physiologic process of bone remodelling, in which the activity of osteoclasts (i.e. bone resorption) is coupled to the activity of osteoblasts (i.e. bone formation). Depending on the origin of the metastatic cells and mechanism they induce, osteolysis (in breast cancer, for example) or sclerosis (in prostate cancer, for example) gains the upper hand, although the two processes are often both present in metastatic lesions. Osteolysis is primarily the result of osteoclast stimulation. Tumour-derived parathyroid hormone-related peptide (PTHrP) stimulates the expression of RANKL (receptor activator of nuclear factor-kB ligand) which binds the RANK receptor on osteoclast precursor cells and induces the formation of osteoclasts, that in turn resorb bone.[12] This osteolysis subsequently leads to release of transforming growth factor beta (TGF-B), insulin-like growth factor 1 (IGF-1) and ionized calcium, which then bind to receptors on the tumour-cell surface and promote both tumour growth and PTHrP production. In this manner a 'vicious circle' is formed supporting tumour growth and bone resorption.[13] Sclerosis is caused by factors produced by the tumour cell such as endothelin-1, TGF-B2 and several bone morphogenetic proteins (BMPs) that stimulate osteoblast proliferation.[13]

Bone metastases can cause site-specific symptoms, such as pain or pathologic fractures, or systemic symptoms, such as fatigue, anaemia, nausea or anorexia. Hypercalcaemia, i.e. increased blood calcium levels, occurs in 10% of the patients, predominantly those with lung, breast and kidney cancer. It is caused by calcium which is released during osteolysis. The symptoms of hypercalcaemia are unspecific, including fatigue, depression, constipation, and vomiting. Urgent treatment with rehydration and bisphosphonates is required to prevent deterioration in renal function and mental status. If left untreated, hypercalcaemia can lead to cardiac arrhythmias and death.[14,15]

Clinical features of long bone metastases

Pain is the most prominent and common symptom for which patients seek medical attention.[16] Painful bone metastases have a major impact on quality of life (QoL)[17,18] and effective treatment of pain with radiotherapy has shown to lead to an improved QoL.[19] Seventy-five to ninety percent of patients experience significant cancer-induced pain.[20] The pain is usually localized, constant and dull in character, gradually progressing with time.[21] The presence of pain is not correlated with the type of tumour, location, number or size of metastases, gender, or age of patients.[22] The pathophysiologic mechanisms of bone pain are poorly understood but generally exhibit elements of both inflammatory and neuropathic pain. Inflammatory infiltration occurs as a result of tissue damage caused by tumour growth and release of pain mediators by the cancer cells. The neuropathic component can arise from damage to sensory nerves by infiltration, compression, stretching, or denervation as the tumour expands and the bone degrades.[21]

Pathological fractures, called pathologic because they arise in bone with an abnormal health and generally occur without traumatic force, have large impact on the mobility and independence of a patient. They arise in 5-10% of patients

with symptomatic bone metastases.[14,23] More than half of all pathologic fractures occur in the femur.[24] In the humerus the incidence of pathological fractures ranges between 16-27%.[25] It is important to realise that complete fracture healing of pathologic fractures cannot be expected. Unlike traumatic fractures, only 50% of all fractures will heal in six months, decreasing to merely 37% in breast cancer and no healing at all in lung cancer.[26] The latter results date back to 1983, so it is conceivable that current union rates have increased slightly with the improvement of systemic and local therapies. However, the fact remains that the bone is affected by cancer cells which impair the natural tendency to heal. Subsequent non-union or delayed union can lead to implant failure and revisions.

Impending fractures are lesions at high risk of fracturing and therefore require prophylactic stabilisation. To identify such lesions and select the correct patients for prophylactic treatment, two questions must be answered: (1) how to determine the fracture risk? and (2) what is a *high* risk? To answer the first question, the Mirels' classification (including lesion site, size, and type; and pain) is commonly used, but van der Linden et al. have shown that this classification leads to significant overestimation of the fracture risk with a specificity of 13%.[27,28] The "3-cm axial cortex destruction" rule was developed by van der Linden and Dijkstra et al. for the femur, with a sensitivity of 86% and a negative predictive value (i.e. probability that a negative test result leads to no fracture) of 97%.[29] However, although this axial cortical involvement is accurate in identifying high-risk lesions, it still showed a relatively low specificity (58%). This is where the second question plays a role: how many patients should we unnecessarily operate, to prevent one fracture? The 3-cm rule is associated with a positive predictive value (i.e. probability that a positive test result leads to fracture) of 23%, so three in four patients are over-treated with a surgical procedure. Whether this is acceptable, should be subject of discussion, from both a medical and an economical point of view, but above all from a patient point of view. However, first consensus should be reached on how to determine a patient-specific fracture risk. Such a calculation should not only give a binary answer (yes/no) to whether the chance of a fracture to occur at some time is increased, but should give hazard ratios for specific time-points. Predictive tools using actual CT scan data to calculate a risk of future fracture based on finite element analysis (i.e. a computer model that assembles multiple partial differential equations, called finite elements, into a larger system of equations to model an entire problem) or CT-based structural rigidity analysis are promising tools to give quantitative patient-specific predictions.[30] Although such models provide accurate results in biomechanical lab experiments, and are more predictive than an individual physicians estimated risk based on clinical

experience, they still face several challenges before they can be applied in clinical routine.[31]

Treatment

Symptomatic bone metastases are associated with loss of mobility and social functioning, a decreased quality of life [32] and reduced overall survival (OS),[33,34] and therefore require adequate treatment. The aim of treatment is to offer maximal palliation. This includes maintaining optimal function of the extremities. Only in rare cases (e.g. pure solitary metastases) might aggressive surgical management or high dose radiotherapy using stereotactic techniques and ablative doses lead to cure or substantial prolongation of life.[35,36] Oligometastatic disease, regarded as 2-5 bone metastases, is increasingly being regarded as separate entity between metastatic disease with only a single lesion and diffuse metastasised disease. This group might benefit from more aggressive treatment to achieve local control and delay progression.[37] However, whether this more favourable entity is based on a less invasive tumour biology or on the more aggressive treatment that is increasingly available, is unclear.

Bone-specific treatment options include *systemic* treatments (pain medication, bisphosphonates, denosumab, radionuclides) and *local* treatments (radiotherapy, surgical and percutaneous treatments). The latter are the focus of this thesis.

Pain medication is an essential part of the treatment of painful bone metastases, even though it is symptom management. The World Health Organization has developed a pain ladder for cancer pain relief, starting with non-opioids (first paracetamol, followed by the addition of non-steroidal anti-inflammatory drugs (NSAIDs)) and adding weak or strong opioids, if necessary.[38] In the treatment of bone metastases, the step of weak opioids is usually disregarded because the side effects weigh too strong as compared to their effectiveness. Severe bone pain is one of the most difficult of pains to control as bone metastases are generally not located to a single site, breakthrough pains (short, intermittent episodes of extreme pain with rapid onset breaking through the administered analgesics occurring spontaneously or on weight-bearing) are common, and increasing doses of analgesics is frequently limited by significant side effects.

Bisphosphonates and ***denosumab*** are bone-targeting agents and both decrease bone resorption and increase mineralisation by inhibiting osteoclast activity.[39] While bisphosphonates directly induce osteoclast apoptosis, denosumab is an antibody that binds to RANKL, preventing its interaction with RANK and thus inhibiting osteoclast activity. Especially bisphosphonates are commonly

subscribed to treat and prevent pain and fractures. Denosumab has been described to be effective in patients with a poor response to bisphosphonates,[40] and even superior to Zoledronic acid in several studies.[41,42]

Radiotherapy for painful bone metastases is well established and provides an effective symptomatic treatment in up to 60-80% of patients, although the level of pain relief differs.[43] Radiotherapy causes irreversible damage to the DNA of a cell, which leads to cell death. This mechanism does not completely explain the effect of radiotherapy on bone metastases because the doses used for palliative radiotherapy are lower than doses used for tumour eradication.[44] A single fraction of 8 Gy has been proven as effective as 20 Gy in multiple fractions and it is therefore recommended in cases with uncomplicated bone metastases.[45,46] Nonetheless, when the bone metastasis causes bone destruction, multi-fraction schemes are still commonly used.[47] Radiotherapy is most commonly administered through external beams to local fields, but new modalities such as stereotactic radiotherapy are being introduced, especially in the setting of solitary or oligometastatic disease.[48] Studies are ongoing to investigate the effect of high dose, high precision radiotherapy on the duration of pain response, and on disease-free survival and actual survival of this specific group.

Surgery is required when fractures are present or pending. Options include plate and screw fixation, intramedullary nail fixation, or resection and prosthetic reconstruction. Choices are made depending on location, bone stock, and fracture type, among others. Precise indications for surgery are unclear and the best modalities are a frequently debated subject, as will become apparent in this thesis.

Minimal invasive treatments including ablative techniques (such as radiofrequency ablation, microwaves, cryoplasty, high-intensity focused ultrasound), cementoplasty, and vascular techniques (e.g. trans-arterial embolization), could be options for patients with refractory pain or a short survival,[49,50] although there is currently not much evidence in the literature.

The known Unknowns

Multidisciplinary teams, including medical oncologists, orthopaedic surgeons, and radiation oncologists, work together to find the best possible palliative treatment for each individual patient. To determine the best treatment, multiple factors must be taken into account, including patients' preferences, type or risk of fracture, expected durability and risks of an intervention, location of the lesion, and life expectancy. It is important to balance the expected survival of a patient with the risks and recovery time of an intervention, as well as the

expected life-time of a surgical implant. This means that answers to the following questions are required to provide optimal treatment:

(1) what is the life expectancy of this patient?

(2) is this long bone going to fracture?

(3) what are the pros and cons of this intervention?

Unfortunately, the answers to all three questions are unknown. These three gaps of knowledge, 'the *known Unknowns*', lead to overtreatment in patients with expected short survival or without genuine impending fractures, and to undertreatment in patients with an expected long survival or with genuine impending fractures. Both over- and undertreatment have negative effects on patients' quality of life and should be prevented.

Why is the Unknown unknown?

Survival estimation is extremely difficult. Overall, 1-year survival percentages have been reported between 17% and 70% after surgery for skeletal metastases.[51] Survival ranges from a few weeks to many years, depending on numerous factors. The primary tumour is the most important, but other factors such as coexisting visceral, brain and/or skeletal metastases, performance status, the presence of a pathologic fracture, a history of previous chemotherapy, the disease-free interval, and abnormal laboratory results have also been reported as prognostic.[52-64] To aid physicians in survival estimation, many prognostic models have been developed over the years.[58-64] However, these all have certain limitations, are often based completely on surgical or irradiated patients only, thus introducing confounding, and standard use in clinical practise is uncommon. Instead, survival estimations are made based on clinical experience, which tend to be incorrect.[65]

Adequate fracture prediction is equally intricate. Several criteria have been described, as reported, but to date none are sufficiently specific and sensitive to prevent both unnecessary prophylactic treatments and avoidable fractures. A randomised trial to determine risk factors for fracture is ethically not desirable so evidence must be based on prospective patient cohorts or trustworthy biomechanical models. Promising progress is being made with CT-based and finite element prediction models, but these are not yet reliable for clinical use.[31]

Each surgical intervention has its faults and merits. The technical aspects of the implantation and fixation of prostheses and osteosyntheses are generally well established. However, regarding all events after surgery, the faults and merits are less clear-cut in patients treated for pathologic fractures. The duration of

recovery and rehabilitation after surgery, the duration to full weight-bearing, possible post-operative complications, and durability of an implant are not well-known. Furthermore, the additional value of adjuvant treatments (e.g. cement, radiotherapy) to prevent post-operative events has not been defined. Risk factors for failure are unknown because insufficient adequate and unbiased research has been performed. The lack of evidence is due to the unique patient population, making research complicated, and the palliative intent of the treatment, as opposed to a curative intent, for which physicians are trained and thus seems more appealing to research. The often limited follow-up of this patient population further hinders qualitative sound research.

Given the lack of consensus on the best treatment strategy in different cases, treatment is predominantly based on experience and expert opinion. It is possible that the experience based treatments are actually *unknown Knowns,* but in an era of evidence-based medicine and value based healthcare it is not justifiable that treatment is based on *Unknowns*.

Aim of thesis

As can be concluded from the above, there are multiple *Unknowns* regarding the local treatment for patients with cancer and pathologic fractures of the long bones. To turn the *Unknowns* into *Knowns*, the OPTIMAL Project was initiated by my promotor (prof. dr. P.D.S. Dijkstra) and co-promotor (dr. Y.M. van der Linden) in 2014. The OPTIMAL project consists of a retrospective and a prospective part, together aiming to "*optimise the treatment of patients with long bone metastases".* This thesis entails the first, retrospective part and lays a foundation for the second prospective part of the OPTIMAL project. The aims of this thesis are to develop a prognostic model for estimating survival in patients with cancer and symptomatic metastases of the long bones, evaluate current surgical treatment modalities and trends, and provide rationale for future prospective randomized trials. Determining the definition of an impending fracture and how the fracture risk is best calculated is beyond the scope of this thesis.

Thesis outline

Following this introduction into the field of long bone metastases, ***chapter 2*** describes the accomplishment of the first aim of this thesis: a prognostic model for survival based on a large multicentre retrospective cohort that shows that classification into four prognostic categories is possible with three variables: clinical profile of the primary tumour, Karnofsky Performance Score, and the presence of visceral and/or brain metastases. ***Chapter 3*** shows why the survival prognostic model (as reported in chapter 2) is sustainable in the future. With

improving systemic treatment possibilities, primary tumours will increasingly be differentiated into subtypes that are treated differently and have different expected survival, and therefore require re-classification in the prognostic model. This chapter shows that patients who are diagnosed with non-small cell lung cancer and bone metastases should not be regarded as a single entity for survival estimation; the EGFR mutation status should differentiate non-small cell lung cancer patients into a group with a moderate or unfavourable clinical profile. Radiotherapy is the most common treatment for painful bone metastases. ***Chapter 4*** places a critical note on the use of radiotherapy after surgical fixation of a pathologic fracture. As discussed in this chapter, evidence behind adjuvant treatment is meagre. ***Chapter 5*** reports on the outcomes of a questionnaire among Dutch and international orthopaedic surgeons. The results show that better selection of patients who would require more specialised care as opposed to standard care would improve overall care of patients with pathologic fractures. ***Chapter 6*** evaluates the treatment of actual and impending pathologic fractures of the femur with intramedullary nails and reports on risk factors for failure. A sequel is presented in ***chapter 7,*** which focusses on the same questions for intramedullary nails in the humerus. ***Chapter 8*** aims to identify factors that indicate the need for an endoprosthesis in distal femur pathologic fractures, based on previous literature. ***Chapter 9*** gives an overall overview of the current surgical treatment of pathologic fractures of the long bones. It provides a step-by-step guide to be used when patients present with a pathological fracture. The chapter concludes with specific treatment recommendations for femur and humerus fractures.

Chapter 10 summarizes the main results of the studies in this thesis**.** ***Chapter 11*** discusses the outcomes of the previous chapters and places them into a clinical context. Chapter 5 to 9 have provided rationale for the second, prospective part of the OPTIMAL Project, as will be discussed in this chapter. The chapter concludes with future directions for research and treatments of long bone metastases. In ***chapter 12*** a Dutch summary of this thesis is presented. The protocol of the prospective OPTIMAL study and the Dutch translation and validation of the Toronto Extremity Salvage Score (TESS) questionnaire are included in the ***appendix***.

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Chapter 2

An easy-to-use prognostic model for survival in patients with symptomatic long bone metastases

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Abstract

Background

A survival estimation for patients with symptomatic long bone metastases (LBM) is crucial to prevent overtreatment and undertreatment. This study analyzed prognostic factors for overall survival and developed a simple, easy-to-use prognostic model.

Methods

A multicenter retrospective study of 1520 patients treated for symptomatic LBM between 2000 and 2013 at the radiation therapy and/or orthopedic departments was performed. Primary tumors were categorized into three clinical profiles (favorable, moderate, unfavorable) according to an existing classification system. Associations between prognostic variables and overall survival were investigated by using the Kaplan Meier method and multivariate Cox regression models. The discriminatory ability of the developed model was assessed with Harrell's C-statistic. Observed and expected survival was compared based on an external cohort.

Results

Median overall survival was 7.4 months (95% CI 6.7-8.1). Based on the independent prognostic factors clinical profile, Karnofsky Performance Score, and presence of visceral and/or brain metastases, twelve prognostic categories were created. Harrell's C statistic was 0.70. A flowchart was developed to easily stratify patients. Based on cut-off points for clinical decision-making, the twelve categories were narrowed down to four categories with clinical consequences. Median survival was 21.9 (95% CI 18.7-25.1), 10.5 (95% CI 7.9-13.1), 4.6 (95% CI 3.9-5.3) and 2.2 (95% CI 1.8-2.6) months, for the four categories.

Conclusion

This study presents a model to easily stratify patients with symptomatic LBM according to their expected survival. The simplicity and clarity of the model facilitate and encourage its use in routine care of patients with LBM, to provide the most appropriate treatment for each individual patient.

Introduction

Long bone metastases (LBM) are a common occurrence in patients with advanced cancer, arising in up to 70% of the patients with advanced disease.[1] As the prevalence of cancer rises[2] and survival rates for even metastatic cancer increase, the number of patients with symptomatic LBM is likely to grow. Pain is the most common symptom, followed by actual or impending pathologic fractures in 10% to 25% of the patients, causing immobility and a decreased quality of life.[3] Local treatment options primarily consist of radiation therapy and multiple types of surgical stabilization. All treatments have the same aims: to reduce pain, preserve the function of the extremities, and maintain or improve quality of life for patients with mostly limited life expectancy.[4,5]

An accurate estimation of the survival at a specific time is essential to avoid overtreatment and undertreatment. Treatments that do not fit the expected survival time of patients with advanced cancer, with either recovery and rehabilitation times that are too long relative to a mostly limited survival, or, insufficient stabilizations when a long survival is expected, have a negative effect on their mobility and independence and, hence, the quality of life. For patients expected to have a short survival, radiation therapy or minimally invasive surgical treatments (e.g., intramedullary nail fixation) would be preferable, while for patients expected to have a long survival, resection and reconstruction with a regular or modular tumor prosthesis could provide a lifelong solution. Correct estimates of survival, however, are difficult, and physicians tend to be inaccurate.[6] For patients with LBM, several tools have been developed to aid physicians.[7-14] However, they have several shortcomings. First, most models are based on small cohorts from either radiation therapy[11,14] or orthopaedic[7-9,12,13] departments, instead of both. Survival predictions that are based on a mixed cohort would be more consistent when discussing multidisciplinary treatment strategies. Second, many models include multiple myeloma as primary tumour;[7-10,12,13] however, as a primary hematological cancer, it is a different entity and has a very different prognosis than osseous metastases from solid carcinomas. Third, the development of targeted treatments for several primary tumors has subdivided primary tumors into different entities, which makes some models outdated.[7-9,11-14] Finally, most models include numerous variables, including some that are not part of standard work-up (e.g. laboratory results).[7,8,10,12,13] The complexity of these models, caused by the number of variables, inhibits effective clinical use of survival estimation tools in daily practice.

With these limitations in mind, our group previously developed a simple prognostic model for overall survival in patients with spinal metastases from

carcinoma.[15] The model contains only 3 clinical variables: the clinical profile, the Karnofsky Performance Score (KPS), and the presence of visceral and/or brain metastases (VBM). These led to a categorization in 4 prognostic groups with the following median overall survival results: 31.2 months (95% confidence interval [CI], 25.2 to 37.3 months), 15.4 months (95% CI, 11.9 to 18.2 months), 4.8 months (95% CI, 4.1 to 5.4 months), and 1.6 months (95% CI, 1.4 to 1.9 months).

The purposes of this study were to (1) identify prognostic factors for survival in patients with LBM, (2) develop an accurate and easy-to-use prognostic model similar to the previously developed model for spinal bone metastases, and (3) test the applicability of the model in an external cohort.

Materials and methods

Patients

A multicenter, retrospective analysis of patients with cancer who were treated for symptomatic metastases in the long bones between 2000 and 2013 was performed. Consecutive patients from 4 orthopaedic departments and 4 radiation therapy departments in 6 Dutch hospitals were included. Exclusion criteria were: a lesion due to multiple myeloma, solitary plasmacytoma or other hematological disease, or a lack of sufficient follow-up data regarding final status (alive or dead). After exclusion of 72 patients (no LBM [19], no local treatment [43], duplicate patient [5], or lack of sufficient data [5]), 1520 patients were eligible for participation in the cohort.

Medical, radiology, and pathology records were reviewed to record the following data at baseline: sex, age, primary tumor, pretreatment performance score, presence of visceral and/or brain metastases, location of the metastasis, presence of (impending) pathologic fracture, and whether the metastasis was a solitary lesion. If patients were treated multiple times, the first treatment (radiation therapy or surgery, or both) in the study period was included.

The local medical ethical committees approved this study and granted a waiver for informed consent.

Clinical profile

Primary tumors were categorized into 3 clinical profiles (favorable, moderate or unfavorable) on the basis of the classification system established by Bollen et al.[15] Several tumor types that were not included in the previous classification were registered in the current study. Where reasonable, these were added to existing primary tumor types: carcinomas of the rectum were added to the group of colon carcinomas and the group "tongue cancer" was expanded to include all head and neck cancers. Soft-tissue sarcomas (STS) and "other primary tumors" were added as new tumor groups. Classification of STS was based on the literature.[10] Finally, the classification was adjusted from unfavorable to moderate for endometrial carcinoma[16] and Ewing sarcoma[17] on the basis of new insights in the literature. In addition, breast cancer and kidney cancer were divided over 2 clinical profiles on the basis of receptor (estrogen, progesterone and Her2/neu) status for breast cancer,[18] and the number of bone metastases for kidney cancer.[19,20]

Pretreatment performance was scored by the KPS to reflect the performance before a fracture (if present); a higher score means the patient is better able to perform daily activities.[21] KPS scores were categorized into 2 groups: ≤70% (impaired functioning) and 80% to 100% (normal functioning).[15] Eastern Cooperative Oncology Group/World Health Organization (ECOG/WHO) scores, if used, were converted to the corresponding KPS group.[22] If the performance was recorded without use of a scoring system and only by descriptive notes (e.g. good health, vital, or poor status), the descriptions were categorized into the two groups by 1 of the authors (J.J.W.).

The presence of visceral metastases was determined on the basis of radiology reports available to the treating physician at the time of decision-making before treatment. If radiology reports were not available or the presence of visceral metastases was genuinely unclear, this was scored as unknown. The same approach was used to assess whether a bone metastasis was a solitary lesion. The presence of brain metastases (including metastases of the central nervous system) was based mainly on clinical reports because whole brain computed tomography (CT) or magnetic resonance imaging (MRI) scans were not routinely performed. Only when the presence was unclear for the treating physicians, was this scored as unknown.

Statistical analysis

Statistical analyses were performed with the use of SPSS software (version 24.0; IBM). Survival time was calculated as the difference between the date of first treatment for the bone metastasis and the date of death or latest follow-up. Survival curves were estimated with the Kaplan-Meier method. Median follow-up was estimated with the reversed Kaplan-Meier method.[23] The following variables were used to investigate a possible association with overall survival: clinical profile, KPS, presence of VBM, location of the metastasis, sex, and a solitary metastasis. A multivariate Cox regression model was estimated with clinical profile, KPS, and the presence of VBM as risk factors. Sex and solitary

metastases were not included in the multivariate analysis because they are strongly entwined with specific primary tumors; breast cancer is more common in women, and solitary metastasis are more common in kidney cancer. To further analyze the effect of KPS and the presence of VBM for each clinical profile, the multivariate analysis was stratified for clinical profile. Hazard ratios (HRs) and their corresponding 95% confidence interval (CI) were estimated. Not all participating departments provided data for the entire study period. Two variables, "center" and "year of treatment" were included in all Cox regression analyses to account for the presence of heterogeneity between the treatment centers and the time period in which the patient was treated. P values of <0.05 were considered significant. Following the study design by Bollen et al,[15] combinations of the independent prognostic variables led to 12 prognostic categories that were visualized in a flowchart. To compress the 12 categories to a clinically applicable classification, median overall survival results of all categories were compared. As treatment strategies generally differ among an expected survival of <3 months, 3 to 6 months, 6 to 12 months and >12 months, these cutoff points were applied to narrow the 12 survival categories down to these 4 clinically relevant categories. To assess the discriminatory ability of these categories, the Harrell C-statistic was used.[24]

External cohort

The developed prognostic model was used on an external cohort. The cohort consisted of patients receiving surgical treatment between 2000 and 2013 at an Austrian hospital. Observed and expected survival (based on the external cohort) for each clinical profile at 1, 3, 6, 12 and 24 months were compared.

Results

Baseline characteristics of the patients and metastases are presented in table 2.1. The most common primary tumor types were breast (33%), lung (24%), prostate (15%), and kidney (8%) (table 2.2). Indications for treatment were pain (48%), and actual (30%) or impending fractures (23%). The details of the treatment strategies are given in table 2.3.

Survival

The median follow-up for all patients was 79.1 months (95% CI, 71.0 to 87.2 months). The median overall survival was 7.4 months (95% CI, 6.7 to 8.1 months). The 529 patients (35%) with a favorable clinical profile, 419 (28%) with a moderate profile, and 472 (38%) with an unfavorable profile had a median overall survival of 18.6 months (95% CI, 15.8 to 21.4 months), 7.7 months (95% CI, 6.6 to 8.7 months), and 3.1 months (95% CI, 2.7 to 3.5 months) months, respectively (figure 2.1).

Prognostic factors

Univariate analyses showed that the clinical profile, the KPS, evidence of VBM, a solitary bone metastasis, and sex were significantly associated with OS (p < 0.001 for all). A multivariate Cox regression analysis was performed based on the basis of the 1131 patients for whom full information was available. The clinical profile (moderate [HR of 1.8; 95% CI, 1.5 to 2.1] or unfavorable [HR of 3.3; 95% CI, 2.8 to 3.8]), a KPS of ≤70 (HR of 2.0; 95% CI, 1.8 to 2.3), and evidence of VBM (HR of 1.4; 95% CI, 1.2 to 1.5) were significantly associated with a higher risk of death. Stratification according to clinical profile in the multivariate analysis showed that a low KPS and the presence of VBM were associated with a shorter survival for all 3 profiles. A KPS of ≤70 doubled the risk of death in all profiles, with a HR of 1.9 (95% CI, 1.5 to 2.4), 2.2 (95% CI, 1.7 to 2.8), and 2.0 (95% CI, 1.7 to 2.5) for a favorable, moderate, and unfavorable clinical profile, respectively. The effect of VBM was the largest in the favorable profile, with an HR of 1.7 (95% CI, 1.3 to 2.1), 1.3 (95% CI, 1.0 to 1.7), and 1.3 (95% CI, 1.0 to 1.5) for a favorable, moderate, and unfavorable clinical profile, respectively.

Prognostic model

The cohort was divided into 12 categories on the basis of the combination of the 3 prognostic variables. The median survival and survival at 1, 3, 6, 12, and 24 months per category are presented in table 2.4. The discriminatory ability of these categories was 0.70. Figure 2.2 shows the flowchart to guide the stratification of patients with symptomatic LBM, with the corresponding 95% CIs for median overall survival for each category. The 4 clinically relevant categories (A [29% of the patients], B [19%], C [31%], and D [21%]) represent median survival of 21.9 months (95% CI, 18.7 to 25.1 months), 10.5 months (95% CI, 7.9 to 13.1 months), 4.6 months (95% CI, 3.9 to 5.3 months), and 2.2 months (95% CI, 1.8 to 2.6 months), respectively (figure 2.3), with a discriminatory ability of 0.69.

Table 2.1 Patient demographics

Characteristic	
No. of patients	1520
Age* (yr)	65.0 (12.8)
Sex (no. [%])	
Male	690 (46.4)
Female	830 (54.6)
Karnofsky Performance Score† (no. [%])	
80-100	648 (42.6)
≤70	512 (33.7)
Unknown‡	360 (23.7)
Visceral metastases§ (no. [%])	
Present	588 (38.7)
Not present	890 (58.6)
Unknown‡	42 (2.8)
Metastases to brain and/or central nervous system# (no. [%])	
Present	85 (5.6)
Not present	1413 (93.0)
Unknown‡	22 (1.4)
Tumor location (no. [%])	
Femur	1029 (67.7)
Humerus	399 (26.3)
Tibia	60 (3.9)
Radius	14 (0.9)
Ulna	11 (0.7)
Fibula	7 (0.5)
Location in bone (no. [%])	
Proximal	1066 (70.1)
Shaft	303 (19.9)
Distal	133 (8.8)
Unknown	18 (1.2)
Solitary bone metastasis (no. [%])	
Yes	162 (10.7)
No	1181 (77.7)
Unknown	177 (11.6)

*The values are given as the mean, with the standard deviation in parentheses. †Determined on the basis of the clinical description in 47% of the patients. ‡In total, data were missing for 389 patients; for 35 patients, data for >1 of the variables were missing. §As reported in recent radiology reports. #Presence of metastases was determined on the basis on recent radiology reports; metastases were considered not present if there was no clinical suspicion of brain metastases (therefore, no radiology).

Table 2.2 Primary tumors and their corresponding clinical profile

Primary tumor	*No. (%) of patients*	*Median Overall survival (95% CI) (mo)*	*Clinical profile*
Breast - positive*	369 (24.3)	18.7 (15.2–22.1)	Favorable
Breast - unknown†	112 (7.4)	18.7 (14.1–23.2)	Favorable
Kidney - solitary metastasis	25 (1.6)	18.1 (0.0-37.7)	Favorable
Thyroid	23 (1.5)	9.8 (0.0–23.5)	Favorable
Prostate	233 (15.3)	7.8 (6.5–9.1)	Moderate
Kidney - multiple metastases	85 (5.6)	8.1 (4.6–11.7)	Moderate
Other primary tumor‡	20 (1.3)	3.8 (0.0-12.4)	Moderate
Soft tissue sarcoma	19 (1.3)	6.8 (5.5–8.1)	Moderate
Breast - triple negative§	16 (1.1)	3.4 (1.4–5.4)	Moderate
Kidney – unknown#	16 (1.4)	10.3 (4.1-16.4)	Moderate
Endometrial carcinoma	9 (0.6)	12.2 (4.3–20.2)	Moderate
Osteosarcoma	8 (0.5)	4.0 (0.2-7.9)	Moderate
Ewing sarcoma	7 (0.5)	17.4 (10.8–54.1)	Moderate
Ovary	6 (0.4)	2.6 (2.0–3.2)	Moderate
Lung	363 (23.9)	2.9 (2.4–3.3)	Unfavorable
Colorectal	48 (3.2)	3.9 (2.6–5.2)	Unfavorable
Unknown primary	44 (2.9)	3.3 (1.5–5.1)	Unfavorable
Esophagus	32 (2.1)	3.4 (1.4–5.4)	Unfavorable
Bladder	25 (1.6)	3.8 (1.9–5.7)	Unfavorable
Melanoma	23 (1.5)	3.9 (2.2–5.6)	Unfavorable
Head and neck cancer	19 (1.3)	3.2 (0.7–5.6)	Unfavorable
Liver and/or pancreas	10 (0.7)	2.3 (0.2–4.4)	Unfavorable
Stomach	8 (0.5)	2.1 (0.7–3.4)	Unfavorable

*Estrogen, proesterone or Her2/neu positive; †Hormone receptor status and Her2/neu status were unknown; ‡Consisting of 5 patients each with cervical carcinoma and with multiple primary tumors; 2 patients each with Merkel cel carcinoma, carcinoma of the adnexa, and uterine sarcoma; and 1 patient each with a retroperitoneal paraganglioma, a neuroblastoma, a fibrous tumor of the thorax, and a carcinoma of the vulva. §Estrogen, progesterone, and Her2/neu negative. #The number of metastases was unknown. Mo: months.

Table 2.3 Details of local treatment of bone metastasis

Treatment	*No. (%) of patients*
Overall	
Radiation therapy	1041 (68.5)
Surgery only	130 (8.6)
Surgery + adjuvant radiation therapy*	349 (23.0)
Radiation therapy	
1x8 Gy	656 (63.1)
2x8 Gy	83 (8.0)
5x4 Gy	124 (11.9)
6x4 Gy	133 (12.8)
Single fraction other	1 (0.1)
Multiple fractions other:	
Total dose <20 Gy	12 (1.2)
Total dose >20 Gy	20 (1.9)
Unknown	2 (0.2)
Surgery	
Plate	30 (6.3)
Intramedullary nail	317 (66.2)
Endoprosthesis†	106 (22.1)
Dynamic hip screw	8 (1.7)
Resection only	7 (1.5)
Curettage and cement only	2 (0.4)
Unknown	9 (1.9)

*Radiation therapy was considered adjuvant if administered within 8 weeks of surgery. †Including total prosthesis, hemiprosthesis, and modular prosthesis.

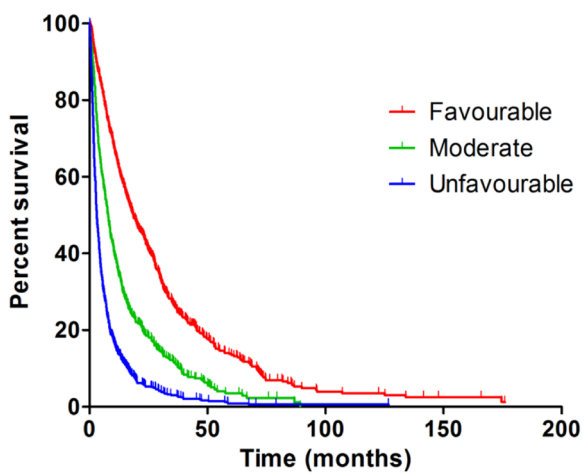

Figure 2.1 Kaplan-Meier curve for overall survival stratified by the clinical profile and according to the time (in months) since treatment.

Table 2.4 Overall survival in months and percentage of patients alive for each category

					Overall survival (mo)		*Survival at various intervals (%)*					*Clinically relevant categories**
Category	*Clinical profile*	*KPS*	*VBM*	*No.*	*Median*	*95% CI*	*1 mo*	*3 mo*	*6 mo*	*12 mo*	*24 mo*	
1	Favorable	80-100	No	145	30.4	26.8-33.9	97.9	93.1	87.6	81.4	58.4	Green (A)
2	Favorable	80-100	Yes	102	17.9	12.4-23.4	98.0	89.2	78.4	62.7	41.0	Green (A)
3	Favorable	0-70	No	77	12.8	9.5-16.0	94.0	83.1	75.3	53.2	27.3	Green (A)
4	Favorable	0-70	Yes	41	7.4	5.5-9.2	90.2	78.0	65.9	36.6	16.1	Yellow (B)
5	Moderate	80-100	No	108	11.4	8.9-14.0	98.1	88.0	72.2	48.1	24.9	Yellow (B)
6	Moderate	80-100	Yes	66	9.5	5.2-13.9	93.9	78.8	60.8	45.5	23.9	Yellow (B)
7	Moderate	0-70	No	104	5.0	3.7-6.4	88.5	66.3	43.3	21.2	12.4	Orange (C)
8	Moderate	0-70	Yes	37	3.4	2.4-4.4	81.1	54.1	29.7	8.1	0.0	Orange (C)
9	Unfavorable	80-100	No	100	5.4	2.7-8.1	96.0	69.0	49.0	25.0	9.0	Orange (C)
10	Unfavorable	80-100	Yes	109	4.5	3.7-5.3	88.1	62.4	36.7	19.3	8.3	Orange (C)
11	Unfavorable	0-70	No	120	2.2	1.7-2.7	85.0	40.0	23.3	11.4	1.8	Red (D)
12	Unfavorable	0-70	Yes	122	2.2	1.7-2.7	79.5	32.0	10.2	3.4	0.8	Red (D)

*The colors correspond to the four clinically relevant categories as seen in figure 2.2. Mo: months.

Table 2.5 Patient demographics of external cohort

Characteristic	
No. of patients	250
Age* (yr)	66.3 (11.4)
Sex (no. [%])	
Male	112 (44.8)
Female	138 (55.2)
Karnofsky Performance Score (no. [%])	
80-100	79 (68.4)
≤70	171 (31.6)
Visceral metastases† (no. [%])	
Present	129 (51.6)
Not present	121 (48.4)
Metastases to brain and/or central nervous system‡ (no. [%])	
Present	15 (6.0)
Not present	235 (94.0)
Tumor location (no. [%])	
Femur	189 (75.6)
Humerus	39 (15.6)
Tibia	21 (8.4)
Ulna	1 (0.4)
Location in bone (no. [%])	
Proximal	162 (64.8)
Shaft	61 (24.4)
Distal	27 (10.8)

*The values are given as the mean, with the standard deviation in parentheses. †As reported in recent radiology reports. ‡Presence of metastases was determined on the basis on recent radiology reports; metastases were considered not present if there was no clinical suspicion of brain metastases (therefore, no radiology).

External cohort

The external cohort included 250 patients (45% were male, with a mean age 66.3 [and standard deviation] of 66.3 ± 11.4 years) (table 2.5). The median duration of follow-up and overall survival of the patients in the external dataset were 84.7 months (95% CI, 58.4 to 111.1 months) and 7.8 months (95% CI, 6.2 to 9.3 months), respectively. Overall survival rates at 1, 3, 6, 12, and 24 months (after stratification) are given in table 2.6. A large difference in overall survival between observed and expected was seen for category 5. This was predominantly due to 2 patients in the external cohort with kidney cancer and a long survival of 89 and 110 months.

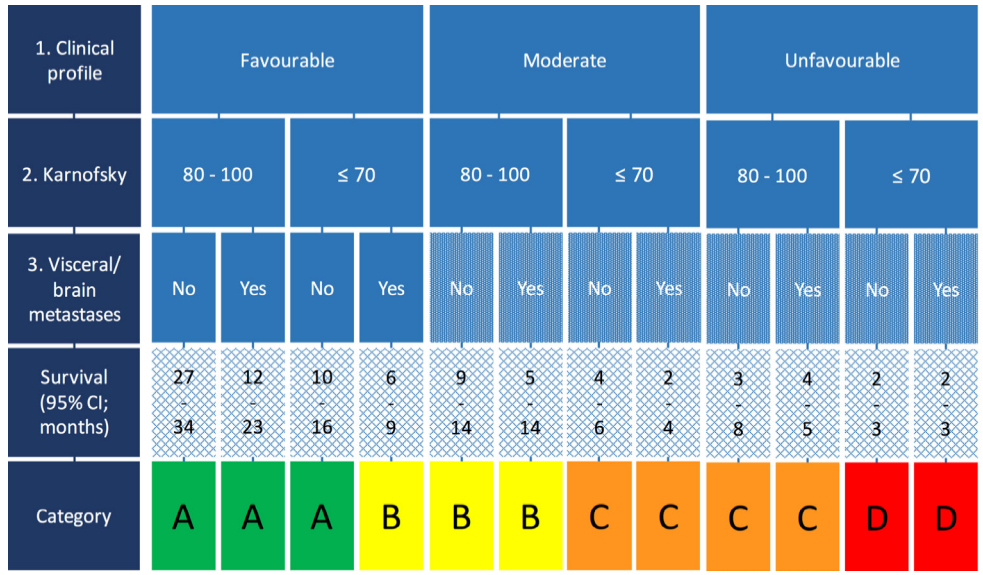

Figure 2.2 Flowchart for stratification of patients with LBM.

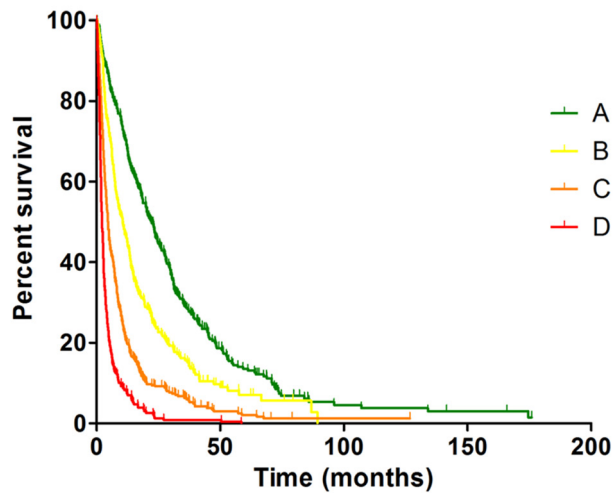

Figure 2.3 Kaplan Meier curve for overall survival stratified by prognostic groups A-D. Time in months since treatment.

Table 2.6 Overall survival in months and percentage of patients alive for each category of the original and external cohort (surgical patients only)*

						Median overall survival (95% CI) (mo)		*Survival at various intervals (%)*				
Category	*Clinical profile*	*KPS*	*VBM*	*O/Et (no. of patients)*		*Original*	*External*	*1 mo*	*3 mo*	*6 mo*	*12 mo*	*24 mo*
1	Favorable	80-100	No	48/16		29 (13-47)	25 (1-48)	100/94	92/88	88/88	79/69	58/50
2	Favorable	80-100	Yes	31/8		28 (10-46)	30 (0-64)	97/100	90/88	77/75	61/75	51/50
3	Favorable	0-70	No	28/25		13 (10-16)	7 (1-13)	100/96	89/72	79/60	50/44	29/28
4	Favorable	0-70	Yes	14/24		7 (7-8)	5 (3-6)	93/83	79/63	64/40	29/31	21/18
5	Moderate	80-100	No	25/15		14 (7-21)	33 (13-53)	96/93	80/93	64/93	52/86	28/50
6	Moderate	80-100	Yes	27/12		14 (10-18)	12 (0-63)	93/100	82/92	70/58	56/50	33/50
7	Moderate	0-70	No	19/13		5 (0-10)	9 (1-16)	95/100	74/77	47/62	21/31	16/8
8	Moderate	0-70	Yes	11/28		6 (2-10)	6 (1-10)	91/93	64/68	46/46	18/29	0/21
9	Unfavorable	80-100	No	40/8		7 (0-15)	7 (3-11)	98/100	68/89	50/63	33/31	10/16
10	Unfavorable	80-100	Yes	43/8		5 (2-7)	5 (1-9)	98/88	61/63	40/38	16/25	9/13
11	Unfavorable	0-70	No	33/22		4 (1-6)	4 (1-6)	91/86	52/55	21/27	11/14	0/0
12	Unfavorable	0-70	Yes	34/30		3 (2-3)	3 (1-6)	94/77	41/53	10/18	3/7	0/4

*O = original cohort, and E = external cohort. †Data concerning 1 of the 3 variables were missing for 126 and 41 patients for the original and external cohort, respectively. Mo: months.

Discussion

To offer patients with cancer and symptomatic LBM the most appropriate and tailored treatment, thus balancing morbidity and adverse effects with effectiveness, an accurate estimation of the expected survival is crucial. The survival estimation should be as precise as possible while obtainable in daily clinical practice. This study shows that a simple and clinically relevant estimation can be made based on clinical profile, KPS, and the presence of VBM.

The prognostic significance of these 3 variables has been reported previously.[8-11,13,14] The primary tumor, which is the basis for the clinical profile in this study, is the foundation of all prognostic models. Performance status is also included in almost all recent models.[8-11,13,14] The role of the evidence of VBM is less consistent. Although incorporated in several models,[8,10-13] others state that the effect of VBM is not[11] or only partially[15] present. The transition from 12 to 4 categories in the current study shows that, while the presence of VBM is associated with survival in all profiles, the impact on clinical decision-making is minimal. This is in accordance with the spinal metastasis prognostic model by Bollen et al.,[15] in which the presence of VBM affects only the favorable clinical profile.

Considering some of the shortcomings of previous prognostic models, the present study aimed to develop a quick and easy-to-use yet accurate prognostic model. The current model is thus based on a multidisciplinary cohort, excludes patients with multiple myeloma, and is up-to-date and easy to use. The clinical profile ensures sustainability of the model because of its dynamic description; it encompasses not only tumor growth speed, but also contributing factors, such as the effectiveness of evolving systemic treatments, which allow adjustment of the classification of a primary tumor. The increase of targeted therapies will create subtypes in various primary tumor types in the future, and thus flexibility in the categorization is essential. Future adjustments could be changes in the classification of lung tumors with EGFR (epidermal growth factor receptor) mutations,[25] melanomas with BRAF mutations,[26] and prostate cancers with low initial prostate-specific antigen (PSA) levels and favorable Gleason scores.[27]

The presented flowchart is simple to use; only 3 common variables are required, without the need for scoring. The chart stratifies between 12 different categories that can be narrowed down to 4 clinically relevant categories. The 12 categories provide a detailed insight into the expected survival, which can be helpful knowledge to fine-tune an individuals' treatment. The 4 grouped categories (A through D) are based on the cutoff points relevant for more general decision-making (i.e. 3, 6, 12 months) in a clinical setting and can be used

to translate the median survival times to clinical decisions. This more simplistic version of the model could be envisioned without the shaded areas (VBM for moderate and unfavorable clinical profiles and the 95% CI for the median overall survival) in figure 2.2.

An important limitation of the present study is the retrospective design. With this design, uniformity in diagnostics and treatments are not possible. The time frame of diagnostic tests has an influence on the interpretation of the presence of visceral, brain, and other bone metastases. Differences in local treatments between centers and over time are possible. Although a large influence of these factors on survival is not expected, they were incorporated in the multivariate analyses to correct for any possible effect. Systemic treatments were not taken into account in the analysis because they were beyond the scope of this study. Missing data are also a drawback of retrospective studies. In this study, the KPS was the most common missing variable. This was partly solved by interpreting clinical descriptions, but the latter is also a limitation as it is less objective than a scoring system. Finally, the cohort includes only patients who received local treatment for a symptomatic bone metastasis. This introduces confounding by indication because patients who received solely systemic and/or supportive care were not represented in this study. This might have led to selection bias and possibly to estimations in this study that are too optimistic. Although this could have some influence on the generalizability of the study, the minimal life expectancy for referral for palliative radiation therapy is approximately 2 months, so the effect of selection is expected to be minimal.[28]

The discriminatory ability of the model presented in this study (0.70) is comparable to the model recently reported by Westhoff et al. They described a model that was based only on patients treated with radiation therapy for bone metastases throughout the skeleton and contained 2 variables (primary tumor and KPS) that yielded a C-statistic of 0.71.

It is possible that higher discriminatory abilities might be obtainable in models with numerous variables; however, studies with such models have not noted C-statistics and therefore cannot be compared.[12,13,29] Additionally, it is important to note that the discriminatory ability in the current study is an accepted trade-off against the simplicity, and thus convenience, of the current model in comparison to models with numerous variables. Also, while models with numerous complex variables might be able to discriminate in great detail, it is relevant to wonder whether such models lead to more relevant or better clinical decision-making.

The application of the model to the external cohort shows similar results between observed and expected survival, suggesting that that the model stratifies sufficiently in other data sets. Patients with a moderate clinical profile and good KPS (mostly patients with prostate or kidney cancer) showed better survival in the external population. This could be attributed to the heterogeneity of the populations and differences in systemic treatment and local treatment regimens between the 2 countries.

In conclusion, the current study presents a model for easy and accurate stratification of patients with symptomatic LBM according to their expected survival. The versatility of the model enables easy adaptation to future developments concerning systemic treatments of primary tumors. The simplicity of the model should facilitate its use and result in an overall movement towards appropriate treatments of patients with metastases of the long bones to improve their quality of life.

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Chapter 3

Epidermal growth factor receptor mutations should be considered as a prognostic factor for survival of patients with pathological fractures of painful bone metastases from non-small cell lung cancer

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Abstract

Aims

This study aims to assess first, whether mutations in the epidermal growth factor receptor (EGFR) and Kirsten rat sarcoma (kRAS) genes are associated with overall survival (OS) in patients who present with symptomatic bone metastases from non-small cell lung cancer (NSCLC) and second, whether mutation status should be incorporated into prognostic models that are used when deciding on the appropriate palliative treatment for symptomatic bone metastases.

Patients and Methods

We studied 139 patients with NSCLC treated between 2007 and 2014 for symptomatic bone metastases and whose mutation status was known. The association between mutation status and overall survival was analysed and the results applied to a recently published prognostic model to determine whether including the mutation status would improve its discriminatory power.

Results

The median OS was 3.9 months (95% confidence interval (CI) 2.1 to 5.7). Patients with EGFR (15%) or kRAS mutations (34%) had a median OS of 17.3 months (95% CI 12.7 to 22.0) and 1.8 months (95% CI 1.0 to 2.7), respectively. Compared with EGFR-positive patients, EGFR-negative patients had a 2.5 higher risk of death (95% CI 1.5 to 4.2). Incorporating EGFR mutation status in the prognostic model improved its discriminatory power.

Conclusion

Survival prediction models for patients with symptomatic bone metastases are used to determine the most appropriate (surgical) treatment for painful or fractured lesions. This study shows that NSCLC should not be regarded as single entity in such models.

Introduction

Lung cancer is the most common type of cancer worldwide and has the highest mortality.[1] Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers.[2-4] In addition to the histological classification (adenocarcinoma, squamous cell carcinoma, and large cell carcinoma) NSCLC is increasingly defined at the molecular level by mutations which underlie the disease process. The most common are mutations in the epidermal growth factor receptor (EGFR) gene, which is present in approximately 10 to 15% of patients, and the Kirsten rat sarcoma (kRAS) gene, which is present in approximately 30%.[5]

EGFR and kRAS function sequentially in the same signalling pathway and are therefore mutually exclusive.[6] The discovery of these oncogenes has led to the development of targeted systemic therapies in the form of tyrosine-kinase inhibitors (TKIs; e.g. erlotinib, gefitinib) for patients with an active mutation in the EGFR gene: these gave an increased survival of four to five months.[7-9] Similarly effective treatment is not currently available for kRAS mutations. The predictive role of kRAS mutations is still unclear: some trials report a worse overall survival,[10,11] while others do not identify a difference.[12,13]

Bone metastases occur in 30 to 40% of patients with lung cancer.[14] However, this figure can be expected to increase as the survival of patients with lung cancer improves with treatment that is more effective. The local treatment of BM consists of radiotherapy and/or surgery, depending on the presentation and symptoms. If pain is the most predominant symptom, radiotherapy is the mainstay of treatment: it is not invasive and reduces pain in more than 60% of patients.[15] Surgical treatments, whether for fracture or prophylaxis of impending fracture, range from minimal invasive procedures to extensive resection and reconstruction. It is usually indicated when mobility and/or neurological functioning are affected.

While the treatment of bone metastases can relieve pain and increase mobility and quality of life, it can also cause complications, additional toxicity, and co-morbidity. The need for local treatment should be weighed against a patients' predicted survival to ensure the best treatment.

Several methods of estimating survival have been developed to help patients and their doctors choose the most appropriate palliative local treatment for a painful or fractured metastatic lesion.[16-20] Although the models differ, they all include the primary tumour type as the most important variable. In all models, the primary tumour is subdivided into several categories, based on speed of tumour growth and, in some cases, the therapeutic possibilities. Currently, all NSCLC patients are categorized as having 'unfavourable/poor' tumours.

However, with the increased effect of mutations on outcome, consideration should be given to whether lung cancer should remain included as single tumour type. For example, patients with EGFR mutations might fit better in a 'moderate/intermediate' tumour profile. A different tumour profile in these models would give a more optimistic prognosis and result in other strategies of local treatment being considered. For example, a prosthesis might be used instead of an intramedullary nail to treat a pathologic fracture if a longer survival was expected.

The aim of this study was to determine first, if EGFR and kRAS mutations are associated with overall survival in patients with NSCLC who present with symptomatic bone metastases, and secondly whether mutation status can be used to differentiate between patients when estimating survival.

Patients and Methods

We carried out a retrospective analysis of all patients with NSCLC who had been treated for bony metastases of the spine, pelvis or long bones in the radiotherapy and/or orthopaedics departments of a tertiary referral centre between 2007 and 2014. Patients were identified from a search of our surgical and radiotherapy databases. Only patients with metastases in the spine, pelvis or long bones caused by histologically-proven NSCLC whose tumours had undergone analysis for EGFR and kRAS mutations were included. Patient characteristics at the time of treatment were collected from medical and pathology records and included age; gender; location of bone metastasis; presence of visceral or brain metastases; Karnofsky Performance Scale (KPS);[21] local treatment of the bone metastasis; (previous) systemic treatment for the primary tumour; mutation status and outcome (alive or dead).

The presence of visceral metastases was determined on radiology reports. Brain metastases were identified clinically; whole brain CTs or MRIs were not routinely undertaken. The KPS scores the functional ability of patients with a range from 0 to 100; with a higher score meaning the patient is better able to perform daily activities.[21] KPS scores were divided into two groups: 0 to 70 and 80 to 100. Systemic treatment was described as 'standard chemotherapy' for platinum-based chemotherapy regimens and 'targeted therapy' for tyrosine kinase inhibitors. The use of systemic treatment was registered at the time of treatment of local bone metastasis. Mutation status was defined as EGFR-positive, kRAS-positive, or 'wild type' if neither EGFR nor kRAS mutations were present. EGFR and kRAS mutations were determined by competitive allele-specific hydrolysis probes (Taqman) PCR technology (CAST).[22] If this proved inconclusive, additional classic DNA Sanger sequencing of exon 18 to exon 21 of the EGFR-gene was undertaken. All analyses were performed in the same laboratory at the Leiden University Medical Center.

Statistical analysis

Survival time was calculated as the interval between the treatment for the bone metastasis and death or final follow-up. Survival curves were produced using the Kaplan-Meier method and compared with log-rank tests. Median follow-up was estimated with the reversed-Kaplan-Meier method.[23] The association between EGFR and kRAS mutations on overall survival (OS) was assessed using Cox proportional hazards models. A *p*-value of <0.05 was considered statistically significant.

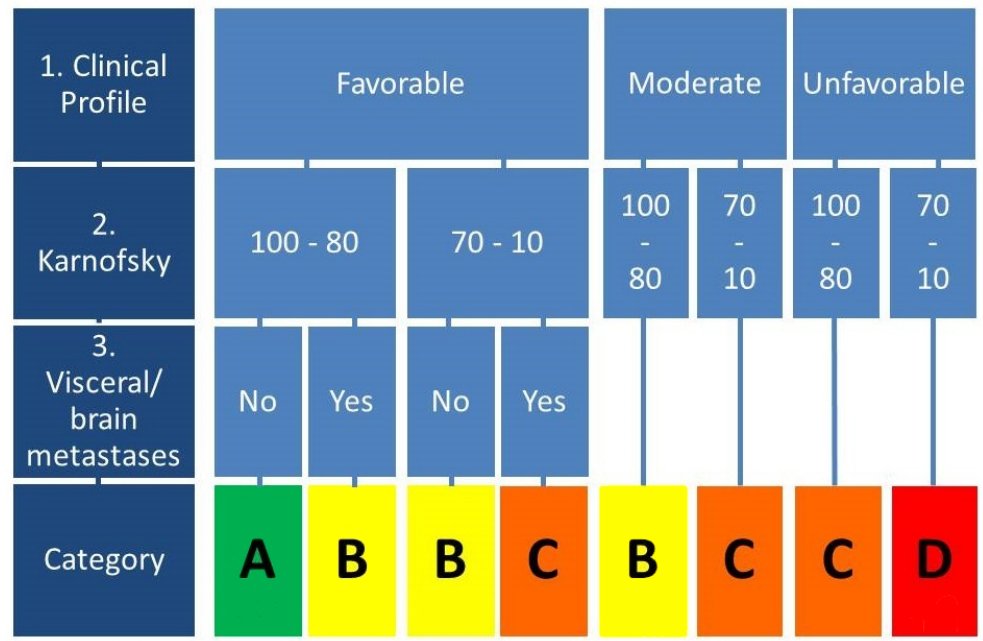

Figure 3.1 Prognostic model for overall survival as developed by Bollen et al.. Categories (A-D) correlate with expected survival in months.

To illustrate the association of EGFR with overall survival in survival prediction, the cohort was stratified according to a previously published model (figure 3.1)[16] both before and after adjusting the primary tumour type for the presence of the EGFR mutation. In the model, based on a Cox proportional hazards model, primary tumours are divided into three different tumour profiles: favourable (median survival 18.6 months; 95% confidence interval (CI) 15.1 to 22.1), moderate (median survival 5.9 months; 95% CI 4.8 to 7.0), and unfavourable

(median survival 2.2 months; 95% CI 1.9 to 2.6). In combination with two other factors (KPS and the presence of visceral and/or brain metastases) the tumour profile leads to a final category (A to D). These final categories correlate with survival. The median overall survival is 31.2 (95% CI 25.2 to 37.3), 15.4 (95% CI 11.9 to 18.2), 4.8 (95% CI 4.1 to 5.4) and 1.6 (95% CI 1.4 to 1.9) months for category A, B, C, and D respectively. Harrell's C-statistic was used to assess whether adding EGFR to the tumour profile improved the discriminatory ability of the prognostic model.

All analyses were performed using SPSS 23.0 (SPSS Inc., Armonk, New York).

Results

In the study period, 432 patients with lung cancer underwent local treatment for symptomatic bone metastases. The mutation status was available for 139 patients (32%) (53% male) with a mean age of 63.6 years (range 36.3 to 80.9). The baseline patient and tumour characteristics are presented in table 3.1. An EGFR mutation was present in 21 patients (15%) and a kRAS mutation was present in 47 patients (34%), 71 patients (51%) were wild type for both mutations.

All patients with EGFR mutations received TKIs at some point during their disease process, however only five (24%) were already on TKI treatment when they presented with symptomatic bone disease for a mean of 3.5 months (range 0.8 to 6.4). The other patients received TKIs after a mean of 2.3 months (range 0.1 to 10.1). The most commonly prescribed TKI was erlotinib (67%; 14 patients). Most patients without EGFR mutations (72%; 85 patients) underwent platinum-based chemotherapy: in 42% (36), chemotherapy was started after local treatment of the bone metastasis. The most common chemotherapy regimens were carboplatin/vinorelbine (20%) and carboplatin/pemetrexed (20%).

The median follow-up was 38.1 months (95% CI 26.9 to 49.3). Median OS was 3.9 months (95% CI 2.1 to 5.7), while mean OS was 8.4 months (95% CI 6.5 to 10.3). At final analysis, nine patients (6.5%) were still alive, four had EGFR mutations, two had kRAS mutations and two patients had 'wild type' NSCLC. No patients were lost to follow-up.

Overall survival differed significantly between patients with EGFR mutations, kRAS mutations and 'wild type' patients. For patients with EGFR mutations, the median OS was 17.3 months (95% CI 12.7 to 22.0), while the median OS was 1.8 months (95% CI 1.0 to 2.7) and 4.0 months (95% CI 1.2 to 6.8) for patients with kRAS mutations and 'wild type' patients, respectively (p = 0.001, log rank test; figure 3.2).

The difference in OS between patients with kRAS mutations and 'wild type' patients was not significant (p = 0.200, Cox regression), so kRAS was added to the wild type group, leading to a combined category 'EGFR-negative'. The median OS for the combined category was 2.8 months (95%CI 1.4 to 4.2). The corresponding hazard ratio (HR) for EGFR-negative compared with EGFR-positive for the endpoint overall survival was 2.5 (95% CI 1.5 to 4.2, p=0.001; figure 3.3).

Table 3.1 Patient and tumour characteristics in 139 patients with NSCLC treated with radiotherapy and/or surgery for symptomatic bone metastases

Characteristic	*All*	*EGFR mutation*	*kRAS mutation*	*Wild type*
Number of patients (% all patients)	139	21 (15)	47 (34)	71 (51)
Age; mean in years	63.6	62.5	64.8	63.2
Gender: male	73 (53)	7 (33)	17 (36)	49 (69)
Karnofsky Performance Score				
80 – 100	39 (28)	10 (48)	10 (21)	19 (27)
0 – 70	86 (62)	9 (43)	34 (72)	43 (61)
Unknown	14 (10)	2 (10)	3 (6)	9 (11)
Visceral or brain metastases				
Present	66 (48)	8 (38)	25 (53)	33 (47)
Not present	73 (52)	13 (62)	22 (47)	38 (54)
Location bone metastasis				
Spine	47 (34)	4 (19)	21 (45)	22 (31)
Long bone and/or pelvis	44 (32)	9 (43)	8 (17)	27 (38)
Spine & long bone and/or pelvis	48 (35)	8 (38)	18 (38)	22 (31)
Stage IV at diagnosis				
Yes	118 (85)	18 (86)	43 (91)	57 (80)
No	21 (15)	3 (14)	4 (9)	14 (20)
Treatment of primary tumor				
None	106 (76)	18 (86)	37 (79)	51 (72)
Radiotherapy	24 (17)	1 (5)	9 (19)	14 (20)
Surgery	6 (4)	1 (5)	0	5 (7)
Radiotherapy & surgery	3 (2)	1 (5)	1 (2)	1 (1)
Local therapy bone metastasis				
Radiotherapy	123 (89)	18 (86)	42 (89)	63 (89)
Surgery	1 (1)	0	0	1 (1)
Radiotherapy & surgery	15 (11)	3 (14)	5 (11)	7 (10)

EGFR: epidermal growth factor receptor; kRAS: Kirsten rat sarcoma.

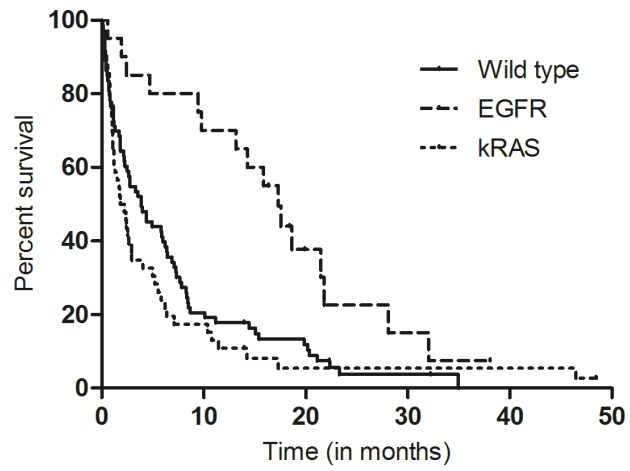

Figure 3.2 A Kaplan Meier curve shows the overall survival of 139 non-small cell lung cancer patients with bone metastases by mutation status ('wild type' for both mutations n = 71; epidermal growth factor receptor (EGFR) n = 21; Kirsten rat sarcoma (kRAS) n = 47) (p = 0.001). Time (0) = moment of local treatment of symptomatic bone metastasis.

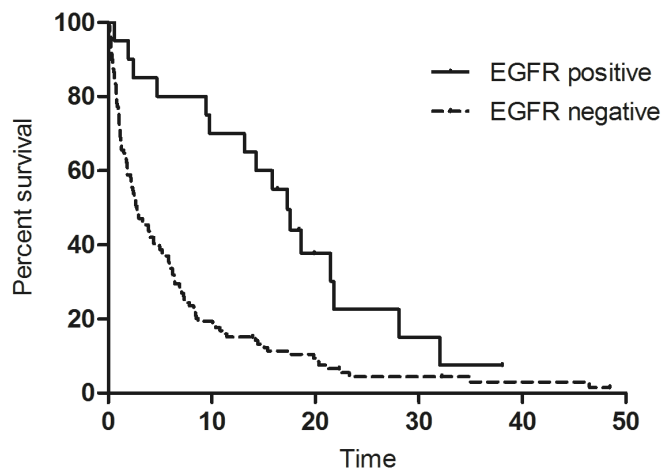

Figure 3.3 A Kaplan Meier curve shows the overall survival of 139 non-small cell lung cancer patients with bone metastases by epidermal growth factor receptor (EGFR) mutation status (EGFR-positive n = 21; EGFR-negative n = 118) (p = 0.000). Time (0) = moment of local treatment of symptomatic bone metastasis.

Table 3.2 Median survival times before and after model adjustment for EGFR mutation

*Predictive category**	*N (%)*	*Median OS (95% CI)*	*Hazard ratio*	*95% CI*	*p-value*[±]
Before adjustment					
A	NA	NA	NA	NA	NA
B	NA	NA	NA	NA	NA
C	39	10.1 (3.0 – 17.2)	0.5	0.3 – 0.7	<0.001
D	86	2.0 (1.3 – 2.7)	-	-	-
After adjustment					
A	NA	NA	NA	NA	NA
B	10	17.3 (12.3 – 22.3)	0.3	0.1 – 0.6	0.001
C	38	6.0 (2.4 – 9.6)	0.5	0.3 - 0.7	0.001
D	77	1.8 (0.9 – 2.8)	-	-	-

*Categories A-D based on model in figure 3.1; [±]log rank test; OS: overall survival; CI: confidence interval; NA: not applicable (no patients in this category).

Based on the overall survival results, the classification of primary tumours in the model was re-evaluated. The median survival of patients with EGFR mutations differs from that of patients with an unfavourable profile. The classification was therefore adjusted and NSCLC with an EGFR mutation was categorized as 'moderate' profile. As a result, ten patients were reclassified as category B instead of category C and nine patients as category C instead of category D. The median survival of category C decreased from 10.1 months (95% CI 3.0 to 17.2) to 6.0 (95% CI 2.4 to 9.6) (table 3.2). The C-statistic was 0.60 before the adjustment and 0.63 after the adjustment, indicating an improvement in the discriminatory ability of the model.

Discussion

The aim of this study was to determine whether EGFR and kRAS mutations are associated with overall survival and can therefore be used as discriminating factors for survival in patients presenting with symptomatic bone metastases from NSCLC. The results show a significant difference in median survival between patients with EGFR mutations (17.3 months, 95% CI 12.7 to 22.0), kRAS mutations (1.8 months, 95% CI 1.0 to 2.7), and 'wild type' patients (4.0 months, 95% CI 1.2 to 6.8). The difference in overall survival between patients with kRAS mutations and wild type patients was not significant, but the lack of an EGFR mutation resulted in a significantly shorter overall survival compared with patients with EGFR mutation (HR 2.5; 95% CI 1.5 to 4.2). Applying this result to the tumour stratification category of a prognostic model improved the discriminative ability of the model.

An important limitation of this study is its retrospective design and associated risk of missing data. In particular, the mutation status was not available for many patients who could not therefore be included in the analysis. Due to the retrospective design, there is also a risk of indication bias about the systemic treatments that patients underwent. The aim of this study, however, was not to determine the effect of treatment but whether it is possible to distinguish patients who had a better survival. Therefore, although mutation status and treatment are inseparably linked, the impact of indication bias on our research question is limited. The period of illness will not have influenced the use of TKI because the cohort only contained patients from 2007 onwards to avoid bias from the availability of the treatment. When predicting survival, factors such as visceral metastases and performance score were taken into account as separate variables, so they need not be considered when categorising the primary tumour.

The development of TKIs has made EGFR a widely recognized positive predictive factor for survival in patients with both early and advanced disease.[24-26] With only standard platinum-based chemotherapy, patients with an EGFR mutation survived longer than patients without the mutation.[6] Although the percentage of detected EGFR mutations (15%) in the current study was lower than that in other studies (25% to 27%)[5,27] it was sufficient to detect a significant effect on overall survival. This difference in overall survival between patients with and without EGFR mutation must be attributed to the effect of TKIs.[7,24,28] However, considering all patients have stage IV disease, the difference in survival is astonishingly large. This makes one wonder whether the effect of TKIs is possibly even greater when patients present with symptomatic bone metastases than in earlier stage disease.

The current study does not explore the role of TKIs because all patients received TKIs at some point in the disease process. However, many patients did not receive TKIs until after treatment of the bone metastasis because the diagnosis of the bone metastasis was made at the same time as that of the primary tumour. Any effect of treatment after the baseline cannot be taken into account when determining the expected survival at baseline.

When using the results from the current study to predict survival in current clinical practice, it does not matter if the difference in survival is made by the treatment or the mutation, since most patients will receive or have received TKIs. The apparent difference in survival shown by this study applies to any NSCLC patient who presents with symptomatic bone metastases, whatever their previous course of disease and its treatment.

This single-centre study provides a comprehensive analysis of a recent cohort of patients with NSCLC and bone metastases. One of the relevant aspects of the current study is the timing of assessment (i.e. at presentation with symptomatic bone metastases). Although many studies have analysed the risk factors for developing symptomatic bone metastases in patients with NSCLC,[29-31] only a few have studied the prognostic factors once these symptoms become apparent.[32-35] It is exactly at this point that it is important to predict survival so that the appropriate local treatment can be chosen. Studies that have focused on this time-point are limited either because of the absence of EGFR and kRAS mutations in the analyses[33-35] or by the relatively small number of patients included.[32] Sugiura et al.[35] reported an increased survival with TKI treatment but did not state whether these patients had EGFR mutations. Bae et al.[32] have also described a protective effect of TKI treatment and, although they note lack of significance for an EGFR mutation, this is based on only ten patients with EGFR mutations.

The updated survival prediction model of Katagiri et al.[17] is currently the only method of distinguishing between different types of lung cancer, albeit in an indirect manner. In their model, patients treated with TKIs (gefitinib and/or erlotinib) were described as having a 'moderately growing' tumour, while all other lung cancer patients had 'rapidly growing' tumours. Classifications based on the medication received or the characteristics of the primary tumour (i.e. mutations) probably have the same outcome as it is assumed that most patients with an EGFR mutation receive these drugs. However, it is possible that a classification based on the medication received is more difficult to apply in daily practice because of changes over time in the use of medication. Meanwhile, the presence of a mutation is established at baseline and does not fluctuate over time, making it a constant variable.

In conclusion, this study shows that NSCLC patients with bone metastases and EGFR mutations who are treated with TKIs have an improved overall survival when compared with EGFR-negative patients. This is of importance for all those involved in the care of patients with metastatic bone disease from NSCLC because prediction of survival is crucial in determining the most appropriate treatment strategy, especially the type of surgical treatment, for painful or fractured lesions. The sub-types of NSCLC should be incorporated in prognostic models for survival of patients with bone metastases.

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Chapter 4

Lack of clinical evidence for postoperative radiotherapy after surgical fixation of impending or actual pathologic fractures in the long bones in patients with cancer; a systematic review

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Abstract

Patients with disseminated cancer and bone metastases have a limited life expectancy and therefore any treatment should have a clear beneficial effect, outweighing all possible downsides. This systematic review aims to identify and evaluate available evidence regarding function, pain, quality of life, survival and complications of postoperative radiotherapy (RT) after surgical stabilization of impending or actual pathologic fractures of the long bones due to bone metastases.

A literature search resulted in two articles reporting on 64 and 110 patients of whom 55% and 28% received postoperative RT, respectively. Both studies were retrospective cohort studies and postoperative RT had been administered depending on the surgeons' choice. The first study reported better outcomes regarding function, re-interventions and survival in patients receiving postoperative RT. The second study reported no significant difference regarding complications between the two groups. The quality of the evidence was very low due to the observational character of both studies, risk of indication bias, small study sizes, use of non-standardized outcome measures, and limited statistical analyses.

The current available literature is insufficient to conclude whether postoperative RT after surgical stabilization should be standard care. It is important to realize this lack of clear evidence when calling upon RT as adjuvant palliative treatment.

Introduction

Bone metastases arise in up to 70% of all patients suffering from advanced cancer.[1,2] Half of those patients develop one or more complications, with pathologic fractures occurring in 5-10% of patients.[3,4] When a fracture affects the long bones a surgical stabilization of the bone is required to treat the pain and to retain a functional limb.[5] Surgery is also indicated as prophylaxis for patients with metastatic lesions at a considerable risk of fracturing. Surgical treatment options are vast and choices are made depending on localization, size and type of lesion, mechanical stability (i.e. fracture or impending fracture), and expected morbidity of the procedure in relation to the condition and expected survival of the patient. After surgery, patients are often referred for adjuvant radiotherapy (RT). Multiple reviews advise a short-course RT using five to ten fractions after surgical treatment as it would promote bone healing, prevent tumor progression, minimize the risk of implant failure, and decrease the rate of secondary procedures.[6-12] However, all these studies base their advice on a single, retrospective cohort study.[13] This was perceived as remarkable by the authors, especially because postoperative radiotherapy concerns a prophylactic treatment in patients with generally a limited life expectancy.

The life expectancy plays a large role in determining the most suitable treatment, including the necessity of postoperative RT. Several factors play a role to determine survival,[14,15] however primary tumor type is the most important. Postoperative events that could be prevented by radiotherapy, such as tumor progression and implant-failure, need time to develop. Therefore, the majority of the complications will likely occur only in patients who live long enough. For all other patients, the downsides of RT might outweigh the potential benefit. Downsides consist of the risk for complications, such as skin and gastro-intestinal problems, wound-healing problems in the post-operative period,[16] and non-union.[17] In addition, despite the generally short schedules that are given, multiple (up to ten) extra visits to the hospital are needed for planning and performing the treatment.

On the whole, this palliative, adjuvant and prophylactic treatment requires time and energy of a fragile patient and might negatively affect the quality of life, while the beneficial effect is unclear. The purpose of this systematic review was to identify and evaluate available evidence regarding function, pain, quality of life, survival and complications of postoperative RT after surgical stabilization compared to surgery only in patients with impending or actual pathologic fractures of the long bones due to bone metastases.

Methods

We report our results according to the MOOSE Guidelines for reporting systematic reviews.[18]

Search strategy

A literature search with the help of a medical librarian was performed on July 6th 2015 using the Pubmed, Embase, Web of Science and Cochrane databases without publication-date limits. The following keywords were searched: bone metastasis, skeletal metastasis, osseous metastasis, skeletal metastatic disease, secondary bone neoplasm, spontaneous fracture, pathologic fracture, postoperative radiation, postoperative radiotherapy, post-operative irradiation. Additionally, reference lists of retrieved papers, review articles, and clinical practice guidelines were checked for relevant publications.

Study selection

Two authors (JW, PDS) independently selected studies for inclusion. Titles and abstracts were screened using predefined eligibility criteria. Studies reporting on outcomes regarding function, pain, quality of life, survival and complications of patients undergoing surgery and adjuvant radiotherapy compared to patients undergoing surgery only for metastases of the long bones in English, Dutch or German were included. Meeting abstracts, case reports, guidelines, reviews and editorials were excluded (figure 4.1).

Data extraction

One author (JW) abstracted the following data items: patient demographics, treatment details, follow-up reports, functional outcomes, complications, failures, and quality of evidence.

Quality assessment

Assessment of the methodological quality of the included articles was performed according to the grading of recommendation, assessment, development and evaluation (GRADE) approach.[19] The evidence for each outcome is rated as high, moderate, low or very low. Randomized controlled trials (RCTs) provide high-quality evidence unless they are downgraded depending on risk of bias, inconsistency, indirectness, imprecision and publication bias. Evidence from non-randomized studies is regarded low-quality evidence unless they are up- or downgraded.[19]

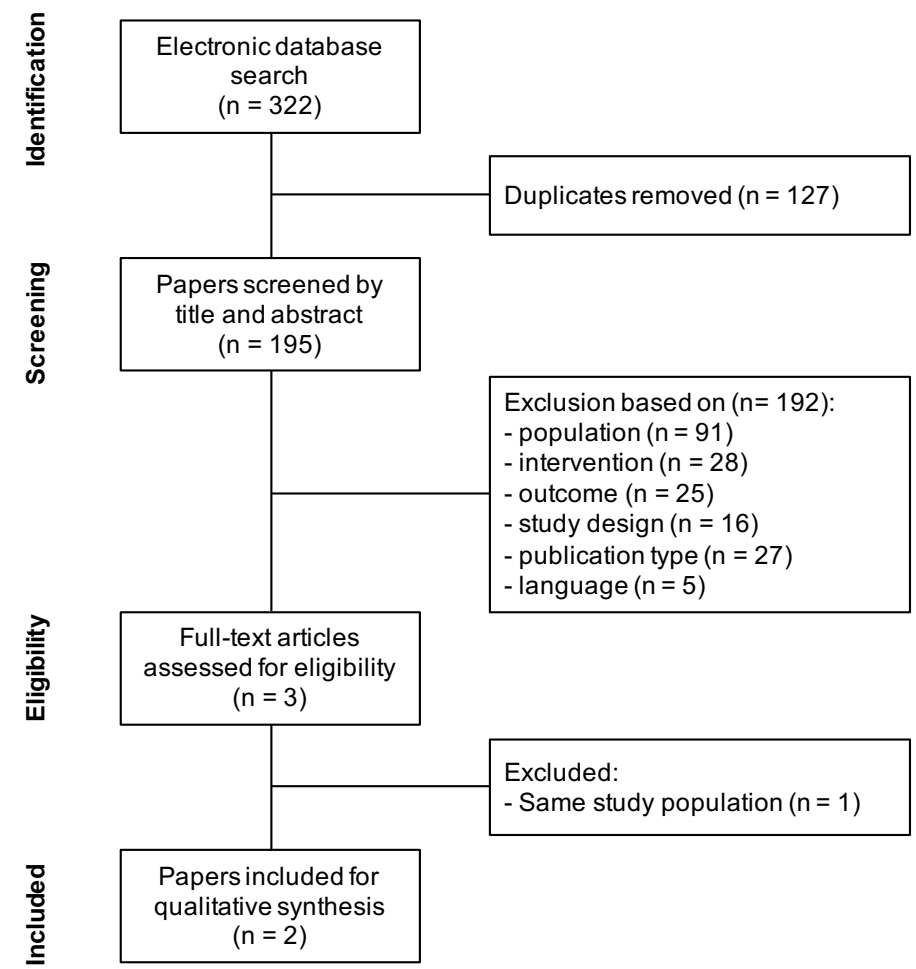

Figure 4.1 Flowchart of the study selection process. *N* = number of studies.

Results

Study selection

The search strategy resulted in 195 unique titles. Reviewing the reference lists did not lead to additional papers. After screening, three studies[13,20,21] met the inclusion criteria (figure 4.1). However, two publications by Townsend et al. were nearly identical; they describe the same cohort with the same research questions and multiple identical paragraphs. The most complete paper was included in the current study.

Study description

Both included studies were retrospective reviews of patient cohorts. Table 4.1 presents the characteristics of the included studies. The outcome measures differed between the studies and therefore a quantitative analysis was not possible.

Table 4.1 Descriptive data of included studies

Author (year)	*Study design (study period)*	*Nr of patients (lesions)*	*Actual fractures / impending fractures*	*Surgical treatment*	*Mean follow-up in months (range)*	*Outcome parameters*
Townsend (1994)[20]	Retrospective cohort study (1979 – 1992)	60 (64)	39 (55%) / 25 (45%)	Arthroplasty 16 (25%) Fracture fixation 48 (75%) + Methyl-methacrylate 23 (36%)	10.7 (3 days – 32.4)	1. Function 2. Re-interventions 3. Survival
van Geffen (1997)[21]	Retrospective cohort study (1983 – 1993)	116 (152)	85 (56%) / 67 (44%)	Surgery (72%) - plate-osteosynthesis 51% - intramedullary nail 23% - prosthesis 14% - (partial) resection 6% Irradiation only (18%) Conservative (10%) + Methyl-methacrylate 60 (55%)	**	1. Complications

**Data not reported.

Townsend et al.[20] aimed to compare the outcome of orthopedic stabilizations for impending or pathologic fractures with or without postoperative RT in 60 patients with 64 procedures. Patients who had received previous RT to the fracture site were excluded. After surgery patients were referred for RT if the treating orthopedic surgeon ought this necessary. This occurred in 55% of the cases (table 4.2).

Table 4.2 Distribution of treatments by fracture type

		Surgery only	*Surgery + RT*
Townsend (1994)[20]	All fractures	29 (45%)	35 (55%)
	Actual fracture	21 (72%)	18 (51%)
	Impending fracture	8 (28%)	17 (49%)
van Geffen (1997)[21]	All fractures	79 (72%)	31 (28%)
	Actual fracture	**	**
	Impending fracture	**	**

**Data not reported. RT: radiotherapy.

Table 4.3 Outcomes and results per treatment group

	Outcome	*Total*	*Surgery only*	*Surgery + RT*	*p*
Townsend (1994)[20]	1. Function status 1 or 2		11.5%	53%	<0.01
	2. Re-intervention	5 (7.8%)	4 (14%)	1 (3%)	0.035
	3. Survival (months; median)	7.3 (3 days – 40.6)	3.3 (3 days – 43.5)	12.4 (8 days – 48.6)	0.025
van Geffen (1997)[21]	1. Complications	21 (20%)	17 (21%)	4 (13%)	0.301*

RT: radiotherapy. *As calculated by the authors of this review (Chi-square test). Van Geffen et al. reported the outcome merely as 'not significant'.

A self-developed scoring system was used to analyze functional outcomes. The endpoint for analysis of function (functional status 1 or 2) was defined as 'normal, pain-free use of the extremity (status 1)' or 'normal use with pain (status 2)'. The other functional outcomes (status 3 or 4) were defined as 'significantly limited use requiring some type of prosthesis (e.g. walker, cane, crutches)' or 'non-functional (e.g. wheelchair-bound or bedridden)'. In the group of patients who had received RT the observed proportion of patients with a functional limb at any time was 53% versus 11.5% for surgery only (table 4.3). On multivariate analysis, including postoperative RT (univariate p = 0.026), pre-fracture functional status (univariate p = 0.045), type of surgical procedure (univariate: not reported), and use of methylmetacrylate (univariate: not reported), only

postoperative RT was significant to achieve a functional status 1 or 2 (p=0.026). It is not reported why fracture type was not included in the multivariate model. Moreover, according to the methods section of the article, the Cox model analysis was run twice with different sets of variables because of the limited sample size, however this is not described as such in the results section. The study reports less second orthopedic procedures to the same site for patients receiving surgery and RT (1 of 35 sites vs. 4 of 29 sites; table 4.3). Finally, the study reports a better survival in patients receiving surgery with RT: median 12.4 months compared to 3.3 months (p=0.025; table 4.3). At univariate level, postoperative RT (p=0.025) and type of fracture (p=0.05) were significant predictors for survival. On multivariate analysis, postoperative RT (p=0.025; table 4.3) and type of surgery (p=0.05) remained significant. No results of other variables in uni- or multivariate analysis are reported.

Van Geffen et al.[21] reported on the effect of RT on complication rate as a secondary outcome in their retrospective cohort study. The study focused primarily on the mobility levels before and after surgery, independent of adjuvant therapy. Postoperative RT was administered to 28% of all surgical patients (table 4.2). Details concerning indications for certain strategies are not provided. The results concerning postoperative RT report 21% complications in the non-irradiated group versus 14% of the patients receiving postoperative RT (table 4.3). All complications were bone-related, i.e. failure of the osteosynthetic device or implant, and progression or recurrence of disease. The authors describe this as a remarkable, but not statistically significant difference. Unfortunately, no further details are presented. The authors report no difference in pain relief, or use of analgesic drugs between the two groups however this is not supported by reported numbers.

Quality assessment

Due to the retrospective cohort design and the risk of bias of both included studies, the evidence for all study outcomes is regarded as 'very low' quality according to the GRADE approach.

Discussion

This study aimed to evaluate available evidence regarding the effect of postoperative RT after surgical stabilization of (impending) pathologic fractures. A search of the literature resulted in only two publications that met the inclusion criteria. The outcomes of the included studies should be interpreted with caution due to the very low quality of the evidence.

Firstly, the study designs lead to a large risk of indication bias. In both studies the allocation of adjuvant RT was performed by judgment of the surgeon. Neither article elaborates on the reasons for referring some patients for postoperative RT and not referring others. However, it is very plausible that patients who are in relatively good health and with a longer expected survival are considered for postoperative RT, while those in poor health and with a short expected survival are not referred. As Townsend et al. acknowledge, this is likely to explain the large difference in survival they register between the groups with or without postoperative RT. The distribution of the number of patients with an actual fracture between the treatment groups also supports this bias; a larger proportion of surgery-only patients had an actual fracture (72%) than the surgery plus radiotherapy patients (51%) (table 4.2). Patients with actual fractures are generally in a more advanced disease stadium. Moreover, in the study by Townsend et al. these patients were older and had worse pre-fracture functional status. It is quite likely that these patients had further progressive disease.

Secondly, the small number of patients (64 and 110 patients) limits the generalizability of the studies. Although Townsend et al. had enough patients to detect a significant difference, the results of these small retrospective, non-randomized cohorts cannot be projected as advice for treatment in future patients.

Thirdly, Townsend et al. applied a self-designed, non-validated functional scoring system as outcome. The authors do not describe the definition of normal use; is normal use implied if walking-aids were not needed, or if a patient was not wheelchair-bound or bedridden? Furthermore, a more detailed functional outcome by the range of motion or impairment of flexion or extension for example, is not described. The difference between status 1 and 2 is defined by the presence of pain, however the use of pain medication is not taken into account. Neither does the article report whether the function is reported by the patient, or whether it is interpreted by the clinician.

Fourthly, due to the lack of complete reporting of uni- and multivariate analyses it is unclear how the authors adjusted for confounding variables and the effect this had on the outcomes. Hazard ratios are not presented, so the actual effect of the prognostic factor is not known. In the article by van Geffen et al. statistical results were not described at all. For the functional status in the article by Townsend et al. the p-value for post-operative radiotherapy was the same on uni- and multivariate analysis without further clarification; this appears as a strange coincidence. Neither article describes how they accounted for the effect of primary tumor type, while this is of great effect on the both functional

outcome[17,22] and survival.[15,23] Also, the analysis on the effect of RT on functional outcome should not only have considered the type of fracture and surgery, but also the extent of tumor excision. Extensive surgery including curettage and possibly augmentation will leave less residual tumor, while minimally invasive procedures leave all tumor mass in situ. The expected benefit of radiotherapy is thus less likely after a more extensive excision, than after a minimally invasive procedure. The manner in which the surgery types have been classified in the study by Townsend et al. does not sufficiently take the extent of tumor excision into consideration.

Finally, the statistical analyses do not take the competing risk of death into account when analyzing the risk factors for local progression and implant failure. This would have given a more realistic, and possibly reduced, risk of complications.[24]

It is remarkable that although the supporting evidence of postoperative RT is limited to only two studies with low quality of evidence this adjuvant treatment has found such a widespread implementation throughout the Western countries. In addition, although a few other studies on the same topic report on outcomes after surgery with or without RT, they lack a comparison of the outcomes between both treatment strategies.[22,25,26] Comparing the outcomes of all these studies was not possible due to the heterogeneity of the treatments and study populations. Also, the descriptions of the results concerning postoperative RT are not detailed enough to enable analysis. This leaves the significant clinical question of the efficacy of postoperative RT unanswered. Reasons for the apparent lack of research are unclear, but might be due to the palliative setting of the surgical treatment, the way surgeons are trained and the multidisciplinary aspect of the treatment. Together this might lead to less awareness of the need for evidence of this adjuvant treatment.

The article by Townsend et al. has been cited multiple times, however referring papers seldom question the quality of the study.[7,8,12,27] Several authors have reported a possible irrelevance or disadvantage of adjuvant RT, however not based on concise research.[28-31] Dijkstra et al. report the risk of impaired healing due to the suppression of the chondrogenetic phase of secondary ossification caused by radiotherapy.[29] Hoskin mentions that postoperative RT might be irrelevant in many patients due to the short survival.[31] He makes an important comment on the lack of knowledge concerning the true incidence of tumor progression as well as the clinical significance of progression. However, Hoskin also warns for potential problems when a patient survives a sufficient time for tumor progression to occur. Epstein et al. also recognize the limited available evidence for postoperative RT.[32]

The effect of postoperative RT should be analyzed with consideration of the expected survival of patients with disseminated cancer and in the context of quality of life, instead of in quantitative outcomes such as number of complications or revision surgeries. Despite improvements in survival over the last decades, median survival for patients ranges from 2 months for lung cancer to 7 months for prostate and 19 months for breast cancer.[14] It is plausible that the benefits of RT will outweigh the downsides in patients with a long-term survival. However, for patients with a medium-term or short-term survival, the negative effects of RT on the quality of life might be larger than the risk of local progression or implant-failure. While a beneficial effect of radiotherapy on the quality of life has been shown in the setting when radiotherapy is the only treatment, this has not been investigated when radiotherapy is administered post-operatively. It is possible that all improvements in quality of life for patients after surgery and adjuvant radiotherapy are due to the surgical stabilization. In that case, adjuvant radiotherapy costs time and brings a risk of side effects, which can negatively influence the quality of life.

Additionally, it is essential to recognize the increase of pharmacological bone-directed therapies and their role in bone strengthening and prevention of complications. Although the specific impact of such treatments on postoperative quality of life is unknown, it is not unimaginable that they reduce the risk of local tumor expansion and corresponding complications. This would even further dilute any effect of postoperative radiotherapy. Furthermore, the role of these therapies should be taken into account when interpreting the results of the study by Townsend et al., for this study was performed in an era before systemic therapies were widely administered.

Based on the results of this review, a firm conclusion on the standard use of postoperative radiotherapy cannot be drawn. However, it can be concluded that substantial evidence for postoperative radiotherapy is lacking. In an era where evidence-based medicine is the backbone of all decision-making, this can be considered as peculiar at the least, especially when it concerns a palliative treatment in patients with a limited life expectancy. The number of patients with bone metastases in need of surgical fixation will increase in the future. To provide the most optimal palliative care to maintain quality of life, conclusive research should determine whether postoperative RT has a beneficial effect. Establishing a large, multi-center randomized study will provide further insights and lead to a firmer substantiated treatment plan for patients with bone metastases of the long bones. Foremost, all clinicians should realize that any firm evidence for or against postoperative RT is lacking and that it is unknown whether the treatment is a superfluous or vital element of optimal care.

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Chapter 5

Trends in surgical treatment of pathologic fractures of the long bones advocate the use of prognostic models to identify patients who benefit from centralized care

Based on a questionnaire among members of the Dutch Orthopaedic Society and EMSOS

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Abstract

Aim

The aim of this study was to assess the current trends in the estimation of survival and the preferred forms of treatment of pathological fractures among national and international general and oncological orthopaedic surgeons, and to explore whether improvements in the management of these patients could be identified in this way.

Methods

All members of the Dutch Orthopaedic Society (DOS) and European Musculoskeletal Oncology Society (EMSOS) were invited to complete a web-based questionnaire containing 12 cases.

Results

A total of 96 (10.1%; groups 1 and 2) of 948 members of the DOS and 33 (18.1%; group 3) of 182 members of the EMSOS replied. The estimation of survival was accurate by more than 50% of all three groups, if the expected survival was short (<3 months) or long (>12 months). General orthopaedic surgeons preferred using an intramedullary nail for fractures of the humerus and femur, irrespective of the expected survival or the origin of primary tumour or the location of the fracture. Oncological orthopaedic surgeons recommended prosthetic reconstruction in patients with a long expected survival.

Discussion

Identifying patients who require centralised care, as opposed to those who can be adequately treated in a regional centre, can improve the management of patients with pathologic fractures. This differentiation should be based on the expected survival, the type and extent of the tumour, and the location of the fracture.

Introduction

The most common malignant bone tumours in adults are metastases.[1] The increased number of patients with cancer, due to the ageing population, and their increased survival due to continuously improving systemic treatments, have increased the number of patients with bone metastases.[2] Although primary bone tumours are usually treated by specialized oncological orthopaedic surgeons, pathological fractures caused by metastases are generally treated by all orthopaedic surgeons, and in some countries also by trauma surgeons. Some hospitals may have protocols that assign the care of these fractures to a certain specialist, but generally treatment is performed by whomever the patient is referred to. It is not known whether this has an adverse effect on the standard of care, but it can be hypothesized that the frequent routine treatment of pathologic fractures leads to an increased understanding of these fractures, which may improve their management. In an attempt to optimize the care of these patients, there may be room for improvement in the current systems, in which pathologic fractures are treated by too many surgeons with only some experience in the fixation of pathologic fractures.

The aim of this study was to assess the current trends in the estimation of survival and preferred treatment among national and international general and oncological orthopaedic surgeons to explore whether areas of improvement in the care of patients with a pathologic fracture might be identified.

Methods

All members of the Dutch Orthopaedic Society (DOS) and European Musculoskeletal Oncology Society (EMSOS) were invited by email to participate in an anonymous web-based questionnaire (enclosed at the end of this chapter), followed by a reminder email five weeks later. Dutch oncological orthopaedic surgeons were approached through the EMSOS. The first section of the survey covered the demographics of the surgeons. The second section dealt with the estimation of survival and which factors surgeons considered of influence. The third section consisted of 12 clinical cases including actual and impending fractures of the humerus and femur. All answers were multiple choice. The cases were based on patients who had been treated by the authors to reflect daily practise. Six cases were described as the patients had presented; subsequently, one aspect of each case, such as the age of the patient or the number of bony metastases, was altered to establish the paired cases, leading to a total of 12 cases.

Descriptive statistics were applied for the outcomes of the questionnaire.

Table 5.1 Demographics of respondents of the questionnaire

	Group 1 n (%)	*Group 2 n (%)*	*Group 3 n (%)*
Total respondents	50	46	33
Experience			
Resident	15 (30)	13 (28)	0
≤ 5 years	5 (10)	8 (17)	5 (15)
6 – 10 years	11 (22)	13 (28)	10 (30)
11 – 20 years	14 (28)	6 (13)	7 (21)
> 20 years	5 (10)	6 (13)	11 (33)
Frequency of pathologic fracture treatment			
> 2 times per month	0	2 (4)	17 (52)
1 – 2 times per month	0	15 (33)	11 (33)
1 – 2 times per 3 months	0	29 (63)	5 (15)
1 – 2 times per 6 months	29 (58)	0	0
1 – 2 times per year	21 (42)	0	0
Subspecialty*			
Hip/knee	21 (42)	18 (39)	13 (39)
Arthroplasty	17 (34)	15 (33)	15 (45)
General orthopaedics	10 (20)	12 (26)	13 (39)
Traumatology	10 (20)	15 (36)	6 (18)
Upper extremity	13 (26)	6 (14)	6 (18)
Foot/ankle	3 (6)	7 (15)	2 (6)
Paediatrics	4 (8)	6 (14)	3 (9)
Oncology	0	3 (7)	33 (100)
Sports	9 (18)	1 (2)	2 (6)
Spine	3 (6)	9 (20)	1 (3)
In training	15 (30)	13 (28)	0

*Respondents (excl. residents) can have more than one subspeciality.

Respondents

Of the 948 members of the DOS who were approached, 96 (10.1%) completed the survey. Of the 182 members of the EMSOS who were approached, 33 (18.1%) replied. Respondents of the DOS were categorized into groups according to the frequency with which they treated pathologic fractures: once or twice every six months or less was classified as group 1 (52%; 50 of 96) and once or twice every three months or more was classified as group 2 (48%; 46 of 96). Respondents from the EMSOS were categorised as group 3. The demographics of the respondents are shown in table 5.1.

OPTIModel

The OPTIModel for the estimation of survival of patients with metastases of the long bones was used as the gold standard for the expected survival. These estimations were caterogized as: less than three months, three to six months, six to 12 months, and more than 12 months. This model is based on a large retrospective cohort and has been externally validated.[3]

Table 5.2 Prognostic factors for and methods to estimate survival according to respondents

	Group 1 (n=50) (%)	*Group 2 (n=46) (%)*	*Group 3 (n=33) (%)*
Prognostic factor[1]			
Primary tumour	48 (96)	45 (98)	28 (85)
Performance score	40 (80)	36 (78)	21 (64)
Visceral metastases	30 (60)	27 (58)	27 (82)
Brain metastases	24 (48)	33 (72)	22 (67)
Presence of other bone metastases	24 (48)	24 (52)	15 (45)
Age	15 (30)	19 (41)	13 (39)
Interval between primary tumour and metastasis	7 (14)	11 (24)	9 (27)
Number of other bone metastases	13 (26)	6 (13)	7 (21)
Actual fracture	8 (16)	4 (9)	7 (21)
Laboratory values	7 (14)	4 (9)	6 (18)
Pain	4 (8)	4 (9)	3 (9)
Gender	3 (6)	1 (2)	1 (3)
Survival estimation method[2]			
Ask oncologist	46 (92)	33 (72)	13 (39)
Tool/predictive model/nomogram	4 (8)	12 (26)	9 (27)
Own experience	0	1 (2)	9 (27)
Do not estimate survival	0	0	2 (6)

[1]Respondents were allowed to give a maximum of five answers. [2]Respondents could give one answer.

Results

What factors influence survival?

Respondents reported a mean of 4.6 factors (2 to 5) as being prognostic. The primary tumour was selected as a prognostic factor by 121 respondents (94%). An overview of the factors that were selected is shown in table 5.2.

How is survival estimated?

The methods of estimating survival are shown in table 5.2. A total of 79 respondents (82%) in groups 1 and 2 asked an oncologist for an estimation. This portion was smaller for group 3 (13/33; 39%). Almost one third of the latter group (9/33; 27%) based their estimate on their experience, while only one respondent in group 2 provided this answer. Prognostic models, tools, or nomograms were used by 25 (19%) respondents.

The estimation of survival for the cases

Respondents were asked to estimate survival in 11 cases (table 5.3). If a short survival of less than three months was expected according to the OPTIModel, the answers mainly corresponded in all groups (81%, 68%, and 79% for groups 1, 2, and 3, respectively). An effect of age was observed; the answers were more unequivocal if the patient was older. Group 3 respondents answered most consistently for patients with a long expected survival (>12 months); the mean rate of correct answers was 80% (64 to 97). The non-expert, not-frequent group 1 was less consistent if a long survival was expected; the mean rates of correct answers was 52% (45 to 58), while the non-expert, frequent group 2 recognized a long survival quite reliably with a mean rate of 68.5% (59 to 76). The difference in the estimation of long survival was especially evident in two cases with a solitary metastasis of a renal cell carcinoma (case 3a and 4a). In these two cases, the non-expert groups less frequently recognised the long expected survival. In the other four cases with a long survival, the difference between the expert and non-expert groups was less evident. In these more common cases from daily practice, the difference in the estimation of survival was more apparent between those that treat these patients regularly or not (groups 1 and 2). It was also easier for respondents to estimate a long survival in younger patients, as in cases 1a and 6a. In the older patients, as in case 1b and 6b, respondents were more inclined to give a shorter prognosis. Likewise, more respondents estimated a short survival for an older patient as when comparing case 2a with 2b. The cases with an intermediate expected survival (three to six months or six to 12 months) had low rates of correspondence between the respondents of each group (37%, 52%, and 52% for group 1, 2, and 3, respectively). The variation of answers was especially evident in group 1; in the other groups, however, the percentages of 'correct' answers were also not high (up to 64%).

Treatment

In 12 cases, respondents were asked to choose the most appropriate treatment bearing in mind the location and the type of lesion (i.e. actual or impending fracture), as shown on a radiograph, and the expected survival. Six cases had comparable fractures of the proximal humerus. Table 5.4 shows the preferred form of treatment chosen by the respondents. If survival was expected to be short (less than three months or between three and six months) the choices did not differ much between the three groups. The most popular choice within each group was an intramedullary nail (62%, 48%, and 68%, for group 1, 2, and 3, respectively), although fixation with a plate, radiotherapy, and conservative therapy were also well-considered options. If survival was expected to be between six and 12 months, differences between the groups became clear: groups 1 and 2 were indecisive about the most appropriate option, with answers ranging between all options, while group 2 predominantly remained to have a preference for intramedullary nails. Group 3 also continued to consider nails or plates, but increasingly tended towards prosthetic reconstruction. If a survival of >12 months was expected, the difference between the groups was most evident: group 3 would treat almost every patient (90%) with a prosthesis, while groups 1 and 2 considered all surgical options, treating only approximately 50% to 60% with a prosthesis. Of the latter respondents, one third (33%) would use a conventional shoulder prosthesis as opposed to a tumour reconstruction, while most of group 3 (84/90; 93%) would use a tumour prosthesis.

Six other cases described patients with a fracture of the proximal femur. Responses of the appropriate treatment in relation to the estimated survival are shown in table 5.5. Approximately 20% of the respondents in all groups would choose conservative treatment if survival was less than three months. Most (60%-77%), however, preferred fixation with an intramedullary nail, despite the short survival. If survival was expected to be between three and six months, an intramedullary nail was the most preferred treatment for groups 1 and 2 (80%), while group 3 considered prosthetic reconstruction (61%). The latter respondents wavered between a hemiarthroplasty, a total hip arthroplasty or a modular tumour prosthesis. When the expected survival became longer, and especially >12 months, most (73%) of group 3 would choose a tumour prosthesis, while most (55%) of groups 1 and 2 preferred an intramedullary nail.

Discussion

In the future, surgeons should have more specific knowledge about the indications for treatment and the varying forms of treatment that are available for the increasing number of patients who will present with a pathological fracture, in order to ensure the best outcome. Many aspects of this treatment remain controversial.

Table 5.3 Survival estimations by respondent groups per case. For survival estimation answers there were four choices: <3 months, 3-6 months, 6-12 months, >12 months. Answers are presented as percentage within each respondent group per case. The second column (OPTIModel) states the expected survival according to the OPTIModel

		Group 1 (n=50)				*Group 2 (n=46)*				*Group 3 (n=33)*			
	Estimated Survival (months)	*<3*	*3-6*	*6-12*	*>12*	*<3*	*3-6*	*6-12*	*>12*	*<3*	*3-6*	*6-12*	*>12*
	OPTIModel												
Case 1a	>12 months	0	8	38	54	0	7	17	76	0	0	18	82
Case 1b	>12 months	2	10	46	42	2	11	24	63	3	12	21	64
Case 6a	>12 months	0	8	37	55	0	0	28	72	0	6	15	79
Case 6b	>12 months	2	14	39	45	2	7	24	67	3	6	27	64
Case 3a	>12 months	2	10	30	58	2	9	30	59	0	0	6	94
Case 4a	>12 months	0	14	30	56	0	4	22	74	0	3	0	97
Case 4b	6-12 months	24	30	34	12	13	28	44	15	6	9	64	21
Case 5a	3-6 months	42	40	16	2	24	50	22	4	33	39	27	0
Case 5b	3-6 months	50	38	12	0	26	61	11	2	36	52	12	0
Case 2a	< 3 months	72	22	6	0	54	35	4	7	73	18	9	0
Case 2b	< 3 months	90	8	2	0	83	13	4	0	85	15	0	0

Table 5.4 Treatments of actual pathologic fractures of the humerus by survival estimation per respondent group; results of six cases (1a, 1b, 3a, 3b, 5a, 5b). The results are given as percentages within each survival estimation subgroup of each respondent group (e.g., <3 months, group 1). Totals of each subgroup (denominator) are reported in the last row.

	Group 1				*Group 2*				*Group 3*			
Estimated Survival[1]	*<3*	*3-6*	*6-12*	*>12*	*<3*	*3-6*	*6-12*	*>12*	*<3*	*3-6*	*6-12*	*>12*
Conservative	13	3	2	0	21	4	0	0	15	0	2	1
Radiotherapy	12	13	15	12	3	5	6	4	19	16	7	1
Nail	68	67	41	24	48	68	55	26	62	51	38	2
Plate	7	7	11	12	24	15	21	9	4	30	24	5
Shoulder prosthesis	0	4	15	12	0	4	13	25	0	0	0	6
Tumour prosthesis	0	7	15	39	3	5	5	36	0	2	29	84
Total responses	60	72	85	83	29	82	62	100	26	43	45	82

Table 5.5 Treatments of actual pathologic fractures of the proximal femur by survival estimation per respondent group; results of six cases (2a, 3b, 4a, 4b, 6a, 6b). The results are given as percentages within each survival estimation subgroup of each respondent group (e.g., <3 months, group 1). Totals of each subgroup (denominator) are reported in the last row.

	Group 1				*Group 2*				*Group 3*			
Estimated Survival[1]	*<3*	*3-6*	*6-12*	*>12*	*<3*	*3-6*	*6-12*	*>12*	*<3*	*3-6*	*6-12*	*>12*
Conservative	18	0	0	0	19	3	0	0	22	0	0	0
Radiotherapy	0	0	0	0	1	0	0	0	0	0	0	0
Nail	70	81	63	55	77	80	76	54	60	39	11	14
Hemi	9	10	23	1	1	3	10	3	5	11	21	5
THP	2	6	1	11	1	3	14	14	2	11	8	8
Tumour prosthesis	1	2	12	33	0	13	0	30	13	39	61	73
Total responses	94	48	73	83	70	40	58	108	55	18	38	86

THP: total hip prosthesis

We should, however, wonder whether it is feasible for all surgeons currently managing these fractures, to remain up to date in this area. Should the treatment of pathologic fractures become a sub-speciality and should patients with these fractures be referred to such specialists? In order to assess whether these ideas are worth exploring, we designed a study based on a questionnaire to evaluate current similarities and differences in treatment between orthopaedic surgeons who treat pathologic fractures infrequently (group 1) or frequently (group 2), and those who specialize in oncology (group 3).

This study has limitations. First, the response rate of the questionnaire was low. The method of distribution of the questionnaire, by email, carries the risk of not reaching all the intended recipients. Although email lists of both societies were used, we do not know whether the email reached and was read by its recipient.

The low response rate might also be due to a low interest in pathologic fractures, compared with general orthopaedic problems, such as arthroplasty or traumatic fractures. Second, there might have been response bias among the respondents. Third, the groups of respondents were not completely comparable, as, for instance, group 3 did not contain residents. The distribution of experience is thus less broad in group 3 than in the other groups. This could affect the interpretation of the results as the differences could be attributed to the extent of experience. However, in the Netherlands, all residents receive training in orthopaedic oncology. It thus may have been that the residents who responded to the questionnaire were those with an interest in oncology after their oncology internship. Despite not having completed their training, these residents might have more knowledge about pathologic fractures and treat them more often than orthopaedic surgeons with extensive experience. This issue remains debatable, but it was clearly appropriate to include residents in the general orthopaedic categories in this exploratory study. Fourth, with regard to the survival estimation, the fact that the questionnaire was only sent to surgeons can be regarded a limitiation. In the light of the results of the question on how survival is estimated, to which many respondents replied that they ask the opinion of the medical oncologist, it could be that medical oncologists should have been included in the study. Although it would be interesting to compare the estimations of medical oncologists, orthopaedic surgeons, and prognostic models, this was not the aim of the study. Fifth, despite aiming to present varying cases, few fitted into the "intermediate" survival groups (three to six months, six to 12 months) compared with those with a long survival (>12 months). A more equal distribution among survival groups would have provided more insight into this difficult group, regarding both the estimate of survival and preferred treatment. Finally, in order to encourage completion of the questionnaire, the descriptions of the cases were based on real clinical cases and the replacement of clinical variables in the paired cases was limited to one variable, either age of the patients or number of metastases. Although there were three comparable cases with fractures of the proximal humerus and femur each, this is not a great number of comparable cases. As a result of these limitations, the outcomes of this study should be interpreted with care. The conclusions should be regarded as foundation for further research that should take these limitations into account.

The palliative intent of the treatment of pathologic fractures aims for a "once-in-a-lifetime fixation" and the correct estimation of survival is important in order to prevent over treatment in patients with a short survival, and undertreatment in those with a long survival. The results show that in most cases the estimation of survival of most respondents in each group was in accordance with the

estimation of the OPTIModel, but number of correct estimations differed greatly. Overall, the mean proportions of respondents estimating the correct survival were 53%, 64%, and 72% for groups 1, 2, and 3, respectively. The highest correct rates in group 1 were for the cases with a short estimated survival, while group 3 scored best on the cases with a solitary kidney metastasis. The long survival of the latter cases was not recognised by as many respondents in the other two groups, possibly indicating that recent studies showing a favourable outcome for patients with solitary kidney metastases[4] are less known among general orthopaedic surgeons. It is interesting to note that all three groups had difficulty with the cases with an intermediate survival. This, together with the good short-term estimations by group 1, might be due to the so-called "horizon effect", which suggests that clinicians are more accurate when recognising a shorter survival than a longer survival, similar to that recognized in weather forecasting.[5] The relatively good estimations for patients with a long estimated survival, especially respondents in groups 2 or 3, however, shows a trend opposite to the "horizon-effect". These differences cannot be explained. However, based on the answers respondents gave to the question "*how do you estimate survival?*" we can conclude that the non-experts consult an oncologist more frequently and are probably less used to estimating survival in general, compared with the oncological orthopaedic surgeons, who are more frequently confronted with this question when treating primary bone tumours.

The results show an influence of the age of the patient in all three groups. More respondents identified a long survival if the patient was younger, and a short survival if the patient was older. Thus, while few respondents identified age as prognostic factor for survival in the first question, it might play a role subconsciously. It may simply reflect human nature in that death is easier to accept when it occurs at an older age. However, no prognostic studies for survival after a pathologic fracture have shown an effect of age.[3,6-8] Surgeons should be aware of the subliminal effect of age and not let their estimations of survival be biased by it.

The results dealing with the estimation of survival cannot be compared with other studies, because to our knowledge no other questionnaires dealing with pathologic fractures asked respondents to give an estimation of survival.[9-11] One could discuss whether these results agree or disagree with those of studies that report that estimation of survival by physicians is frequently inaccurate.[5,12] Depending on the interpretation of the rate of correct estimation in this study, is a correct estimation of 60% accurate or is it too inaccurate? This is a difficult question to answer. The answer partly depends on the amount of influence of the expected survival on the choice of treatment. Also, although the OPTIModel

is a validated tool, its estimation of survival cannot be 100% correct. 'Correct' estimation in the context of this study should therefore be interpreted with caution, for we will never have a 100% correct estimation. Finally, it is not known whether some respondents already used a prognostic model to estimate survival for the cases in the questionnaire. If that is the case, the true estimations based on ones' experience might be even less correct, for the results might be biased by 'correct' estimations by models. Nonetheless, we believe that an overall rate of 'correct' estimations of 63% would suggest that prognostic tools should be used. The most benefit can be gained for the mid-term estimations. The use of a prognostic model would lead to more accurate estimation in the approximately 25% who estimated survival incorrectly in cases with an evidently short or long survival.

Respondents were asked to choose the most appropriate treatment for 12 cases, taking the estimated survival into account. For fractures of both the humerus and femur, most general orthopaedic surgeons would treat the fracture with an intramedullary nail, irrespective of the expected survival. Oncological orthopaedic surgeons, however, preferred to use a prosthesis if expected survival was >12 months. The percentage of oncological surgeons who recommended a prosthetic reconstruction for cases with a long expected survival was approximately twice that of general orthopaedic surgeons. This is in accordance with a previously performed survey by Janssen et al. regarding fractures of the humerus.[11] The fact that oncological surgeons are more comfortable with prosthetic reconstruction is not surprising, as their expertise lies in this field. However, the answers regarding resection and prosthetic reconstruction included the option to refer a patient for such treatment. The answers of general surgeons thus do not reflex the fact that they uncommonly perform this procedure, but that they less frequently recognise the need for such an implant. Many recent studies, however, have shown that prosthetic reconstruction is preferable to an intramedullary nail, especially if a long survival is expected.[13-16] The difference in this study is important for these patients, as currently their chance of receiving what is regarded as most appropriate treatment depends on the surgeon to whom they are referred. This trend should be further evaluated on a broader scale and by country, in order to further improve care. Should all orthopaedic surgeons be better educated, or should the care of certain patients be assigned to those with oncological training? Both are probably not feasible. The first because accumulating detailed knowledge is only regarded as worthwhile if the knowledge can be applied regularly. The second because of the incidence of pathologic fractures and the limited number of oncological orthopaedic surgeons in a region. Additionally, many of the pathologic fractures are excellently treated by general orthopaedic

surgeons and do not require specialized care. The most important issue is the selection of those patients who need centralized, specialized care. In order to aid that selection, a digital application can be used. The OPTIModel provides insight into both the expected survival, based on a recently published prognostic model,[3] and possible forms of treatment as suggested by experts in the field using the OPTIModel app, available in app stores and on www.optimal-study.nl/tool. The use of such a supportive tool can help differentiate patients with a short survival who are adequately treated with an intramedullary nail in a regional hospital from patients with a long expected survival who need referral to a specialized centre for prosthetic reconstruction.

This study focused on a different aspect than most studies that aim to improve the treatment of patients with a pathologic fracture. While asking detailed questions about treatment in the questionnaire, the conclusions were used to evaluate how the care can be improved on a more general scale. Based on the results, patients might benefit if there were better differentiation between those who are adequately treated in a regional centre and those who require referral for specialist care. This differentiation should be based on expected survival, the location of the fracture and the type of fracture (impending or actual). Digital applications can help match patients to the most appropriate treatment.

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Questionnaire

General questions

How many years have you been working as a (consultant) orthopaedic surgeon?

- ○ Resident
- ○ Less than 5 years
- ○ 6 – 10 years
- ○ 11 – 20 years
- ○ More than 20 years

How often do you treat patients with a pathologic fracture?

- ○ More than 2 times per month
- ○ 1 – 2 times per month
- ○ 1 – 2 times per 3 months
- ○ 1 – 2 times per half year
- ○ 1 – 2 times per year
- ○ (almost) never

Other subspeciality interests: *check all that apply*

- ○ General orthopaedics
- ○ Joint reconstruction
- ○ Hip/knee
- ○ Foot/ankle
- ○ Upper extremity
- ○ Spine
- ○ Sport orthopaedics
- ○ Paediatric orthopaedics
- ○ Traumatology

Survival estimation

Which factors do you regard as influencers of the remaining survival when patients present with an actual or impending pathologic fracture? *select at most 5 answers*

- ◊ Age
- ◊ Gender
- ◊ Primary tumour
- ◊ Presence of other bone metastases
- ◊ Number of other bone metastases
- ◊ Presence of brain metastases
- ◊ Presence of visceral metastases
- ◊ General health / performance status
- ◊ Pain
- ◊ Interval between diagnosis of primary tumour and diagnosis of pathologic fracture
- ◊ Actual fracture or impending fracture
- ◊ Blood values (e.g. Hb, leukocyte count, thrombocyte count, albumin, calcium, biliribine, LDH, CRP)

How do you estimate the remaining survival?

- ○ Based on my own experience
- ○ Using a tool/nomogram/model
- ○ I ask the oncologist/radiotherapist
- ○ I do not estimate the remaining survival

If using a tool/nomogram/model, please state which one is used:

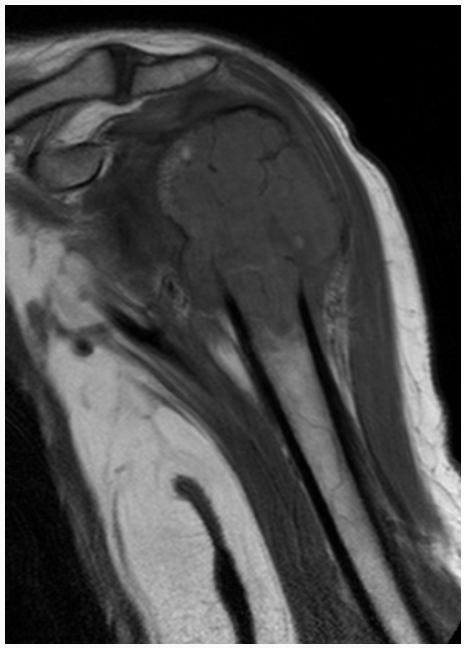
_____

Case 1

1A. A 35-year-old woman presents with a pathologic fracture of the proximal humerus caused by a breast cancer (ER/PR+, HER2-) metastasis. There are no brain or lung metastases, but eight other bone metastases (located in spine, pelvis and femurs) are present. The other bone metastases give no complaints and the patient is able to continue her daily living. Her left arm is now however causing continuous pain.

1B. A 70-year-old woman presents with a pathologic fracture of the proximal humerus caused by a breast cancer (ER/PR+, HER2-) metastasis. There are no brain or lung metastases, but eight other bone metastases (located in spine, pelvis and femurs) are present. The other bone metastases give no complaints and the patient is able to continue her daily living. Her left arm is now however causing continuous pain.

See the X-ray and MRI image below for more information. Distally in the humerus no other lesions are present.



Case 2

2A. A 32-year-old man presents with a subtrochanteric pathologic fracture caused by lung carcinoma (EGFR negative). The disease has spread diffusely throughout the lungs and skeleton. Brain metastases are suspected because of significant changes in the behaviour of the patient. He has been bedridden since several weeks due to the pain in the hip.

2B. A 70-year-old man presents with a subtrochanteric pathologic fracture caused by lung carcinoma (EGFR negative). The disease has spread diffusely throughout the lungs and skeleton. Brain metastases are suspected because of significant changes in the behaviour of the patient. He has been bedridden since several weeks due to the pain in the hip.

See the X-ray below. Further distally in the femur there are no lesions.

Case 3

3A. A 68-year-old woman has a fracture of the humerus shaft caused by a solitary metastasis of a renal cell carcinoma. There are no visceral metastases and the primary tumour has been resected. The arm is very painful (despite pain medication: paracetamol 4g/day and fentanyl transdermal patch 50µg/3 days) and the patient is unable to use her arm.

3B. A 68-year-old woman has a fracture of the humerus shaft caused by a metastasis of a renal cell carcinoma. Multiple other bone metastases are present in the spine and pelvis. There are no visceral metastases and the primary tumour has been resected. The arm is very painful (despite pain medication: paracetamol 4g/day and fentanyl transdermal patch 50µg/3 days) and the patient is unable to use her arm.

See the X-ray below and a transverse slice of the CT.

Case 4

4A. A 40-year-old man presents with an intertrochanteric fracture caused by a solitary metastasis of a renal cell carcinoma. There are no visceral metastases and the primary tumour has been resected. The hip is painful and limits the walking ability of the patient. Otherwise the patient is able to lead his life relatively normal.

4B. A 40-year-old man presents with an intertrochanteric fracture caused by a metastasis of a renal cell carcinoma. Multiple bone metastases (>10) are present throughout the entire skeleton. There are no visceral metastases and the primary tumour has been resected. The hip is painful and limits the walking ability of the patient. Otherwise the patient is able to lead his life relatively normal.

See the X-ray below.

Case 5

5A. A 38-year-old man presents with a fracture of the proximal humerus shaft caused by a lung carcinoma (EGFR negative) metastasis. Throughout the mediastinum multiple enlarged lymph nodes have been detected as well as multiple bone metastases (>20) in the entire skeleton. The liver shows several lesions suspect for metastases. Until the current fracture the patient was able to perform his daily activities, however his condition is deteriorating slowly. With a walker he is able to walk 100 meters. The patient has had radiotherapy for several painful spine metastases, with good effect.

5B. A 75-year-old man presents with a fracture of the proximal humerus shaft caused by a lung carcinoma (EGFR negative) metastasis. Throughout the mediastinum multiple enlarged lymph nodes have been detected as well as multiple bone metastases (>20) in the entire skeleton. The liver shows several lesions suspect for metastases. Until the current fracture the patient was able to perform his daily activities, however his condition is deteriorating slowly. With a walker he is able to walk 100 meters. The patient has had radiotherapy for several painful spine metastases, with good effect.

See the X-ray below.

Case 6

6A. A 42-year-old woman presents with a subtrochanteric fracture based on breast cancer (ER+/PR+, Her2-). There are no lung, liver, or brain metastases, but there are other bone metastases present in her pelvis and left femur. The patient is still very active and did not feel limited by her disease until this fracture occurred.

6B. A 72-year-old woman presents with a subtrochanteric fracture based on breast cancer (ER+/PR+, Her2-). There are no lung, liver, or brain metastases, but there are other bone metastases present in her pelvis and left femur. The patient is still very active and did not feel limited by her disease until this fracture occurred.

See the X-ray below. Further distally in the femur there are no lesions.

Questions for case 1A and 1B | case 3A and 3B | case 5A and 5B

What is your estimation of the remaining survival?

- Less than 3 months
- 3 to 6 months
- 6 to 12 months
- more than 12 months

What would your treatment of this patient be (based on the estimated survival)?

- Plate fixation with cement
- Plate fixation without cement
- Intramedullary nail fixation with cement
- Intramedullary nail fixation without cement
- Shoulder prosthesis
- (refer patient for a) (modular) tumour prosthesis after en bloc resection with free margins
- (refer patient for a) (modular) tumour prosthesis after intralesional resection
- Radiotherapy
- Conservative; pain medication

Questions for case 2A and 2B | case 4A and 4B | case 6A and 6B

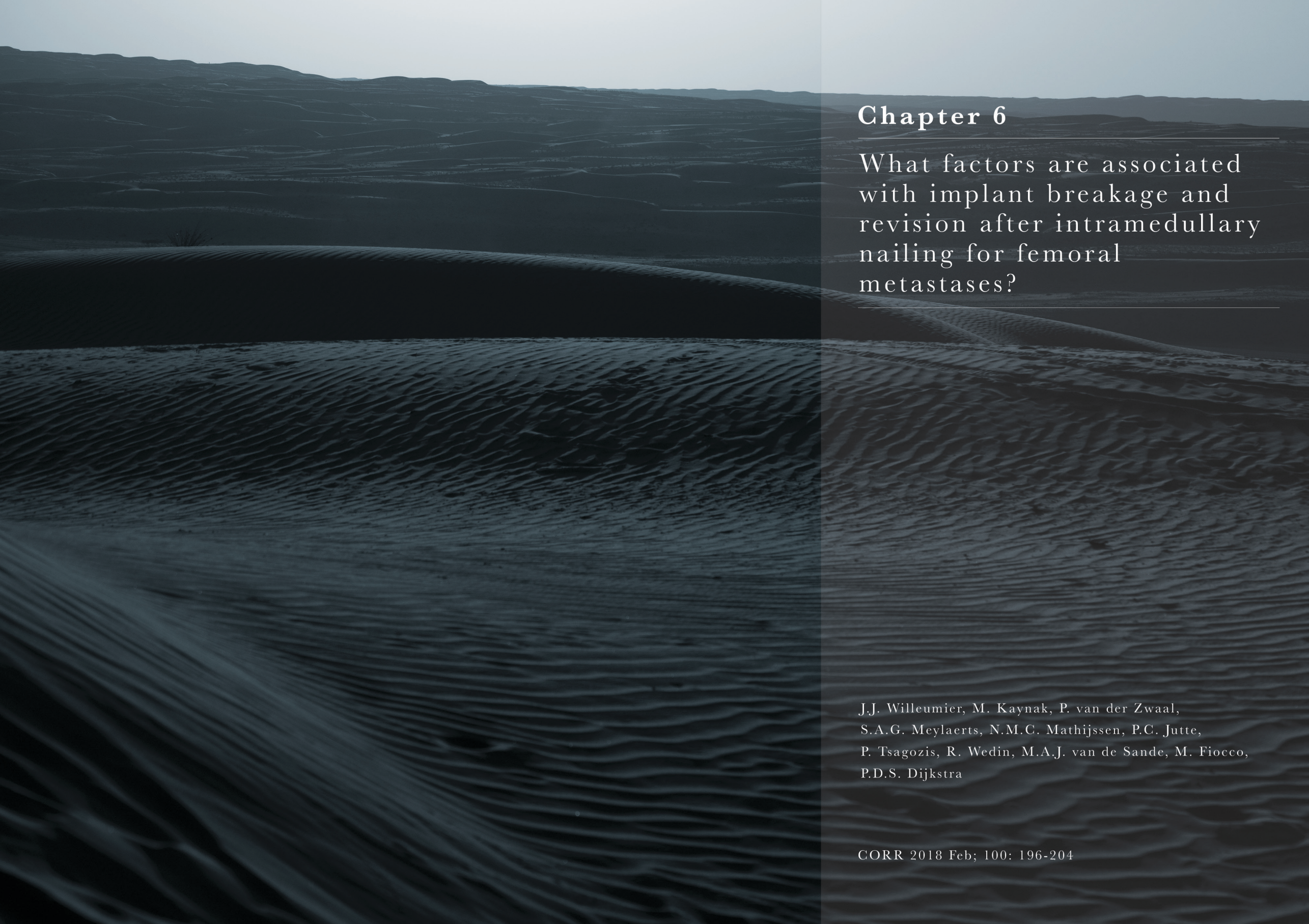
What is your estimation of the remaining survival?

- Less than 3 months
- 3 to 6 months
- 6 to 12 months
- more than 12 months

What would your treatment of this patient be (based on the estimated survival)?

- Intramedullary nail fixation with cement in the collum
- Intramedullary nail fixation with cement in the shaft
- Intramedullary nail fixation with cement to fill the lesion
- Intramedullary nail fixation with cement in the collum and to fill the lesion
- Intramedullary nail fixation without cement
- Hemiarthroplasty
- Total hip arthroplasty

- (refer patient for a) (modular) proximal femur tumour prosthesis after en bloc resection with free margins
- (refer patient for a) (modular) proximal femur tumour prosthesis after intralesional resection
- Radiotherapy
- Conservative; pain medication



Chapter 6

What factors are associated with implant breakage and revision after intramedullary nailing for femoral metastases?

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Abstract

Background

Actual and impending pathologic fractures of the femur are commonly treated with intramedullary nails because they provide immediate stabilization with a minimally invasive procedure and enable direct weight bearing. However, complications and revision surgery are prevalent, and despite common use, there is limited evidence identifying those factors that are associated with complications.

Questions/purposes

Among patients treated with intramedullary nailing for femoral metastases, we asked the following questions:

(1) What is the cumulative incidence of revision surgery and what factors are associated with revision surgery?
(2) What is the cumulative incidence of implant breakage and what factors are associated with implant breakage?
(3) What is the cumulative incidence of revision surgery and what factors are associated with revision surgery?

Methods

Between January 2000 and December 2015, 245 patients in five centers were treated with intramedullary nails for actual and impending pathologic fractures of the femur caused by bone metastases. During that period, the general indications for intramedullary nailing of femoral metastases were impending fractures of the trochanter region and shaft and actual fractures of the trochanter region if sufficient bone stock remained; nails were used for lesions of the femoral shaft if they were large or if multiple lesions were present. Of those treated with intramedullary nails, 51% (117) were actual fractures and 49% (111) were impending fractures. A total of 60% (128) of this group were women; the mean age was 65 years (range, 29-93 years). After radiologic followup (at 4-8 weeks) with the orthopaedic surgeon, because of the palliative nature of these treatments, subsequent in-person followup was performed by the primary care provider on an as-needed basis (that is, as desired by the patient, without any scheduled visits with the orthopaedic surgeon) throughout each patient's remaining lifetime. However, there was close collaboration between the primary care providers and the orthopaedic team such that orthopaedic complications would be reported. A total of 67% (142 of 212) of the patients died before 1 year, and followup ranged from 0.1 to 175 months (mean, 14.4 months). Competing risk models were used to estimate the cumulative incidence of local complications (including persisting pain, tumor progression, and implant breakage), implant breakage separately, and revision surgery (defined as any reoperation involving the implant other than débridement with implant retention for infection). A cause-specific multivariate Cox regression model was used to estimate the association of factors (fracture type / preoperative radiotherapy and fracture type / use of cement) with implant breakage and revision, respectively.

Results

Local complications occurred in 12% (28 of 228) of the patients and 6-month cumulative incidence was 8% (95% confidence interval [CI], 4.7-11.9). Implant breakage occurred in 8% (18 of 228) of the patients and 6-month cumulative incidence was 4% (95% CI, 1.4-6.5). Independent factors associated with increased risk of implant breakage were an actual (as opposed to impending) fracture (cause-specific hazard ratio [HR_cs], 3.61; 95% CI, 1.23-10.53, p = 0.019) and previous radiotherapy (HR_cs, 2.97; 95% CI, 1.13-7.82, p = 0.027). Revisions occurred in 5% (12 of 228) of the patients and 6-month cumulative incidence was 2.2% (95% CI, 0.3-4.1). The presence of an actual fracture was independently associated with a higher risk of revision (HR_cs, 4.17; 95% CI, 0.08-0.82, p = 0.022), and use of cement was independently associated with a lower risk of revision (HR_cs, 0.25; 95% CI, 1.20-14.53, p = 0.025).

Conclusion

The cumulative incidence of local complications, implant breakage, and revisions is low, mostly as a result of the short survival of patients. Based on these results, surgeons should consider use of cement in patients with intramedullary nails with actual fractures and closer followup of patients after actual fractures and preoperative radiotherapy. Future, prospective studies should further analyze the effects of adjuvant therapies and surgery-related factors on the risk of implant breakage and revisions.

Introduction

The femur is the most common long bone affected by bone metastases.[1] Treatment modalities of actual and impending pathologic fractures should provide direct and robust (prophylactic) stabilization to enable immediate weight bearing without pain and to regain quality of life. Intramedullary (IM) nails are commonly used to treat actual and impending pathologic fractures of the femur because of the smaller surgical exposure, which may result in less blood loss and surgical time, perhaps enabling more rapid postoperative rehabilitation. In general, no extensive muscle releases are used and immediate weight bearing is possible.[2] Furthermore, the construct provides prophylactic protection of the long bone against future fractures in other regions as a result of its mechanical support over the entire length. The downside of IM nails is that they are designed as load-sharing devices, but they function as load-bearing devices in actual pathologic fractures that generally show only minimal healing tendencies, unlike traumatic fractures.[3] Should a non-union ensue, hardware breakage (either of the distal interlocking screws or of the nail itself) will occur over time because of the loads involved.[4-6] Although an IM nail suffices as palliative treatment for many patients because their survival will not exceed the fatigue life of the implant,[7] the occurrence of complications and need for revision surgery are not compatible with the palliative intent of the treatment, which aims to meet the patient's need for the balance of his or her lifetime and to require minimal surveillance.[8]

Long survival is recognized as one of the most important risk factors for failure and stresses the importance of adequate survival estimation.[9-12] Previous studies on the use of IM nails have limitations because they are heterogenic and describe small cohorts with short-term followup.[2,5,7,9,11,13,14] Few have looked at treatment-related risk factors for failure or revision. If such factors, however, are prognostic, surgeons can further improve treatment.

Therefore, this multicenter study aims to answer the following questions among patients treated with IM nailing for femoral metastases: (1) What is the cumulative incidence of local complications? (2) What is the cumulative incidence of implant breakage and what factors are associated with implant breakage? (3) What is the cumulative incidence of revision surgery and what factors are associated with revision surgery?

Patients and methods

Between January 2000 and December 2015, 245 patients in five centers were treated with IM nails for actual and impending pathologic fractures of the femur caused by bone metastases. Two hundred twelve patients with 245 actual or impending femoral pathologic fractures were evaluated in this retrospective study after local institutional review board approval. Patients with flexible nails (such as Nancy nails), angle blade plates, dynamic hip screws, retrograde nails (13 patients, 15 nails), IM nails with a bicortical proximal fixation, or in whom the nail was a revision (n = 2) were excluded (total n = 18). During the study period, the general indications for IM nails were impending fractures of the trochanter region and shaft and actual fractures of the trochanter region if sufficient bone stock remained; nails were used for lesions of the femoral shaft if they were large or if multiple lesions were present. Throughout the study period, these indications were generally adhered to. Nails were placed percutaneously except when a large cortical defect called for extensive curettage and cementation. Reaming was performed according to the manufacturers' guidelines. Indications for the type of nail and the use of cement were set by the treating surgeon as was the indication for postoperative radiotherapy. In general, cement was used for additional fixation of the collum screw (the lag screw in the femoral head) or filling of the metastatic lesion. As a result of the multicenter aspect of the study and developments over time, several different IM nails were used (table 6.1). Prophylactic antibiotics were administered to all patients according to each centers' own protocol (most commonly cefazolin). Adjuvant cement was administered to 50 femurs (22%; table 6.1). In general, cement was used if bone stock was regarded insufficient for adequate screw fixation or if the lesion was very large. Thirty-nine patients (17%) had received radiotherapy on the lesion before surgery (table 6.1), of whom the majority (n = 25 [64%]) had received one fraction of 8 Gy. The median time between radiotherapy and surgery was 8 weeks (range, 0.4–134 weeks). Preoperative radiotherapy was most commonly administered for pain. Twenty-seven patients (69%) sustained a pathologic fracture after radiation after a median of 3.5 weeks (range, 0.4-134 weeks), whereas 12 patients (31%) were treated for an impending fracture after a median of 13 weeks (range, 0.9-59 weeks). Postoperative radiotherapy was administered after 124 stabilizations (54%; table 6.1) after a mean of 4 weeks (SD 2.0). No protocol existed for administration of postoperative radiotherapy; whether it was used depended on local practice. The most common regimens were one or two fractions of 8 Gy (n = 29 [23%] and n = 33 [27%], respectively) and five or six fractions of 4 Gy (n = 26 [21%] and n = 27 [22%], respectively). Irradiation schemes were determined by the local protocols of each centers' radiotherapy department. Radiotherapy was given more often to patients after prophylactic stabilization than to those treated for actual fractures (65% versus 44%; p = 0.015) after correction for prior radiotherapy.

Demographic data, fracture and treatment details, and followup data including complications, revisions, and survival were collected from medical files. Fracture details included location, date of diagnosis, type (actual or impending), primary tumor, and previous radiotherapy. Treatment details included type of IM nail, locking mechanism, use and location of adjuvant cement, curettage, and postoperative radiotherapy. Radiotherapy was regarded as postoperative if given within 12 weeks of surgery. Dates of death were obtained from medical records or the municipal personal records database. If patients were alive, the last known dates were collected from the medical records.

After radiologic followup (at 4-8 weeks) with the orthopaedic surgeon, because of the palliative nature of these treatments, subsequent in-person followup was performed by the primary care provider on an as-needed basis (that is, as desired by the patient, without any scheduled visits with the orthopaedic surgeon) throughout each patient's remaining lifetime. However, there was close collaboration between the primary care providers and the orthopaedic team such that orthopaedic complications would be reported. A total of 67% (142 of 212) of the patients died before 1 year and 17% (36 of 212) were alive after 2 years. Followup ranged from 0.1 to 175 months (mean, 14.4 months).

Local complications included persisting pain (that is, lasting pain despite surgery and adequate analgesics), tumor progression, and implant breakage. Persisting pain and tumor progression were scored as such if these were stated as the reason for adjuvant treatment (such as radiotherapy or surgery). The subgroup of implant breakage was further analyzed separately. Implant breakage included all nail and screw fractures, migrations, deformations or malplacements, and peri-implant fractures. Infections and systemic complications (deep venous thrombosis, pulmonary embolism, fat or cement embolism, pneumonia, urinary tract infection, cardiac events, sepsis, intraoperative death, and postoperative death [within 3 weeks of surgery]) were recorded. Revision was defined as any reoperation that was performed as a result of local complications, but reoperations for infection in which the implant was retained were not counted.

Two hundred twelve patients with 228 actual and impending fractures were included in this study with a median age of 65 years (range, 29-93 years) and prominently women (60% [n = 128]). Metastases originated most commonly from breast cancer (36% [n = 76]) followed by lung (24% [n = 51]), kidney (11% [n = 24]), and prostate (11% [n = 23]) cancer. The remaining 18% (n = 38) included primary tumors of the thyroid, colorectum, head and neck, and bladder, among others. Actual fractures (117 [51%]) were most commonly located in the subtrochanteric region (50 [43%]; table 6.2), whereas impending fractures (111 [49%]) were primarily in the shaft (53 [48%]; table 6.2).

Median overall survival (OS) was 6 months (95% confidence interval [CI], 4.4-7.3). Overall 6-month, 1-year, and 2-year survival for the entire cohort was 49%, 33%, and 19%, respectively. Median OS was longer for impending fractures (median, 8 months; 95% CI, 3.1-12.7) than for impending fractures (median, 5 months; 95% CI, 3.5-5.8) (figure 6.1). There were differences in median OS between primary tumor types: 11 months (95% CI, 4.9-17.1) for breast cancer, 7 months (95% CI, 2.4-11.6) for prostate cancer, 6 months (95% CI, 1.5-11.2) for kidney cancer, 3 months (95% CI, 1.0-4.2) for lung cancer, and 6 months (95% CI, 3.8-7.4) for other primary tumors (figure 6.2).

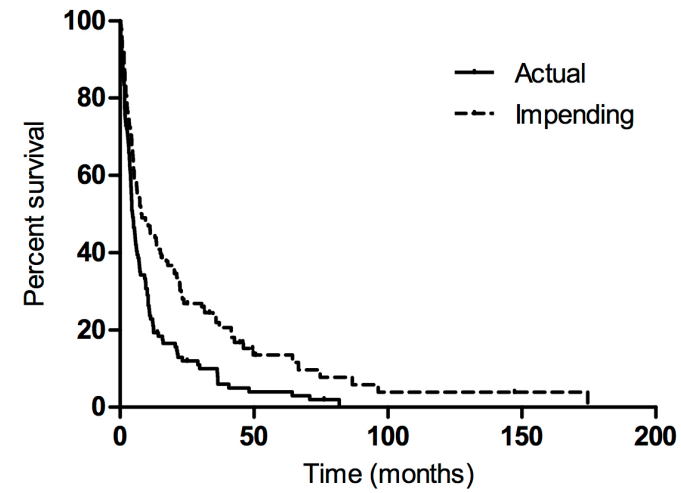

Figure 6.1 The Kaplan-Meier curve for OS is stratified for fracture type.

Statistical Analysis

Time to local complication, implant breakage, revision, and survival time were calculated from the date of surgery. For survival analysis, only the first treatment was included for patients with bilateral treatments. A competing risk model was used to estimate the cumulative incidence of local complication, implant breakage, and revision with death as a competing event.[15] The cumulative incidence was defined as the probability of failing from a specific cause before time (t). Factors (fracture type; fixation type; pre- and postoperative radiotherapy; cement) were explored for the association with implant breakage or revision with a univariate cause-specific Cox regression. Subsequently multivariate cause-specific Cox regression analyses were performed, evaluating the following factors for the endpoints implant breakage and revision,

respectively: type of fracture and postoperative radiotherapy and type of fracture and use of cement. As a result of the limited number of events for both endpoints, we were not able to include a third factor in the multivariate analyses. A p value < 0.05 was considered significant. Competing risk analysis was performed by using the mstate library in R.[16,17]

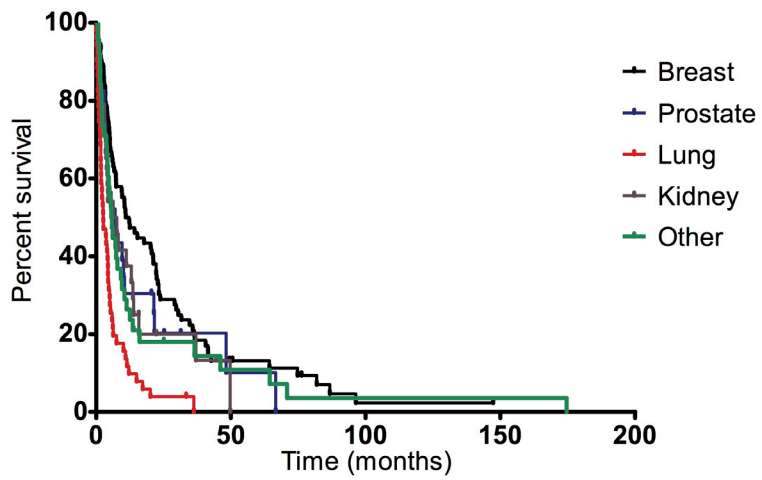

Figure 6.2 The Kaplan-Meier curve for OS is stratified for primary tumor type.

Table 6.1 Treatment characteristics of 228 intramedullary nails

Characteristic		*All*	*Actual fracture*	*Impending fracture*
Total		228	117	111
Nail type				
	Gamma nail†	164 (72)	79 (68)	85 (77)
	PFN/PFNa‡	21 (9)	16 (14)	5 (5)
	IMHS§	24 (11)	8 (7)	16 (14)
	TFN‖	9 (4)	5 (4)	4 (4)
	T2–Recon¶	6 (3)	6 (5)	0 (0)
	UFN**/CFN††	4 (2)	3 (3)	1 (1)
Adjuvant cement				
	Yes, mechanical support*	22 (10)	12 (10)	10 (9)
	Yes, at location of tumor	16 (7)	9 (8)	7 (6)
	Yes, mechanical support* and tumor location	12 (5)	2 (2)	10 (9)
	No	178 (78)	94 (80)	84 (76)
Radiotherapy				
	Previous only	32 (14)	23 (20)	9 (8)

(Table 6.1 continued)

	Previous and postoperative	7 (3)	4 (3)	3 (3)
	Postoperative only	117 (51)	48 (41)	69 (62)
	None	72 (32)	42 (36)	30 (27)
Reaming				
	Yes	213 (93)	109 (93)	105 (95)
	No	7 (3)	5 (4)	2 (2)
	Unknown	7 (3)	3 (3)	4 (4)
Fixation				
	Static	166 (73)	85 (73)	81 (73)
	Dynamic	52 (23)	22 (19)	30 (27)
	Unknown	10 (4)	10 (9)	0 (0)
Proximal locking				
	Femoral head fixation (single)	211 (93)	103 (88)	108 (97)
	Femoral head fixation with second screw	17 (8)	14 (12)	3 (3)
Distal locking				
	None	3 (1)	0 (0)	3 (3)
	1 locking screw	48 (21)	23 (20)	25 (23)
	2 locking screws	176 (77)	93 (80)	83 (75)
	3 locking screws	1 (0)	1 (1)	0 (0)

Values are numbers with percentages in parentheses; *mechanical support of collum screw in the femur neck; †gamma nail (Stryker Trauma GmbH, Schonkirchen, Germany); ‡proximal femoral nail (antirotation) (Synthes GmbH, Oberdorf, Germany); §intramedullary hip screw (Smith & Nephew, Inc, Cordova, TN, USA); ‖titanium trochanteric fixation nail (Synthes GmbH); ¶T2–Recon (Stryker Trauma GmbH); **unreamed femoral nail, ††distal femoral nail (Synthes GmbH).

Table 6.2 Locations of actual and impending pathologic fractures of the femur

Femurs (n = 228)	*Actual fracture, number (%)*	*Impending fracture, number (%)*
Total	117	111
Head and neck	10 (9)	14 (13)
Pertrochanteric	23 (20)	31 (28)
Subtrochanteric	50 (43)	13 (12)
Shaft	34 (29)	53 (48)

Results

Three-month, 6-month, and 9-month cumulative incidences of local complications were 4% (95% CI, 1.7-7.1), 8% (95% CI, 4.7-11.9), and 9% (95% CI, 5.1-12.5), respectively (figure 6.3). Overall, 28 IM nails (12%) were involved with 35 local complications (table 6.3), including tumor progression in nine patients (4%) and persisting pain in five patients (2%). Four of the nine patients with tumor progression and three of the five patients with persisting pain had not received postoperative radiotherapy. Tumor progression was treated with (re)irradiation (n = 6) or revision surgery (n = 3). Persisting pain was treated with adjuvant radiotherapy (n = 5) after a mean of 4 months (range, 3-6 months).

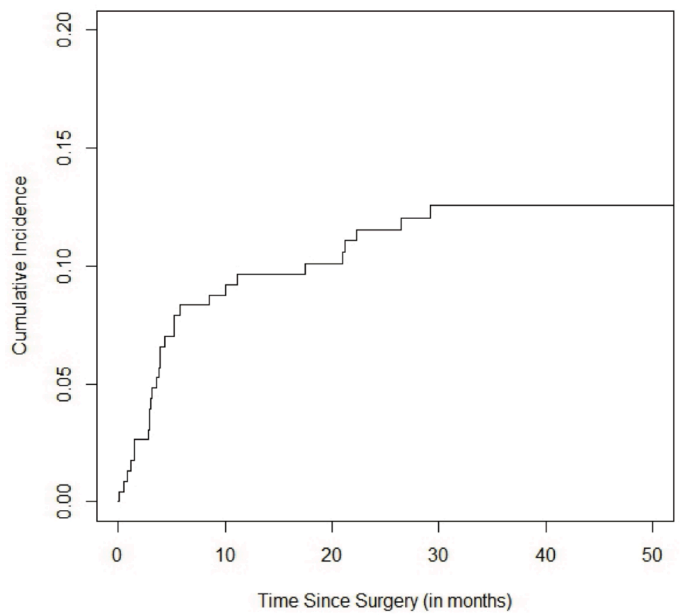

Figure 6.3 Cumulative incidence functions are shown for local complication.

Overall, the 3-month, 6-month, and 9-month cumulative incidences of implant breakage were 3% (95% CI, 0.8-5.3), 4% (95% CI, 1.4-6.5), and 4% (95% CI, 1.7-7.1), respectively (figure 6.4). Overall, 21 implant breakages occurred in 18 IM nails (8%; table 6.3). In three patients one of the distal screws broke before the nail fractured; both complications were registered. Seven nails fractured at the site of the collum screw junction, leading to a nail fracture percentage of 3%. The majority of the structural failures occurred after fixation of actual pathologic fractures (n = 13 of 18 [72%]).

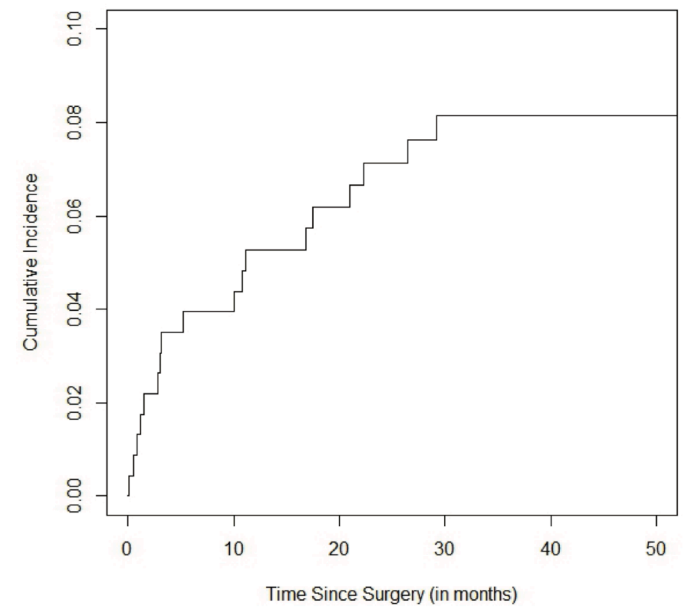

Figure 6.4 Cumulative incidence functions are shown for structural failure.

Table 6.3 Local complications per fracture location

Complication	*All locations A/I*	*Head and neck A/I*	*Pertrochanteric A/I*	*Subtrochanteric A/I*	*Shaft A/I*	*Total*
Implant breakage	16/5	1/0	2/2	7/0	6/3	21
Fracture of nail	6/1	1/0	1/0	3/0	1/1	7
Fracture or migration of distal screw	10/2	-	1/0	4/0	5/2	12
Deformation of nail	0/1	-	0/1	-	-	1
Malplacement	0/1	-	0/1	-	-	1
Persisting pain	5/0	-	1/0	2/0	2/0	5
Tumor progression	4/5	0/1	1/1	1/0	2/3	9
Total	25/10	1/1	4/3	10/0	10/6	35

A = actual fracture; I = impending fracture.

After controlling for confounding between fracture type and radiotherapy, both factors were independently associated with an increased risk of implant breakage: actual (as opposed to impending pathologic) fractures had a cause-specific hazard risk of 3.61 (95% CI, 1.23-10.53, p = 0.019) and radiotherapy before surgery of 2.97 (95% CI, 1.13-7.82, p = 0.027) (table 6.4). Revision surgery resulting from structural failure was performed for the seven fractured nails, the displaced nail, and the initially malplaced collum screw (nine of 18 [50%]).

The 3-month, 6-month, and 11-month cumulative incidences of revision were 0.4% (95% CI, 0.0-1.3), 2% (95% CI, 0.3-4.1), and 3% (95% CI, 0.5-4.7), respectively (figure 6.5). Twelve patients (5%) underwent revision (table 6.5). The majority of the lesions were located per-/subtrochanteric or in the shaft (nine of 12). The presence of an actual fracture was independently associated with a higher risk of revision (cause-specific hazard ratio, 4.17; 95% CI, 0.08-0.82, p = 0.022), and use of cement was independently associated with a lower risk of revision (cause-specific hazard ratio, 0.25; 95% CI, 1.20-14.53, p = 0.025) (table 6.4). Five of the 12 revisions caused further complications that resulted in further interventions. Infection (n = 2), protrusion of the collum screw (n = 1), and loosening or fracture of the collum screw (n = 2) were reasons for rereoperation. In addition to surgery, both patients with infections were treated with lifelong antibiotics. The three patients with implant breakage developed further complications, which all resulted in further surgery.

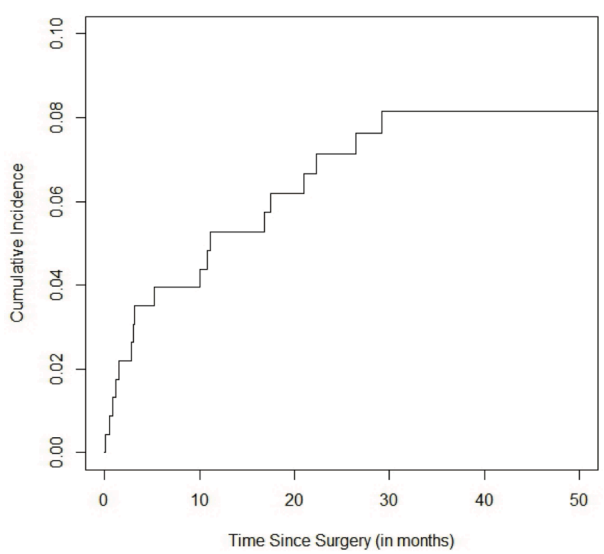

Figure 6.5 Cumulative incidence functions are shown for revision.

Table 6.4 Factors associated with implant breakage (n=18) and revision (n=12)

	Implant breakage						*Revision*					
	Univariate			*Multivariate*			*Univariate*			*Multivariate*		
Variables	*HR*	*95% CI*	*p value*	*HR*	*95% CI*	*p value*	*HR*	*95% CI*	*p value*	*HR*	*95% CI*	*p value*
Location												
Shaft	-	-	0.451				-	-	0.881			
Head and neck	0.27	0.03-2.16	0.216				0.42	0.05-3.60	0.427			
Pertrochanteric	0.57	0.15-2.16	0.408				0.94	0.23-4.00	0.937			
Subtrochanteric	1.20	0.41-3.46	0.741				0.98	0.23-4.11	0.978			
Fracture type*	4.31	1.50-12.37	0.007	3.61	1.24–10.53	0.019	3.55	1.05-12.04	0.042	4.17	0.08-0.82	0.022
Static fixation†	0.52	0.15-1.79	0.517				0.51	0.11-2.35	0.389			
Reamed nail‡	1.33	0.18-10.04	0.781				2.04	0.26-15.93	0.495			
Use of cement‡	0.61	0.22-1.71	0.344				0.31	0.10-1.00	0.044	0.25	1.20-14.53	0.025
Previous RT§	3.84	1.49-9.94	0.006	2.97	1.13–7.82	0.027	0.25	0.08-0.78	0.017			
Postoperative RT‡‖	0.24	0.08-0.70	0.009				0.10	0.02-0.47	0.003			
Primary tumor												
Other	-		0.676				-		0.459			
Breast	0.70	0.21-2.30	0.556				0.29	0.08-1.12	0.073			
Prostate	0.37	0.04-3.30	0.371				0.32	0.04-2.89	0.309			
Lung	0.29	0.03-2.64	0.274				0.00	0.00-3.76	0.962			
Kidney	1.16	0.26-5.20	0.845				0.72	0.13-3.96	0.709			

*Actual versus impending (as reference); †dynamic versus static (as reference); ‡no versus yes (as reference); §yes versus no (as reference); ‖as a time-dependent variable; HR = hazard ratio; CI = confidence interval; RT = radiotherapy. *O = original cohort, and E = external cohort. †Data concerning 1 of the 3 variables were missing for 126 and 41 patients for the original and external cohort, respectively. Mo: months.

Table 6.5 Characteristics of fractures undergoing revision surgery

Characteristics	*Revisions, number (%)*
Total (nails)	12
Primary tumor	
Breast	5 (42)
Kidney	2 (17)
Prostate	1 (8)
Other	4 (33)
Fracture type	
Actual	8 (67)
Impending	4 (33)
Location	
Collum	1 (8)
Pertrochanteric	3 (25)
Subtrochanteric	3 (25)
Proximal shaft	3 (25)
Midshaft	1 (8)
Distal shaft	1 (8)
Radiotherapy	
Previous only: 1*8 Gy	2 (17)
Previous only: 2*8 Gy	3 (25)
Postoperative only: 2*8 Gy	1 (8)
Postoperative only: 6*4 Gy	2 (17)
Previous and postoperative	0 (0)
None	4 (33)
Cement	
Yes	5 (42)
No	7 (58)
Locking	
Static	10 (83)
Dynamic	2 (17)
Local complication	
Structural failure: nail fracture	7 (58)
Structural failure: displaced nail	1 (8)
Structural failure: malplacement	1 (6)
Tumor progression	3 (25)

Discussion

The aim of the IM fixation of actual and impending pathologic fractures is to minimize pain and stabilize the limb for the patient's remaining lifetime. Long survival has been associated with complications of IM nails,[9,18] but only one study has looked into factors associated with these complications.[11] Our study presents a larger cohort and aims to identify treatment-specific factors as opposed to patient-specific factors. In this study, after controlling for confounding variables, we found that actual fractures (as opposed to impending fractures) and previous radiotherapy were independently associated with an increased risk of implant breakage, actual fractures (again, as opposed to impending fractures) were associated with an increased risk of revision, whereas use of cement was associated with a lower likelihood of a patient undergoing revision during his or her remaining lifetime. Although the cumulative incidences of implant breakage and revision were low in this series, we note that this likely was because of the very short survival of most of these patients (median survival was 6 months after surgery). Finally, we identified an alarmingly high frequency of re-revision once a revision was performed.

This study has several limitations. First, underestimation of all endpoints might be possible because followup was not standardized. However, patients were seen throughout their remaining lifetimes by primary care providers on an as-needed basis and had clinically meaningful problems arisen; it seems likely that these would have been reported, which may mitigate the problem of underestimation. In addition, the methods here probably are fairly reflective of real-world palliative practice. Also, based on the medical system in The Netherlands and Austria and the small sizes of both countries, we can assume that loss of patients to other hospitals is limited. Second, the retrospective design may have introduced selection bias. This bias may involve details of the surgical strategies such as nail type, adjuvant cement, and postoperative radiotherapy, but it probably does not influence the choice of the IM nail itself, because general indications are recognized for the main implant choice and we are not comparing IM nails with other treatment modalities in this study. The decisions for the details of treatment were made by the surgeons as opposed to according to a pre-set, shared algorithm.

The study also is limited by the small number of events of interest. This is predominantly caused by the short survival of patients with metastatic cancer, which is inevitable with the study population, but nonetheless limits the analytic possibilities, especially with regard to the multivariate analysis. As a result of the few implant breakages (n = 21) and revisions (n = 12), only two factors could be included in the multivariate analyses for each event. For both multivariate

analyses, confounding by adjuvant radiotherapy could therefore not be excluded; however, this was regarded as less relevant for our specific (implant-related) research questions. The results imply that further research should focus on the role and effect of adjuvant treatments (cement and radiotherapy). Finally, patients might have received systemic treatments, which we did not include in the analysis. This could be regarded as a limitation, because it might have affected the course of disease of patients. However, the focus of our study was on a detailed analysis of local treatment and the complexity of systemic treatments would intervene too much with obtaining these local results. Given the personalization of systemic therapies, there is such a variety of systemic treatments given at different time points that the factor cannot be regarded as one. Including this variable would complicate the analysis to such level that the results would stray from our initial research questions.

The frequency of complications we observed (12% [28 of 228]) is comparable to some studies,[6] whereas others report fewer complications.[9,13] The differing results can be attributed to the definitions for complication. The current study regarded all causes of secondary treatment for mechanical stabilization (surgery and/or radiotherapy) and all structural problems of the implant as complications because the surgical treatment of an actual or impending fracture is meant to meet the patient's needs for his or her remaining lifetime. The cumulative incidence of complications (figure 6.3) shows that although the assumption might be that all complications occur in the short term, this is not the case.

Implant breakage caused most of the observed local complications (60% [21 of 35]). As a result of the nature of pathologic fractures and their general lack of bone healing, IM nails and locking screws carry more pressure and during a longer period than in general trauma care. The common persisting non-union often leads to implant fractures (that is, breakage of screws and nails) over time.[19] In the current cohort, 3% (seven of 228) of the nails fractured, all at the junction with the collum screw. The design of modern IM nails, with the collum screw locked into the proximal nail, prevents protrusion of the collum screw through the femur head, but inevitably causes a weak point of the nail by reducing the diameter (1.5-3 mm) of the nail adjacent to the hole.[20] Although the power of this study was insufficient to perform any further analyses into specific causes of the nail breakage (e.g., nail diameter, collum screw length, type of screws for distal locking), the frequent fractures at the junction with the collum screw suggest that a larger proximal diameter of the nail is mandatory, especially in patients with an expected survival of > 6 months. Two independent factors associated with implant breakage were identified: both actual fracture

and previous radiotherapy increase the risk of implant breakage threefold. This emphasizes the importance of accurate fracture prediction. If a lesion erroneously gets classified as low risk for fracture, it is possible that the patient will get referred for radiotherapy, subsequently develops a pathologic fracture, and then has to undergo surgery burdened with both risk factors for complications. Unfortunately, up to date there is still no accurate and quick method for determining the risk of fracture. The well-known Mirels classification is still commonly used[21] despite studies showing its poor predictive value resulting in an overestimation of the fracture risk.[22] We would therefore advise to refrain from using the Mirels classification any longer. Van der Linden et al. advise to use 3-cm cortical involvement as a cut-off point.[23,24] The most promising are CT-based algorithms that are currently being developed.[25] Once such models will be able to provide quick predictions in the clinical setting, hopefully the everlasting question of how to determine the fracture risk will belong to the past. Actual fracture as a risk factor has been recognized previously[26] and the clinical and economic benefits of prophylactic stabilization are well known.[27] The association of radiotherapy before surgery with an increased risk of implant revision has been reported;[11] we were able to analyze the topic further with respect to additional risk factors in the present study. When a patient presents after radiotherapy and with an actual fracture, the prognosis of the implant is already influenced, even before any incision has been made. If these patients are expected to survive for a reasonably long period of time, a prosthesis could be considered. However, in patients with only short- or medium-term expected survival, an IM nail remains an adequate choice because the risk of complications and revision seems low. Use of adjuvant cement and stricter followup with regular radiographs to recognize failure in an early stage could be considered for patients with risk factors.

Others have reported the risk of revision to range between 0% and 14%, which is comparable to the revision percentage in this cohort (5% [12 of 228]).[5,6,9,11,13,14,28-30] It was striking to observe that the early revisions (within 6 months) were predominantly the result of tumor progression (of kidney, thyroid, and breast cancer), whereas implant breakage generally did not occur until later. This observation has not, to our knowledge, been described previously and could be an expression of the aggressiveness of certain tumors. The primary reason for the low frequency of complications and revisions is the short overall survival of this patient population (median, 6 months). Most patients die of metastatic disease before complications have had time to develop. The association between failure and revision and survival is well known,[5,9,11,13,31-33] but to our knowledge, this is the first study that shows this result in such a large cohort. The low percentages of complications and revisions also show that the

implant selection of this cohort was well chosen to the needs of the patient and his or her disease, including survival estimation. The latter is an important step to identify the adequate surgical modality. Only a precise survival estimation will enable a "once and for all" treatment, which should be aimed for in the palliative setting, and prevent over- and undertreatment. Several models have been developed to aid surgeons in estimating survival.[34-36] One of these models has been transformed into a dynamic application (OPTIModel; www.optimal-study.nl/tool), which is available in app stores free of charge. Survival is estimated with a prognostic model including three variables (tumor profile, presence of visceral and/or brain metastases, Karnofsky performance score). The prognostic model was based on a large retrospective study and validated by an external data set. [37]

We found that the cumulative incidences of local complications, implant breakage, and revisions after IM nails for femoral pathologic fractures are low, but that the success rate of revision surgery is poor. Actual (as opposed to impending) fractures and preoperative radiotherapy were independently associated with a higher risk of implant breakage, and actual fractures and lack of the use of cement were independently associated with a higher risk of revision. Surgeons might consider treating patients with these risk factors and a long expected survival with prosthetic reconstructions. If expected survival is short or medium term, IM nailing remains a suitable option; however, adjuvant cement and closer followup should be considered. Future studies should focus on the role of adjuvants (cement and radiotherapy) and their effect on implant survival. To prevent the limitations faced by the current study, these studies should be large, prospective, and, ideally, randomized. In light of the palliative intent of the treatment, not only complications and functional outcomes should be registered, but also the effect of treatment (and possible complications) on the quality of life.

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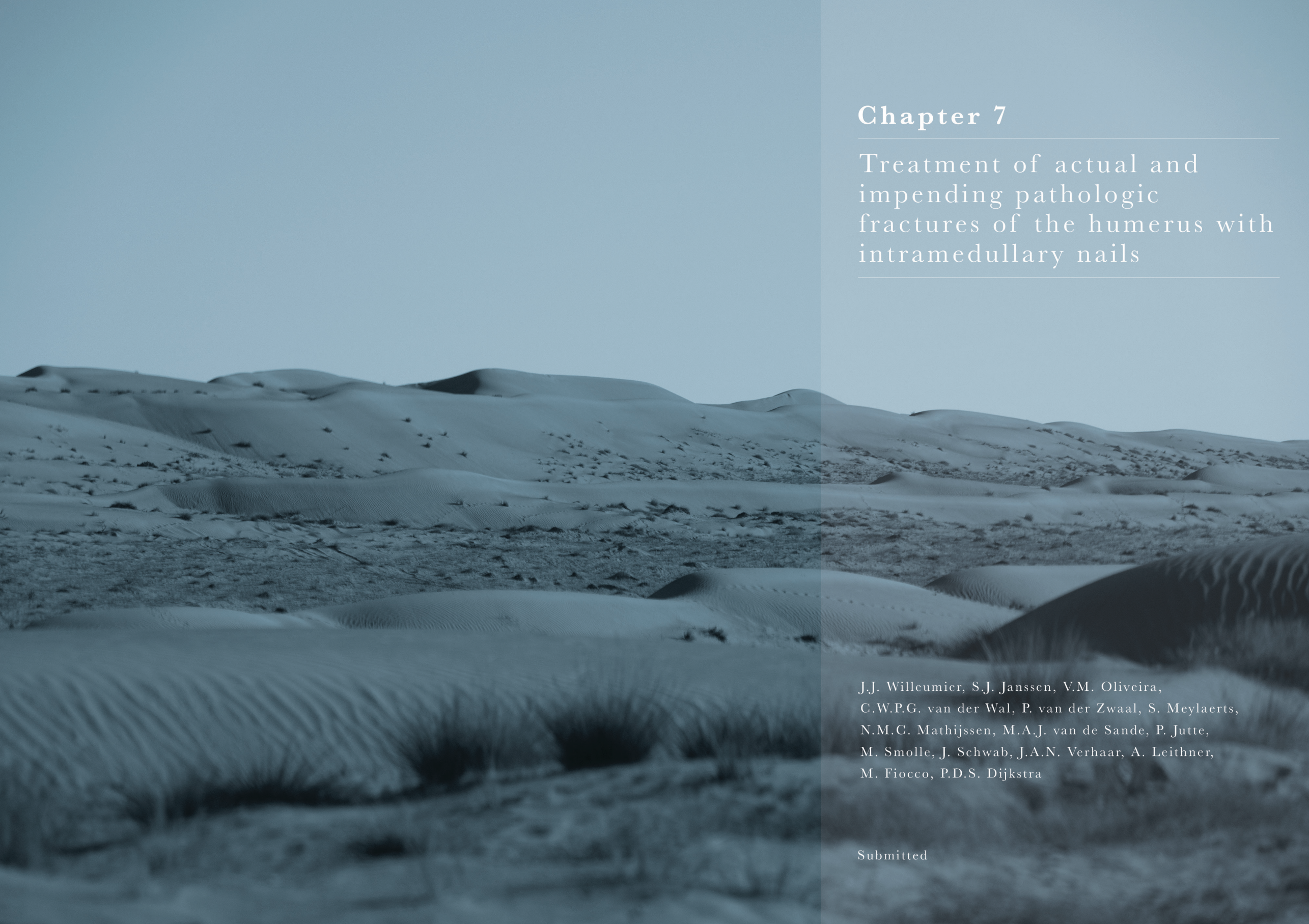

Chapter 7

Treatment of actual and impending pathologic fractures of the humerus with intramedullary nails

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Submitted

Abstract

Background

Actual and impending pathologic fractures of the humerus can be challenging to treat. The (prophylactic) fixation of a pathologic fracture due to bone metastases is a palliative treatment and should aim at direct rotation-stabilization, enabling immediate use while corresponding with the expected survival. Up to date, no risk factors for failure of intramedullary nails in humeral pathologic fractures have been identified.

Purposes

Among patients treated with intramedullary nails for actual or impending pathologic fractures caused by bone metastases of the humerus:

(1) What is the cumulative incidence of failure?
(2) What are risk factors for failure?
(3) What per-operative and postoperative (neurological) complications occur?

Methods

Between 2000 and 2015, 178 patients in eight centers were treated with IM nails for 182 actual (n=143, [79%]) or impending (n=39, [21%]) pathologic fractures of the humerus caused by bone metastases, of which 62% were located in the diaphysis. Throughout the study period general indications for an intramedullary nail were an impending fracture, a fracture of the diaphysis, or a proximal fracture with sufficient bone stock in the humeral head. The cohort consisted predominantly of women (61% [n=108]) and the median age was 62.7 years (range 33.5–88.9).

Results

Twenty-three failures were registered, leading to an overall failure rate of 12.6% (23/182). Cumulative incidence of failure was 1.1% at 1 month (95%CI 0–2.6), 3.3% at three months (95%CI 0.7–5.9), 3.8% at six months (95%CI 1.0–6.6), 8.2% at 1 year (95%CI 4.2–12.3), and 10.0% at two years (95%CI 5.6–14.5). Univariate Cox regression analysis did not show any significant association between risk factors and failures. Intraoperative complications were reported in six patients (3.3%), all concerning fractures caused by introducing the nail. Seven patients (3.8%) had neurological complications of the radial nerve.

Conclusion

Although overall results are good, surgeons should be aware of the fact that intramedullary treatment of pathologic humeral fractures may not prove as simple as one may expect. Most important is to pursue a non-rotating and durable fixation that corresponds with the estimated survival to prevent complications that occur mainly with prolonged survival.

Introduction

After the femur, the humerus is the second most common location for long bone metastases, causing actual and impending pathologic fractures in 16-27% of patients with metastatic bone disease.[1,2] The (prophylactic) fixation of an actual or impending pathologic fracture caused by bone metastasis is a palliative treatment and fixation should be "once and for all" to limit the burden for the patient and to regain quality of life as soon as possible. The treatment of such fractures of the humerus however can be challenging. Like all pathologic fractures caused by bone metastases, fracture healing cannot be expected.[3] Most pathologic fractures in the humerus and femur are due to rotational movements, but reconstruction of the humerus may prove more difficult than of the femur, as the predominant force on the femur is an axial compression, while the humerus is subject to a combination of axial compression (especially if a patient uses crutches or a walking aid), distraction (inherent in lifting and pulling), and rotational forces.[4,5] The rotator cuff, deltoid, pectoralis major and latissimus dorsi muscles can inflict great torsional movement on destructed bone or the fracture parts. Also the movement of the lower arm greatly affects the stability of a fractured humerus. The most important aspect of the fixation is therefore a non-rotating fixation that can withstand the rotational forces as well as control impaction and distraction and therefore enables maximal functioning.

An adequate fixation can be realized with an intramedullary (IM) nail, plate fixation, or prosthetic reconstruction.[4] Cement can be used to provide adjuvant stability.[6] An IM nail is ideally suited for impending fractures and for actual fractures in the area between 2-3 cm distal to the greater tuberosity and 5-6 cm proximal to the olecranon fossa provided that the bone stock on both ends of the humerus is sufficient.[7,8] For such actual fractures a plate fixation can also be regarded a suitable option.[9] Nailing may have several advantages over plate fixation, including; a minimal invasive approach and minimal soft tissue dissection, short operative time, protection of a long segment of bone, rigid fixation possibilities, and early rehabilitation.[8]

Important factors to take into account when deciding on the type of stabilization are the type and location of the fracture, the expected survival, and the amount of bone stock. The choice for a certain modality is currently based primarily on experience and preference of the surgeon.[10] As with the surgical treatment of many other pathologic fractures, insufficient research has been published to adequately determine which modality would fit a patient best. No randomized studies have been performed, and most retrospective studies report only small cohorts. Only two large cohorts of more than 100 patients have been published

that have tried to identify risk factors for poor outcomes related to specific patient characteristics or stabilization modalities.[2,11] Such retrospective studies, trying to make comparisons between treatment modalities, are however strongly affected by indication bias and comparisons should not be made. To derive the most relevant conclusions from retrospective data, we believe focus should be on a single treatment modality in a large dataset. That does not fully eliminate indication bias, but can inform surgeons more specifically about the pearls and pitfalls of the modality once it is selected.

This multicenter study aims to determine the cumulative incidence of and risk factors for failure of intramedullary nailing for actual or impending pathologic fractures caused by bone metastases of the humerus.

Methods

Between 2000 and 2015, 185 patients in eight centers were treated with IM nails for actual or impending pathologic fractures of the humerus caused by bone metastases. One hundred and seventy-eight patients, with 182 actual or impending humeral fractures were evaluated in this retrospective study, after local institutional review board approval. Patients with primary bone tumors (including multiple myeloma, solitary plasmacytoma, or malignant lymphoma of bone), pathologic fractures from other causes than metastases, unavailable medical records (2 patients), or receiving revision surgery after failed stabilization elsewhere (5 patients) were excluded. The study includes 72 patients that were reported in a previous cohort of humerus pathologic fractures.[11]

Surgical treatment

Stabilization was prophylactic for an impending fracture in 21% of the cases (n=39). The most common location for both actual and impending fractures was the diaphysis (62% each; n=89 and n=24, respectively) (table 7.1). The type of operative procedure, including the type of nail, the method of fixation, and the use of adjuvant cement, was determined by the surgeon, taking the location, type of fracture, primary tumor, expected survival and patients' expectations into account. Throughout the study period, indications for an intramedullary nail were generally an impending fracture, a fracture of the diaphysis, or a proximal fracture providing sufficient bone stock in the humeral head. As multiple hospitals participated in this study, a range of intramedullary nails was used. Reaming was performed according to the manufacturers' guidelines. Most commonly, a nail of 250 mm long and 7.5 mm wide was used for stabilization (table 7.1). The proximal fixation method differed between a single spiral blade

(20%; n=36), a spiral blade in combination with a bicortical screw (10%; n=19), or one (24%; n=44), two (34%; n=61) or three (10%; n=18) locking screws (table 7.1). Almost all nails (98%) were fixated distally with one (48%; n=88), two (45%; n=82) or three (3%; n=5) bicortical screws. All patients received pre-operative prophylactic antibiotics according to each centers' protocol (most commonly cefazolin). Adjuvant cement was applied in 10% of the nails (n=19) for reinforcement of the humeral head (11%; n=2) or shaft (11%; n=2), filling of the metastatic lesion (47%; n=9), or a combination (32%; n=6). In general, cement was used if bone stock was regarded insufficient for adequate screw fixation or if the lesion was very large. Mode of cement application was open in 15 cases (79%) and percutaneous in 4 cases (21%). In 21% of the fractures (n=38; 30 actual and 8 impending fractures), radiotherapy had previously been applied, most commonly for pain. Post-operative radiotherapy was given in 58% following surgical stabilizations (n=105) after a mean of 5.1 weeks (SD 6.1). The choice of administering postoperative radiotherapy was not protocol-bound, but subject to local practice.

Primary outcome

The aim of palliative stabilization of actual and impending pathologic fractures of the humerus is to maintain or regain function and control pain with a single intervention. The primary outcome of this study therefore was any failure of achieving this goal. This included all implant failures, and persisting pain or tumor progression requiring local treatment. Medical and radiological records were screened to collect demographic data and details on the fracture (location, type, primary tumor), the treatment (type of nail, number of screws, curettage, use and location of adjuvant cement, post-operative radiotherapy), and follow-up (complications, revisions, and last known date). Intraoperative complications, neurological complications, and infections were recorded separately.

Due to the palliative nature of the treatment and the poor health of many patients in this population, follow-up is not standardized. After radiological follow-up (at 4–8 weeks) at the orthopedic surgeon, subsequent in-person follow-up was generally performed by the primary care giver (for example, general practitioner, referring medical doctor). Follow-up visits to the orthopedic surgeon were made on an as-needed basis, thus when required by the patient. However, close collaboration between the primary care giver and the orthopedic surgeon ensured reporting of orthopedic complications. Among patients who were alive at final analysis, a follow-up moment (either in-person, by telephone or by the primary care giver) at one year was available. A total of 69% (123 of 178) of the patients died within one year, and 17% (30 of 178) were alive at 2 years. Follow-up ranged from 0.03 to 167 months. Median follow-up as calculated by reversed Kaplan Meier was 60.4 months (95%CI 15.0–105.7).

Patients

One-hundred and seventy-eight patients with 182 actual and impending fractures were included in this study with a median age of 62.7 years (range 33.5–88.9) and prominently women (61% [n=108]). Breast (29%), lung (25%), and kidney (16%) cancer were the most common primary tumors (table 7.2). Visceral and/or brain metastases were present in 107 patients (60%).

Survival

Median overall survival (OS) was 5.7 months (95%CI 4.8–6.7). The median OS of patients treated for an impending fracture (8.6 months [95%CI 5.5–11.7]) did not significantly differ from patients treated for actual fractures (5.3 months [95%CI 4.2–6.4]). Between primary tumors there was a large difference in median OS: 2.7 months (95%CI 0.2–5.2) for lung cancer, 6.9 months (95%CI 5.4–8.4) for breast cancer, and 21.6 months (95%CI 0.0–48.2) for kidney cancer.

Statistical analysis

Time to failure and survival time were calculated from the date of surgery. For survival analysis, only the first treatment was included for patients with bilateral nails. A competing risk model was used to estimate the cumulative incidence of failure with death as competing event.[12] The cumulative incidence was defined as the probability of failing from a specific cause before time (t). Univariate cause-specific Cox regression analyses were performed to determine whether factors such as location, fracture type, proximal and distal fixation, cement, and pre- and postoperative radiotherapy were associated with failure. Survival curves were estimated by using the Kaplan-Meier method and compared with log-rank analysis. Median follow-up was estimated with the reversed Kaplan-Meier.[13] A p-value <0.05 was considered significant. SPSS (version 23.0, SPSS Inc., Armonk, NY) was used to perform statistical analysis. The cumulative incidence was estimated with the mstate library in R environment.[14,15]

Results

Twenty-three failures were registered, leading to an overall failure rate of 12.6% (23/182). Cumulative incidence of failure was 1.1% at 1 month (95%CI 0–2.6), 3.3% at three months (95%CI 0.7–5.9), 3.8% at six months (95%CI 1.0–6.6), 8.2% at 1 year (95%CI 4.2–12.3), and 10.0% at two years (95%CI 5.6–14.5) (figure 7.1). Thirteen failures had a predominant mechanical component (including (peri-)

implant fracture, non-union, migration of nail or screw) whereas nine failures had a predominantly oncological cause (ranging from painful moderate tumor progression to massive recurrence) (table 7.3).

One patient developed acute compartment syndrome directly postoperatively, requiring immediate fasciotomy followed by revision surgery several weeks later. All other complications occurred after 0.4 to 57.2 months. The majority of complications with an oncological cause occurred after 12 months, while mechanical complications occurred predominantly between 6 to 12 months after surgery (table 7.4). Seventeen of the 23 failures (74%) underwent revision surgery. Two failed implants were not revised because of the patients' condition. Four patients with progressive disease received radiotherapy or a brace as opposed to revision surgery.

Table 7.1 Fracture and treatment characteristics

	All *N (%)*	*Actual fracture* *N (%)*	*Impending fracture* *N (%)*
Humeri total	182	143	39
Side: right	102 (56)	83 (58)	19 (49)
Location			
Proximal	61 (34)	50 (35)	11 (28)
Diaphyseal	113 (62)	89 (62)	24 (62)
Distal	8 (4)	4 (3)	4 (10)
Median length of nail (SD)*	250 (22)	250 (22)	260 (22)
Median diameter of nail (SD)*	7.5 (1.1)	7.5 (1.0)	7.5 (1.4)
Proximal fixation			
Spiral blade only	36 (20)	30 (21)	6 (15)
Spiral blade + 1 screw	19 (10)	14 (10)	5 (13)
1 screw	44 (24)	31 (22)	13 (33)
2 screws	61 (34)	49 (34)	12 (31)
3 screws	18 (10)	16 (11)	2 (5)
Not reported	4 (2)	3 (2)	1 (3)
Distal fixation			
None	4 (2)	4 (3)	0
1 screw	88 (48)	66 (46)	22 (56)
2 screws	82 (45)	66 (46)	16 (41)
3 screws	5 (3)	5 (3)	0
Not reported	3 (2)	2 (1)	1 (3)
Reamed			
Yes	138 (76)	109 (76)	29 (74)
No	44 (24)	34 (24)	10 (26)

(Table 7.1 continued)

Adjuvant cement			
Yes	19 (10)	15 (10)	4 (10)
No	163 (90)	128 (90)	35 (90)
Location of cement[±]			
Humeral head	2 (11)	2 (13)	0
Fracture / lesion	9 (47)	7 (47)	2 (50)
Humeral head & lesion	6 (32)	4 (27)	2 (50)
Entire shaft	2 (11)	2 (13)	0
Preoperative radiotherapy			
Yes	38 (21)	30 (21)	8 (21)
No	144 (79)	133 (79)	31 (79)
Postoperative radiotherapy			
Yes	105 (58)	79 (55)	26 (67)
No	77 (42)	64 (45)	13 (33)

*in mm; data of 65 nails missing. [±]percentage of nails with cement. SD: standard deviation.

Table 7.2 Primary tumour types

Primary tumour	*N (%)*
Breast	51 (29)
Lung	45 (25)
Kidney	28 (16)
Thyroid	9 (5)
Prostate	8 (5)
Oesophagus	7 (4)
Unknown primary	7 (4)
Melanoma	5 (3)
Colorectal	4 (2)
Liver/pancreas	3 (2)
Bladder	2 (1)
Other	9 (5)

Univariate Cox regression analyses did not show any significant association between factors such as fracture type, fracture location, fixation technique, adjuvant cement, or pre- or postoperative radiotherapy and the risk of failure (table 7.5).

Intraoperative complications were reported in six patients (3.3%), all concerning fractures caused by introducing the nail. Seven patients (3.8%) had neurological complications: one patient had post-operative paresis of the radial nerve for which neurolysis was performed; six patients had post-operative neurapraxia of

the radial nerve, which recovered spontaneously between one week and six months. No local infections were reported.

Table 7.3 Characteristics of patients and treatments with failed intramedullary nails

Characteristic	*Failures no. (%)*
Total (nails)	23
Primary tumour	
Breast	6 (26)
Kidney	6 (26)
Lung	4 (17)
Thyroid	2 (9)
Prostate	2 (9)
Unknown primary	2 (9)
Colorectal	1 (4)
Fracture type	
Actual	20 (87)
Impending	3 (13)
Location	
Proximal	8 (34)
Diaphyseal	14 (61)
Distal	1 (4)
Proximal fixation	
Spiral blade	8 (34)
1 screw	4 (17)
2 screws	6 (26)
3 screws	4 (17)
Not reported	1 (4)
Distal fixation	
None	0
1 screw	9 (39)
2 screws	13 (57)
Not reported	1 (4)
Cement	
No	21 (91)
Yes	2 (9)
Radiotherapy	
Previous only	3 (13)
Postoperative only	14 (61)
Previous and postoperative	2 (9)
None	4 (17)

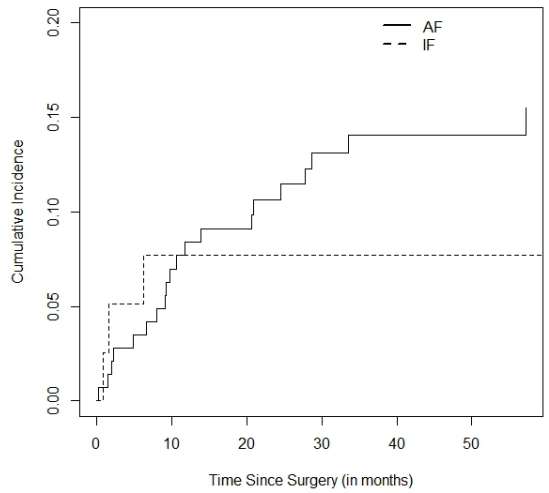

Figure 7.1 Cumulative incidence of failure for actual (AF) and impending fractures (IF).

Table 7.4 Distribution of timing of complications according to origin (mechanical or oncological)

Months after surgery	*Mechanical*	*Oncological*
0 to less than 3	2	3
3 to less than 6	1	0
6 to less than 12	6	1
12 to less than 18	2	0
18 to less than 24	1	1
More than 24	1	4
Total	13	9

Table 7.5 Cause specific hazard ratio (HR) along with 95% confidence interval (CI) from a univariate Cox-regression model for failure

Variables	*HR*	*95% CI*	*P value*
Location			
Proximal	-		0.932
Shaft	1.13	0.47 - 2.72	0.787
Distal	0.82	0.10 - 6.70	0.855
Fracture: actual vs. impending	2.91	0.82 - 10.35	0.098
Proximal spiral blade[a]	0.88	0.37 – 2.10	0.769
Number of distal screws[b]	0.74	0.31 – 1.74	0.486
Use of cement[c]	0.80	0.19 – 3.42	0.761
Previous RT[c]	0.92	0.34 – 2.50	0.868
Post-op RT[a]	1.70	0.71 – 4.60	0.235

[a]no vs. yes; [b]one vs. two; [c]yes vs. no.

Discussion

Pathologic fractures of the humerus account for 15-31% of all pathologic fractures[16-20] and their optimal treatment is unclear. Choices for the optimal surgical modality depend partly on risk factors for failure, but these are unknown for intramedullary (IM) nails of the humerus. This retrospective cohort of 182 IM nails, the largest cohort regarding humeral IM nails for actual and impending pathologic fractures to date, shows an overall good result, but a failure percentage of 12.6% with the cumulative incidence increasing with a longer survival. None of the included variables were identified as risk factors for failure.

This study is limited by several factors. First, it is plausible that the actual incidence of complications is higher and the cumulative incidence is an underestimation because follow-up was not standardized. Nearly all studies on the treatment of bone metastases are limited by this aspect, because these patients, whose treatment is palliative and who are commonly in the last phase of life, are seen on indication as opposed to a pre-determined follow-up scheme. Second, the retrospective design of the study inherently introduces selection bias. Although this study does not compare treatment modalities, indication bias might have affected the Cox regression analyses for factors associated with failure. Furthermore, the retrospective design also limits the extent of available data for analysis. Detailed information on function and pain relief would have provided valuable information for this study, however documentation of these outcome measures has been insufficient in past medical records.

The number of failures (23; 12.6%) reported in this cohort is higher than reported in two other large studies; both Wedin et al. and Janssen et al. report 7% failures. [2,11] All reported failure percentages, including this study, are most likely an underestimation, predominantly due to lack of standardized follow-up. Furthermore, the short survival of this patient population limits the number of registered events and possibly gives a distorted perception of the performance of IM nails. The increasing cumulative incidence over time as shown in this study supports this assumption. To provide the most genuine number of failures, we scored all events that did not meet the primary goal of treatment (i.e. regain function and provide pain control with a single stabilization) as failure. If only revisions are scored, as in the studies by Janssen et al. and Wedin et al., this gives an even greater underestimation, because in the palliative setting it is not uncommon that patients with an indication for revision surgery are treated conservatively because their medical condition is too poor to undergo surgery.

The failures can be roughly categorized by their origin, mechanical or oncological, although a combination of both elements might be present in some cases. The timing of the occurrence of these complications (table 7.4) provides further information of what can be expected during follow-up. Also, based on these results, other surgical modalities could be considered in cases with a long expected survival. Oncological complications predominantly arise very shortly postoperatively or after one year. For patients with large and quick growing tumor masses, an open approach could thus be considered as opposed to a minimally invasive IM nail. In patients with an expected long survival, surgeons should be aware of the risk of failure and perhaps consider more extensive resection and reconstruction. The latter stresses the importance of survival estimation when determining the most appropriate surgical modality for each individual patient.[21] Mechanical complications arise largely between 6 and 12 months postoperatively. All healthcare providers should be aware of this, to provide timely referral and thus keep quality of life as optimal as possible.

In this large cohort, no factors (such as location, fracture type and fixation, use of cement, and preoperative and postoperative radiotherapy) were identified as significantly associated with an increased risk of failure. No previous studies have tried to identify factors related with failures of specifically intramedullary nails in the humerus for pathologic fractures. Studies by Janssen et al. and Wedin et al. only analyzed factors associated with failure of all modalities (i.e. prostheses, nails, and plates).[2,11] Unfortunately, regarding prognostic factors, the current study has brought us no further yet, for it remains questionable whether it is now correct to conclude that these factors play no role in the risk of failure. Based on experience with femoral stabilizations, an association would be expected at least with fracture type (actual or impending).[22] The lack of this association can be due to (a combination of) two factors: first, the number of impending fractures included in the cohort is small. Second, the short survival could eliminate an actual association. The lack of a significant difference in median overall survival between patients with actual or impending fractures corresponds with the results of Wedin et al.,[2] but is in contrast to IM nails in the femur.[22] This is most likely due to the difference in biomechanical loading which causes humeral impending fractures to be diagnosed later than femoral fractures thereby masquerading the difference in remaining survival between impending and actual fractures. Regarding the use of cement and preoperative radiotherapy, the lack of an association is possibly due to small number of patients (10% and 20%, respectively) who had received these adjuvant treatments.

The use of cement is supported by several authors, especially in more dated studies.[6,23] Laitinen et al. showed that the number of complications did not differ between patients treated with and without cement, but that those treated with cement experienced faster pain relief.[24] Choi et al. used cement in all intramedullary fixations, including proximal femoral lesions. They advocate the use of cement, especially in lesions affecting the humeral head; in those cases, a stable fixation could be achieved despite extensive osteolysis and thin cortex due to the use of cement.[25] In other recent studies however, the effect of cement is not evaluated because the outcomes are subject to selection bias, for cement is generally used in larger and more extensive lesions, which are a priori at a higher risk of failure. No biomechanical studies have evaluated the effect of cement in pathologic fractures of the humerus, as opposed to proven effects in the femur.[26] One of the difficulties to take into account when using cement in (extensive) humeral fractures is the risk of cement leakage and, depending on the location, associated damage of the radial nerve or joint space. Based on experience, we would advise to use cement only in situations where an IM nail is indicated but the bone-stock is insufficient to ensure firm stabilization proximal and distal to the fracture.

This study intentionally did not evaluate the indication for an IM nail. The results can however help when choosing between different surgical modalities. When choosing between a prosthesis and an IM nail, the 0% infection in this cohort of IM nails is a factor to take into account. Also, the relatively high percentages of peri-operative complications (3.3%) and postoperative complications affecting the radial nerve (3.8%) show that we should not only associate these complications with plate fixations. Particular focus should be on the radial nerve during reduction of a dislocated fracture and distal fixation.

In conclusion, this large retrospective cohort shows that intramedullary nails should be regarded as a safe and effective treatment for actual and impending pathological humeral fractures. If mechanical failure develops, this occurs mainly 6 to 12 months postoperatively. Although overall results are good, surgeons should be aware of the fact that intramedullary treatment of pathologic humeral fractures may not prove as simple as one may expect. Most important is to pursue a rotation-stable and durable fixation that corresponds with the estimated survival to prevent complications that occur mainly with prolonged survival.

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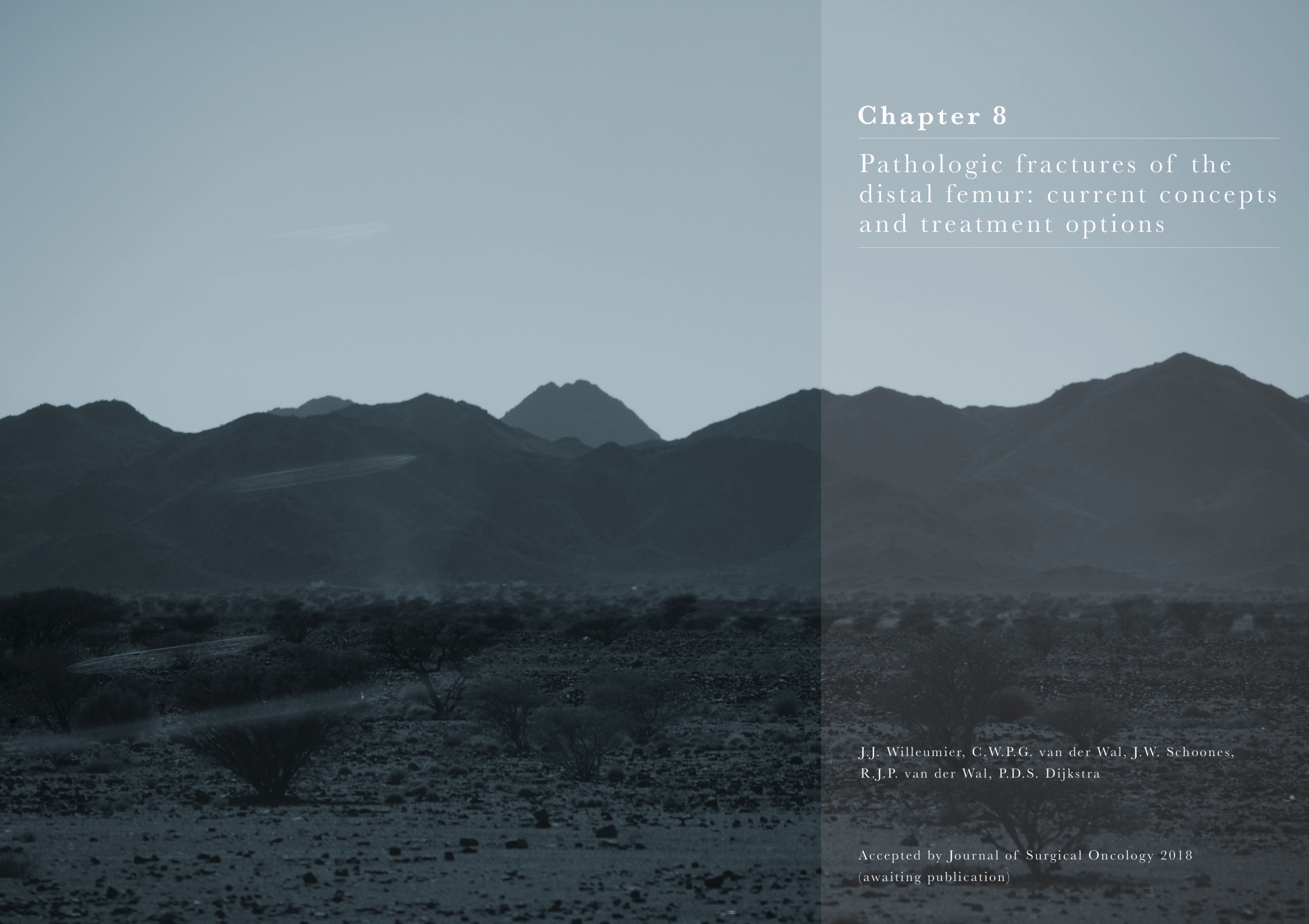

Chapter 8

Pathologic fractures of the distal femur: current concepts and treatment options

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Abstract

Pathologic fractures of the distal femur caused by bone metastases are not as common as those in the proximal femur but provide great difficulty to adequately treat. This systematic review shows that insufficient literature exists to draw clinically relevant conclusions for essential questions, such as 'what factors indicate an endoprosthetic reconstruction for distal femur pathologic fractures?' Due to paucity of literature in the systematic review, a current concepts review (including treatment flowchart), based on instructional reviews and experience, was also performed.

Introduction

Patients with actual or impending pathologic fractures caused by bone metastases require surgical stabilisation to regain function and quality of life. Pathologic fractures show none or only minimal healing tendencies so they cannot be treated with the same principles as traumatic fractures. The palliative intent of the treatment adds further difficulty, because the scope of the treatment should correlate with the expected survival. Stabilisation must enable immediate full weight-bearing, be sufficient for the remaining lifetime while avoiding the need for extensive rehabilitation.

The femur is the most common long bone affected by bone metastases and subsequent pathologic fractures.[1] One third of the femur metastases is located in the inter- and subtrochanteric regions, followed by the neck and diaphysis.[2,3] The distal femur is the least affected region of the femur; in our large retrospective database approximately 10% of all femoral metastases were located distally.[4] However, the distal femur is one of the most difficult areas to treat.

Treatment options include endoprosthetic reconstruction (EPR; total knee or modular tumour prostheses), single or double plate fixation, intramedullary (IM) nail fixation, and cement arthroplasty.[5] Due to the magnitude of prosthetic knee reconstructions, internal fixation is generally preferred, but due to the location sufficient screw fixation on both sides of the lesion is often not possible. Additionally, adequate fixation of screws in the condyls is often difficult due to poor bone stock. Adjuvant cement can provide more grip for the screws, but is challenging to apply to the desired location. Cement alone can also be used to fill the lesions, but is only a short-term solution when a short survival is expected.

A brief glimpse on current literature shows little mentioning of how to treat pathologic fractures of the distal femur, while all orthopaedic and trauma surgeons come across these fractures and need to decide on the most optimal treatment. With the lack of evidence, treatment is based on clinical experience, but only few surgeons have sufficient experience to depend on. The treatment of these difficult fractures is therefore a common subject of discussion and consultation among colleagues. As survival of patients with metastatic disease prolongs [6,7] and the incidence of pathologic fractures grows,[8] including those of the distal femur, the need to identify the optimal treatment of pathologic fractures of the distal femur increases. The optimal treatment however differs for each individual patient. Factors that identify the most suitable treatment would therefore be helpful for clinicians. If possible, this should be based on

peer-reviewed publications. To that end, this study aims to perform a systematic review to identify factors that indicate the need of an endoprosthetic reconstruction for a distal femur pathologic fracture. Additionally, a current concepts review was performed.

Methods

This systematic review is reported according to the MOOSE guidelines for reporting observational studies.[9]

Literature search

The search strategy was developed by an experienced medical librarian (JWS), and applied in the following databases: PubMed, Embase (OVID-version), Web of Science, COCHRANE Library, CENTRAL, CINAHL/Emcare (OVID-version), and ScienceDirect. The following keywords were used and combined with the Boolean operators 'OR' and 'AND': distal femur, metastasis, pathologic fracture, fracture, neoplasm AND surgery, treatment, endoprosthesis, intramedullary nail, plate, implant. For the different concepts, all relevant keyword variations were used (i.e. keyword variations in the controlled vocabularies as well as free text word variations). The search strategy was optimized for all consulted databases. The final search was performed on 15-12-2017. Reference lists of retrieved papers, review articles, and clinical practice guidelines were checked for relevant publications. Inclusion was limited to results in English or Dutch and publications between 1990 and 2017. Meeting abstracts, case reports, and review articles were excluded. Articles reporting on functional outcomes, complications, revisions or survival after treatment with prostheses, plate-screw fixations, IM nails, or cementplasty for an actual or impending pathologic fracture of the distal femur due to bone metastases were defined as eligible.

Articles were selected in two steps, both performed by two authors (JJW, CWPGvdW) independently. First, all titles and abstracts were screened according to the predefined criteria. Subsequently, all potentially eligible studies and all studies that could not be scored based on title and abstract were retrieved in full-text and screened based on the same criteria. Disagreements were dissolved by consensus after both steps.

Data extraction and analysis

The same two authors independently extracted data using an electronic data collection form. Available data concerning study characteristics, patient demographics, and outcome measures was collected. Outcome measures included functional outcomes as measured by an internationally accepted standardized instrument and local complications (infections, structural failures (including implant loosening or breakage, dislocation, peri-prosthetic fracture), and tumour progression).

Statistical analysis

All data were summarized descriptively. Complications were reported as frequencies with percentages for each surgical modality. No pooled effects were estimated because the studies included did not report complication rates (including 95% confidence intervals), but only frequencies.

Quality assessment

The methodological quality of all included studies was assessed using the Methodological Index for non-Randomized Studies (MINORS) scale.[10] MINORS is a validated score for non-randomised studies based on eight items with a maximum score of 16 for non-comparative studies. A score of 12 or higher was considered as 'high' methodological quality, 9-11 was considered 'moderate', and 8 points or less was considered 'low' quality.[11] All included studies were assessed independently by two authors (JJW, CWPGvdW). Any discrepancies were resolved by consensus.

Results

Literature search

The literature search identified 469 unique titles. Figure 8.1 shows the flowchart of in- and exclusion resulting in two articles to be included in this review.[12,13] In total, 441 articles were excluded because the study population did not include distal femoral metastases, and 21 articles were excluded because although the study included distal femoral metastases, the results were not reported specifically for this group. Another 20 articles were excluded because they were reviews or case reports, 11 articles were excluded because they were not in English or Dutch, and one article was excluded because the full-text was not available. The two included studies reported on outcomes after surgery of metastases in the long bones or femur in general, but provided (some of) their results specified per location and were thus eligible for inclusion.

Study characteristics

Mavrogenis et al. report on 29 distal femur fractures in 29 patients, 16 of which treated with femoral reconstruction nails (Grosse & Kempf Locking Nail System and T2 Recon Nailing System, Stryker, Italy) and 13 were treated with fixed hinge

knee distal femoral prostheses (HMRS, Howmedica Modular Reconstruction System, Stryker, UK). Wedin et al. describe the results of 16 distal femoral fractures in 16 patients, one of which treated with a prosthesis, ten treated with plate fixation (eight with gliding screws, two with regular screws), and five with other treatment modalities (e.g. curettage). Unfortunately, no further treatment details are presented. In total, the two studies reported on 45 distal femora: 14 treated with EPR, 16 with IM nails, 10 with plates, and five with other modalities. Baseline patient characteristics were not reported specifically for the distal femur and can therefore not be presented in the current review.

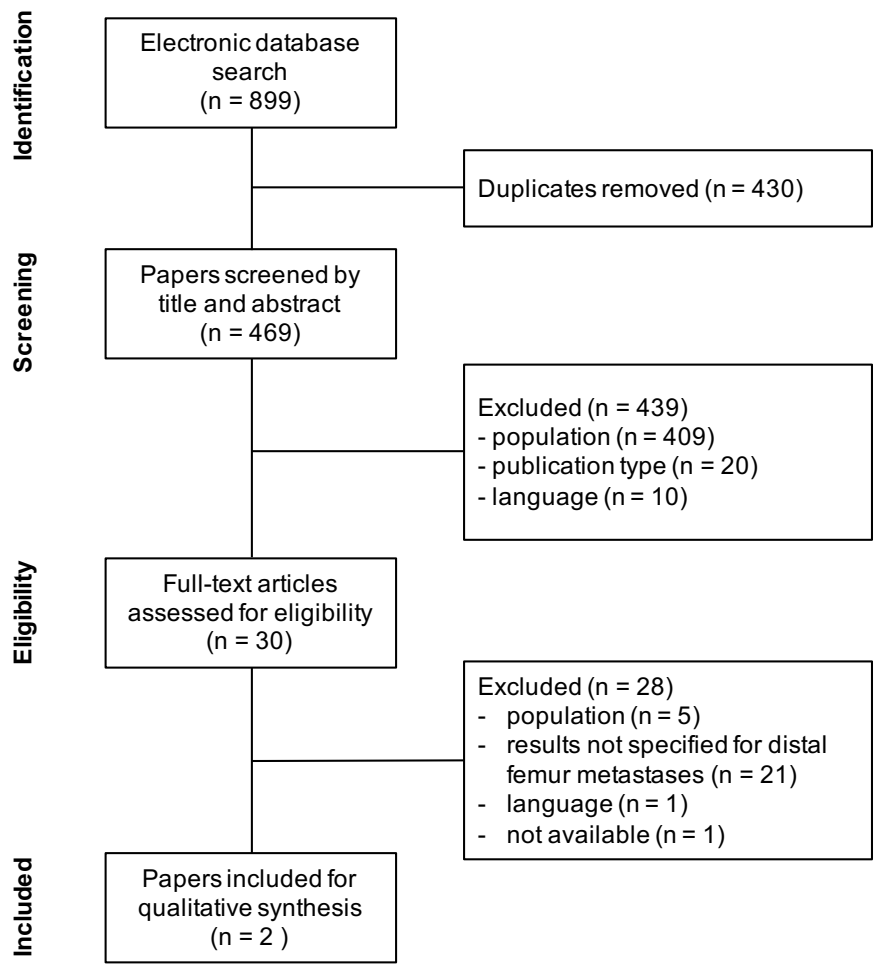

Figure 8.1 Flow chart of in- and exclusion.

Table 8.1 MINORS scale for methodological quality. Items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). Total score of 16 points is possible.

Author	*Aim*[1]	*Inclusion*[2]	*Data*[3]	*End-points*[4]	*Assess-ment*[5]	*Follow-up*[6]	*Loss to FU*[7]	*Study size*[8]	*Total*
Mavrogenis et al.	1	2	0	1	0	2	2	0	8
Wedin et al.	2	2	0	2	0	0	0	0	6

1: A clearly stated aim: the question addressed should be precise and relevant in the light of available literature.
2: Inclusion of consecutive patients: all patients potentially fit for inclusion (satisfying the criteria for inclusion) have been included in the study during the study period (no exclusion or details about the reasons for exclusion).
3: Prospective collection of data: data were collected according to a protocol established before the beginning of the study.
4: Endpoints appropriate to the aim of the study: unambiguous explanation of the criteria used to evaluate the main outcome which should be in accordance with the question addressed by the study. Also, the endpoints should be assessed on an intention-to-treat basis.
5: Unbiased assessment of the study endpoint: blind evaluation of objective endpoints and double-blind evaluation of subjective endpoints. Otherwise the reasons for not blinding should be stated.
6: Follow-up period appropriate to the aim of the study: the follow-up should be sufficiently long to allow the assessment of the main endpoint and possible adverse events.
7: Loss to follow up less than 5%: all patients should be included in the follow up. Otherwise, the proportion lost to follow up should not exceed the proportion experiencing the major endpoint.
8: Prospective calculation of the study size: information of the size of detectable difference of interest with a calculation of 95% confidence interval, according to the expected incidence of the outcome event, and information about the level for statistical significance and estimates of power when comparing the outcomes.

Quality assessment

The mean MINOR quality assessment score was 7 (table 8.1), which was considered low methodological quality. There were no items of major discrepancy between the reviewers.

Functional outcomes

Neither study reported on functional outcomes.

Complications

In the study by Mavrogenis et al. four complications were reported among 13 EPR (31%). The complications included three infections and one aseptic loosening (table 8.2). One of the IM nails failed (1/16; 6%). The complications of

the distal femur made up 83% of all complications reported (5 of 6); only one of 81 (1.2%) treated proximal and diaphyseal fractures failed, while five of the 29 (17.2%) treated distal femurs failed.

Wedin et al. reported two complications in the patients treated with plates (20%), and two in those who received curettage and augmentation (40%). Causes of the latter four failures were stress fractures in two patients and tumour progression in two cases after 7 and 13 months. The distal femur complications were 21% of all femoral complications reported in the study (15 complications in 143 proximal and diaphyseal fractures).

Overall, four of 14 EPR (29%; 9% of all distal femora), one of 16 IM nails (6%; 2% of all distal femora), two of ten plate fixations (20%; 4% of all distal femora), and two of five variety of treatments (40%; 4% of all distal femora) led to complications.

Table 8.2 Complications

Author, year	*Implant*	*Femurs (N)*	*Local complications N (%)*	*Complication*	*Treatment*
Mavrogenis et al. 2012	EPR	13	4 (31)	Deep infection Deep infection Deep infection Aseptic loosening	DAIR DAIR DAIR No treatment
Wedin et al. 1999	EPR	1	0 (0)		
Mavrogenis et al. 2012	IMN	16	1 (6)	Tumour progression	Above-knee amputation
Wedin et al. 1999	Plate	10	2 (20)	Tumour progression Stress fracture	Revision of plate with cement Revision of plate with cement
Wedin et al. 1999	Other[±]	5	2 (40)	Tumour progression Stress fracture	Plate with cement Screw with cement

*Time between surgery and complications. [±] Patients with complications had received curettage and cement; EPR: endoprothetic reconstruction; IMN: intramedullary nail; DAIR: debridement, antibiotics, irrigation, retention.

Discussion

This study aimed to systematically review the literature on treatment of distal femoral pathologic fractures and identify factors that indicate the need for endoprosthetic reconstruction. The predominant conclusion is that there are hardly any studies reporting on pathologic fractures of the distal femur. Despite broad inclusion criteria, this systematic review identified only two studies that reported outcomes regarding this subgroup of fractures; 21 studies were excluded because, despite describing the relevant study population, they did not report the outcomes specifically for the distal femur (figure 8.1). Moreover, there are no studies focussing solely on the treatment of distal femoral pathologic fractures. The paucity of studies on the distal femur as opposed to the elaborate number of studies on the proximal femur is not in proportion with the difference in incidence. A reason for the lack of publications is not apparent and cannot be clearly explained. Rarity cannot be the only reason, for studies have been published on the most uncommon diseases. Perhaps these fractures have up to now simply been overshadowed by those of the proximal femur.

The second conclusion is that based on the included studies no factors can be identified that indicate the need for an EPR. Overall, the revision rates of plates and variety of treatments (e.g. curettage and cement) are higher than of EPRs and IM nails.[13] However, taking the limitations of the studies into account, firm conclusions are not possible. The interpretation of the results of the two included studies is difficult because no baseline data is presented of the patients treated for distal femur fractures. Thus although information on the primary tumour and fracture type is reported in those cases that failed, these factors cannot be placed into perspective of the entire cohort and no risk factors can be deduced. Additionally, only one of the studies reported exactly what implants were placed and neither studies gave details on the extent of the metastatic lesion.

Several limitations are present in this study. An important limitation is the lack of baseline characteristics because it impairs detailed comparison of the cohorts. Follow-up was neither adequately reported in the included studies. Short follow-up or loss to follow-up can lead to underreporting of complications. Although an elaborate literature search was performed in six databases and bibliographies were checked for missed publications, it is possible that relevant publications were not found. Also, restricting the language to English and Dutch possibly excluded relevant studies. Further, despite the aim to focus on only distant femoral metastases, heterogeneity regarding prostheses and implants, surgical techniques and surgeons, and adjuvant treatments could not be prevented. Selection bias undeniably plays a role in the included studies.

Although this is a limitation for this study, it is also a representation of clinical practise and therefore acceptable.

In the light of the conclusions and limitations of this study, advice regarding the use of EPR for distal femoral fractures can solely be expert based. Several instructional reviews make recommendations. Quinn et al. advise to treat smaller lesions in the distal femoral area with plate osteosynthesis and polymethylmethacrylate (PMMA), while larger destructive lesions should be treated with plate fixation when the articular surface can be maintained and the joint is otherwise normal. If the latter is not the case, a total knee replacement is indicated. Quinn et al. do not further elaborate whether plate fixation should be with locking plates or classical plates.[14] Scolaro et al. note that lateral locking plate osteosynthesis (LPO) with lesion curettage and PMMA provide reliable fixation for extra-articular and well-contained lesions, but IM nailing with PMMA or EPR are also options. For intra-articular or uncontained lesions an EPR should be used.[5] A similar conclusion is presented by Bryson et al., noting that if bone stock is adequate conventional fixation with locking plates of retrograde nailing with PMMA is usually sufficient.[15] Anract et al. report that LPO (with cement to strengthen the construct) should be used in patients whose life expectancy is short or when union of the fracture can be expected after adjuvant therapy. In other situations, resection and reconstruction with a tumor prosthesis is advised.[16] Concerning the use of LPO as described by Anract et al. we do not completely agree, for union should rarely be expected. Therefore, in our own instructional review, we recommend locking plate fixation with adjuvant PMMA if the bone stock is sufficient for adequate grip of the screws, irrespective of any expected union. If the condyles are largely affected or a long survival is expected a prosthesis should be considered. If the lesion is more metaphyseal and impending with sufficient bone stock in the condyls, an IM nail should be considered.[17] Whether IM nails should be placed ante- or retrograde is debatable and is not discussed in the cited instructional reviews. In trauma surgery, (reamed) antegrade and retrograde placed nails for distal femur fractures have shown comparable results regarding union and complications.[18,19] These results are however difficult to translate to the (impending) pathologic fracture population. For the fixation of pathologic fractures, all nails should be locked and sufficiently bridge the lesion, which for antegrade nails often means they should extend to the subchondral level. The risk of intra-articular metastatic spread is a proclaimed downside of retrograde nailing. Opening of the joint can lead to other complaints such as knee pain or osteoarthritis. Nail protrusion caused by insufficient distal fixation in poor bone stock can require revision surgery, although adequate use of PMMA can decrease this risk. Also, the alignment of the knee in the frontal plane can be a

problem with retrograde placing of nails. Finally, it should be noted that the use of retrograde nails has its limitations as it leaves the femoral neck unprotected and thus at risk for fracture after stabilisation. The incidence of these complications in pathologic fracture treatment is however not known. One small study reports of one nail protrusion into the knee after retrograde fixation in 12 distal femur fractures.[20]

As mentioned in previous instructional reviews, plate osteosynthesis plays a large role for distal femoral fixations; much larger than for other femoral locations. Osteosynthesis with locking compression (LC) plates is the current standard, as opposed to reduction with dynamic compression (DC) plates. LC plates function as internal fixators with multiple fixation points, creating a stable construct [21] and therefore double plating (two DC plates in 90-degree angle) is redundant. In fractures where both LPO and IM nail fixation would be suitable options, it is not evident which of the two should be preferred. However, PMMA commonly plays a role in the stabilisation – requiring clear access of the fracture – and this is easily combined with open reduction and plate fixation. Adequate cementation with IM nailing is difficult and often insufficient. Some authors prefer IM nails over LPO because less soft tissue dissection is required which is preferable as to prevent local soft tissue complications from post-operative radiotherapy.[20] The necessity of post-operative radiotherapy however, not only after ORIF but also after EPR, should be reconsidered. The use of post-operative radiotherapy has become common practise, but the evidence upon which it is based is limited to one 20-year-old retrospective study with few patients.[22]

Based on the instructional reviews, EPRs are indicated when the articular surface is affected, the condyles are largely affected or a long survival is expected. The latter is the case when it concerns a solitary metastasis, especially from renal cell cancer [23] or a favourable presentation of breast or thyroid cancer. This is illustrated by the case presented in figures 8.2a - d. The depicted case is an example in which a primary en-bloc resection and prosthetic reconstruction should have been considered. The location of the fracture and the expected long-term survival of the patient were signs that a plate fixation could be insufficient. Keeping in mind that a stabilisation of a pathologic fracture should be “once in a lifetime” and that the aim of the surgery is to maintain quality of life (i.e. full weight-bearing), a more durable option as primary stabilisation would have been preferable. Generally, such en-bloc resections and reconstructions are performed in tertiary orthopaedic-oncology centres, so patients should be referred if a more straightforward stabilisation is expected to be insufficient. Once again, the importance of adequate survival estimation is stressed. Multiple tools have been developed to aid surgeons in survival

estimation and these should be used before resection and reconstruction with endoprostheses.[4,24-26] One of the most important aspects to take into account when estimating survival is the primary tumour, for the prognosis can differ widely depending on tumour biology and available systemic options.[4] The primary tumour type and its sensitivity to radiotherapy also influences the local treatment options for impending and actual pathologic fractures. To provide an overview of the current treatment concepts a detailed treatment flowchart was developed (figure 8.3). As shown in this flowchart, the amount of bone stock (i.e. the size of a lesion and amount of cortical destruction) and whether the condyls are affected, are important aspects to take into account, in addition to the fracture type and expected survival.

Despite not answering our research question, the included studies show that the overall revision rate for the distal femur is high compared to other femoral locations. Mavrogenis et al. report a 14% revision rate in the distal femur and only 1% in the proximal femur (1 dislocation in 78 treated proximal femora).[12] Wedin et al. report 25% revision rate in the distal femur and 9% in the proximal femur (10 of 108 treated proximal femora).

The overall failure rate of EPRs in this systematic review (31%) is comparable to the overall failure rate in a study evaluating modular knee prostheses for primary tumours (29%).[27] It is however higher than the 18% complication rate of prosthetic reconstructions of proximal femur metastases as reported by Harvey et al. Moreover, in the latter study infections accounted for only half of the complications, while dislocations caused the other half. For the distal femur, as evident in the current study, infections are the most common cause of complications. This is a well-known problem with endoprostheses,[28] but should be regarded with even more caution in the metastatic population because these patients often are elderly and have further decreased immunity due to the extensive disease. Pre-operative radiotherapy has been reported as risk factor for infection in this patient population, but further analyses are required to determine whether this should affect the choice of a prosthetic reconstruction.[29]

Pathologic fractures of the distal femur are one of the most difficult pathologic fractures to stabilise, but current literature is insufficient to provide evidence based recommendations on when to use an EPR. It is easy to conclude that randomised controlled trials and subsequent meta-analyses based on such randomised studies are required to find answers. However, the heterogeneity of patients with bone metastases and the relatively low incidence of pathologic fractures, especially of the distal femur, challenge performing a valuable randomised study. A second best option would be a prospective, multicentre cohort to record all treatments and complications. Such a cohort will still face

indication bias, but with a sufficient number of patients, some robustness will be granted. A current study (Clinicaltrials.gov NCT02705157) will hopefully provide much needed data.

To conclude, based on this systematic review no evidence based recommendation can be given for the use of EPR in the treatment of distal femur pathologic fractures. The paucity of results in this literature search and poor quality of the few included studies illustrate the issues that surgeons treating pathologic fractures are constantly confronted with: there is insufficient adequate research on the treatment of pathologic fractures to answer relevant questions. International, prospective collaborations are needed to fill this void. Based on literature and expert opinion, indications for EPR in distal femur fractures are solitary metastases in patients with a long survival, a major affected joint surface, and insufficient bone stock for internal fixation.

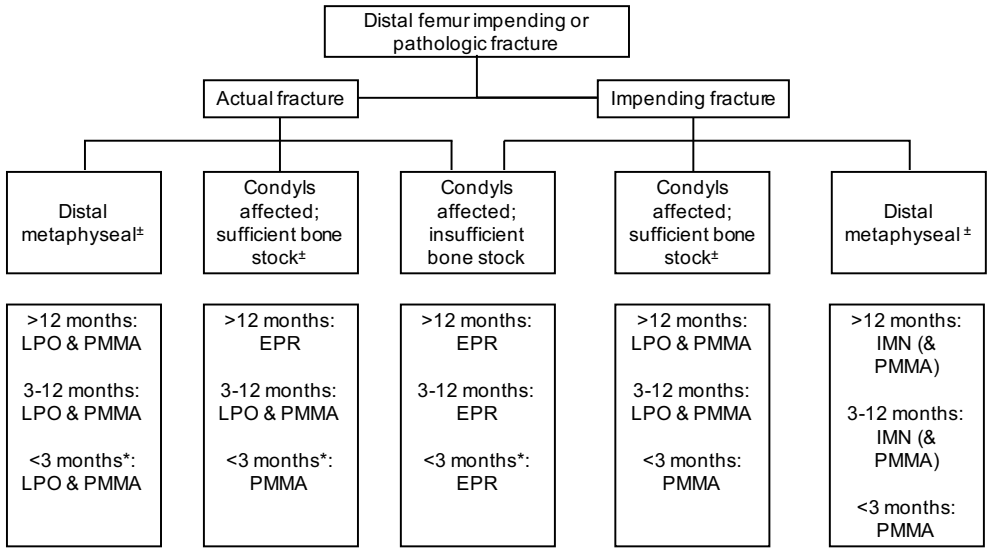

Figure 8.3 Overview of treatment options for pathologic fractures of the distal femur taking estimated survival into account.
±If the lesion concerns a distal metastasis of kidney of thyroid carcinoma an en-bloc resection and reconstruction with EPR should be considered to improve survival. *Taking expected benefit on quality of life into account. If no improvement of quality of life is to be expected, comfort care should be the preferred treatment. LPO: lateral plate osteosynthesis. PMMA: polymethylmetacrylate. EPR: endoprosthetic reconstruction.

Figure 8.2 Distal femur fracture in a 45-year-old woman caused by a solitary metastasis of renal cell carcinoma (figure a). Stabilisation of the distal femur fracture was performed with a plate osteosynthesis without cement (figure b) and post-operative radiotherapy (5 x 4Gy) was administered. A maximum load of 25 kg was set for the left leg, so the patient could only mobilise with crutches. Over the next months the knee remained painful despite optimal pain medication. Further imaging of the knee (figure c) showed that there was no consolidation of the transverse fracture, that there were also vertical fractures, and that the plate was not completely adjacent to

the bone. To improve the quality of life of the patient (i.e. pain reduction and possibility for better mobilisation) the insufficient plate osteosynthesis was revised and a distal femur resection was performed and a modular tumour knee prosthesis was implanted (figure d).
This case is an example in which a primary en-bloc resection and prosthetic reconstruction should have been considered. The location of the fracture and the expected long-term survival of the patient were signs that a plate fixation could be insufficient. Keeping in mind that a stabilisation of a pathologic fracture should be “once in a lifetime” and that the aim of the surgery is to maintain quality of life (i.e. full weight-bearing), a more durable option as primary stabilisation would have been preferable. Generally, such en-bloc resections and reconstructions are performed in tertiary orthopaedic-oncology centres, so patients should be referred if a more straightforward stabilisation is expected to be insufficient.

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Chapter 9

Treatment of pathological fractures of the long bones

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EFORT Open reviews 2016 May; 1 (5): 136-145

Abstract

- Bone metastases of the long bones often lead to pain and pathological fractures. Local treatment consists of radiotherapy or surgery. Treatment strategies are strongly based on the risk of the fracture and expected survival.
- Diagnostic work-up consists of CT and biopsy for diagnosis of the primary tumour, bone-scan or PET-CT for dissemination status, patient history and blood test for evaluation of general health, and biplanar radiograph or CT for evaluation of the involved bone.
- A bone lesion with an axial cortical involvement of >30 mm has a high risk of fracturing and should be stabilised surgically.
- Expected survival should be based on primary tumour type, performance score, and presence of visceral and cerebral metastases.
- Radiotherapy is the primary treatment for symptomatic lesions without risk of fracturing. The role of post-operative radiotherapy remains unclear.
- Main surgical treatment options consist of plate fixation, intramedullary nails and (endo) prosthesis. The choice of modality depends on the localisation, extent of involved bone, and expected survival. Adjuvant cement should be considered in large lesions for better stabilisation.

Introduction

Bone metastases arise most commonly in patients suffering from breast, prostate, kidney or lung cancer.[1] Two-thirds of all patients dying of cancer reportedly develop bone metastases,[2] however a modern, image-based study would probably present an even higher number. Due to constantly improving treatments the duration of the palliative phase is prolonged. Longer survival unfortunately gives each patient more time to develop metastases.

Bone metastases of the long bones may lead to pain, pathological fractures, immobility, decreased functioning, and hypercalcaemia. Over half of the patients experience clinical symptoms for which treatment is required,[3] of whom only a minority is surgically treated.[4] In the long bones, pain is the most common symptom, followed by impending or actual pathologic fractures in 10-25% of the patients.[5] Pathologic fractures of the femur, 75% of which presenting in the proximal part, are roughly 3.5 times as common as fractures of the humerus.[6]

This review discusses the local management of (impending) pathological fractures of the long bones, with focus on surgical treatment strategies.

Diagnosis and evaluation

For successful management the following adage should be followed: stop; think and stage; act. The most important information is gathered with the following four questions and flow-chart (figure 9.1).

What is the origin of the lesion?

A bone lesion with unknown aetiology is a primary bone tumour until proven otherwise. Denying this possibility might deprive patients of correct and curative treatments. If the patient has no history of malignancy a (PET-)CT scan of the chest and abdomen should be performed. In case no primary tumour is visible, a core needle biopsy of the bone lesion should be performed for histologic identification before treatment is engaged. When the patient has already known malignancy, but has no previous metastases and the lesion is solitary, a biopsy should be considered. In case of multiple lesions and a malignancy at high-risk for developing metastases (e.g. lung cancer), generally no additional histological confirmation is necessary.

What is the dissemination status?

The presence of other disease localisations influences the treatment strategy. Bone dissemination can be grouped into three categories: solitary lesion,

oligometastases (between two and four bone metastases), or diffuse. Solitary lesions can in some cases (i.e. primary kidney cancer or bone sarcoma) be treated with curative, albeit generally palliative, intent.[7] Defining a difference between oligometastases and diffuse metastases throughout the skeleton is a relatively new concept. Especially for kidney and breast cancer patients it is hypothesised that a more aggressive local treatment in the case of oligometastases might improve survival.[8] In the past, the principal examination to assess the bone dissemination status was a total-body bone scintigraphy (technetium-99m or fluoride-18 scan). Currently the use of PET-CT is accelerating due to its increased accessibility and superior sensitivity and specificity to bone scintigraphy.[9] Additionally, PET-CT provides information on other (visceral) disease localisations. If PET-CT is unavailable, then an additional CT of the thorax/abdomen should be considered to analyse visceral dissemination.

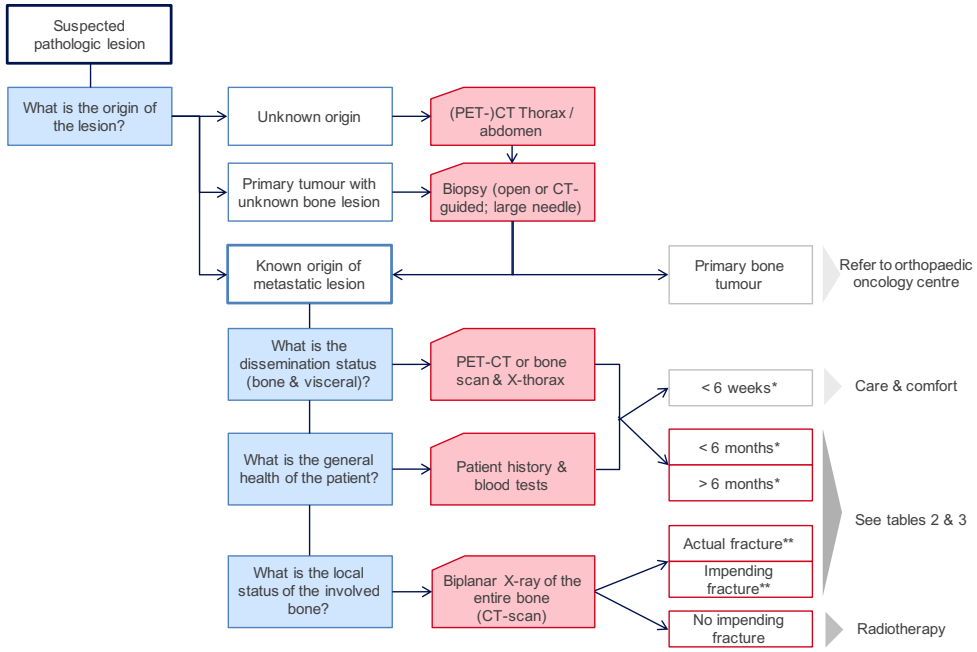

Figure 9.1 Flowchart of diagnostic tests.
*Survival prediction according to primary tumour type, patient performance score, visceral or cerebral metastases.[19] **Fracture risk according to axial cortical involvement or circumferential cortical involvement of >50%.[13]

What is the general health of the patient?

The general health status can be deduced from the patient history (nutritional status, weight loss and cognitive status, for example). Dehydration, thirst or drowsiness can suggest hypercalcaemia and blood tests (serum calcium and albumin) should be performed. If surgery is planned, laboratory studies should include a complete differential blood-cell count, erythrocyte sedimentation rate, C-reactive protein, electrolyte count (sodium, potassium), and serum alkaline phosphate.

What is the local status of the involved bone?

In daily practise, bi-planar conventional radiographs of the whole affected long bone are mandatory to evaluate the extent of the cortical destruction of the involved bone lesion and whether other adjacent bone lesions are present. The cortical destruction is a measure for estimating the fracture risk. A CT scan is a more precise alternative for obtaining this information; however, routine use of CT scans is less practical and more expensive than radiographs and thus not advised as a primary imaging modality.

The information gathered with the standard work-up provides the basis for staging of the patient and determining the treatment strategy. The first step is the decision in a multi-disciplinary meeting on whether surgery is required. Radiotherapy is the treatment of choice for small lesions, while surgery is indicated for actual fractures. The difficulty lies in the group of patients with larger lesions and an uncertain risk of fracturing. All treatments aim to maintain optimal, pain-free function of the extremities and should ensure direct weight bearing and mobility**.** Two important principles should be adhered.

Prophylactic stabilisation of bone should be performed if there is a substantial risk of fracturing. If the risk of fracturing is low, the appropriate treatment is radiotherapy. While there is general consensus about the advantages of operating impending fractures over actual fractures, a clear, international definition of 'a substantial risk' has not been defined.[10] To prevent over- and under-treatment, a careful balance between the advantages of a prophylactic treatment *versus* the risks of surgery and disadvantages of over-treatment for the patient has to be made. Multiple different factors for an impending fracture have been described, such as pain, size, site, and lesion aspect.[11,12] However, because these factors are based on retrospective research, their predictive value is low.[10] Based on prospective research, we advise the use of the axial cortical involvement of > 30mm and a circumferential cortical involvement of >50% as predictive factors for fracturing (figure 9.2).[13] Although the future of

fracture risk analysis is CT-based,[14] the axial cortical involvement is the most practical tool to use if only conventional radiographs are available.

The selected rigid fixation should be durable for the remaining lifetime of the patient, while the recovery and rehabilitation time should not exceed the life expectancy. Survival can range from days to many years depending primarily on the primary tumour type. Median survival for patients with bone metastases from lung cancer is three months, while this extends to ten months for prostate and 17 months for breast cancer.[15] Multiple factors are considered prognostic for survival besides primary tumour type and various prognostic models based on these factors have been designed, as shown in table 9.1.[4,15-20] We advise the prediction of survival according to a simple and straightforward model, including primary tumour type, performance score, and the presence of visceral or cerebral metastases (figure 9.3).[19]

If survival is less than six weeks, the possible benefits of a surgical intervention need to be strongly considered and generally care with conservative measures should be sought (such as care at a hospice). If surgical intervention is absolutely required, it should be as minimally invasive as possible with a short recovery time. For patients with an expected short-term survival (between six weeks and six months), more invasive procedures are warranted. However, the use of extensive reconstructions or large, complication-prone prostheses should not be pursued. Long-term survival (expected survival > six months) justifies and requires comprehensive surgery.

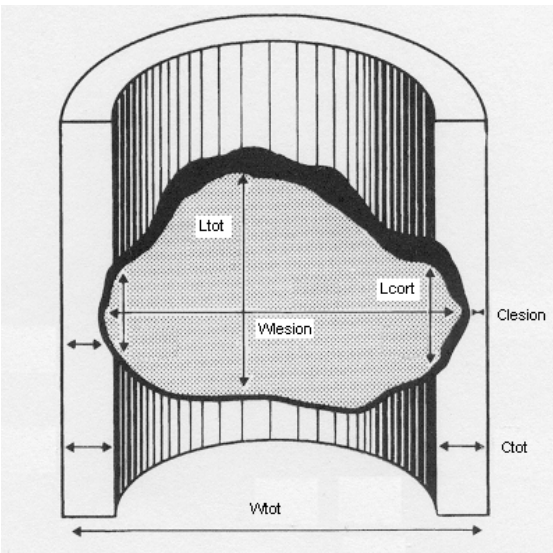

Figure 9.2 Measurement of metastatic lesions in the femur (in mm): largest axial measurement of lesion (L-lesion), largest transverse extension of the lesion (W-lesion), largest axial cortical involvement (L-cort). (Reprinted with permission from: van der Linden YM, Kroon HM, Dijkstra SPDS, Lok JJ, Noordijk EM, Leer JWH, et al. Simple radiographic parameter predicts fracturing in metastatic femoral bone lesions: results from a randomised trial. Radiotherapy and Oncology. 2003; 69(1):21-31)

Table 9.1 Prognostic factors for survival in patients with bone metastases

	BAU	*FOR*	*RAT*	*BOL*	*KAT*	*WES*	*JAN*
Site of bone	Skeletal	Skeletal	Skeletal	Spinal	Skeletal	Skeletal	LB
Number of patients	241	189	1195	1043	350	1157	927
Primary treatment	Sur	Sur	Sur	Con/Sur	Con/Sur	Con	Sur
Primary tumour	X	X	X	X	X	X*+†	X
Performance status			X	X	X	X*+†	
Visceral metastasis	X	X	X	X	X	X†	X
Cerebral metastases	X			X	X		
Lymph node		X					
Number of metastases	X		X		X		X
Chemotherapy					X		
Age							X
Comorbidity							X
BMI <18.5 kg/m^2							X
Laboratory results		X			X		X
Gender		X				X†	
Pathologic fracture	X	X					
Surgeons' estimate		X					
Patient reported pain						X†	

BAU: Bauer 1995[16]; FOR: Forsberg 2011[17]; RAT: Ratasvuori 2013[18]; BOL: Bollen 2014[19]; KAT: Katagiri revised 2014[20]; WES: Westhoff 2014[15] *simplified model, †complex model; JAN: Janssen 2015. Skeletal: all sites. Spinal: axial skeleton. LB: long bones. Con: chemo/radiotherapy, Sur: surgery.

Radiotherapy

Palliative radiotherapy for painful bone metastases is well established and provides an effective symptomatic treatment. Overall response rate is 60%, depending on the primary tumour and the expected survival time.[21] A single fraction of 8Gy is presently considered standard treatment for painful lesions with a low risk of fracture. If pain is recurrent after a single fraction, a second or third fraction of 8 Gy can be given without many treatment side-effects. For large lesions with extensive osseous destruction, it is believed that a higher total dose given in a fractionated scheme will lead to a higher tumour response with remineralisation to strengthen the bone and postpone the occurrence of a fracture.[22]

Post-operative radiotherapy is commonly advised as prophylaxis for tumour progression and implant failure.[23] However, this is not evidence based and further prospective research should be performed before statements can be made concerning the effectiveness of adjuvant radiotherapy for all patients.

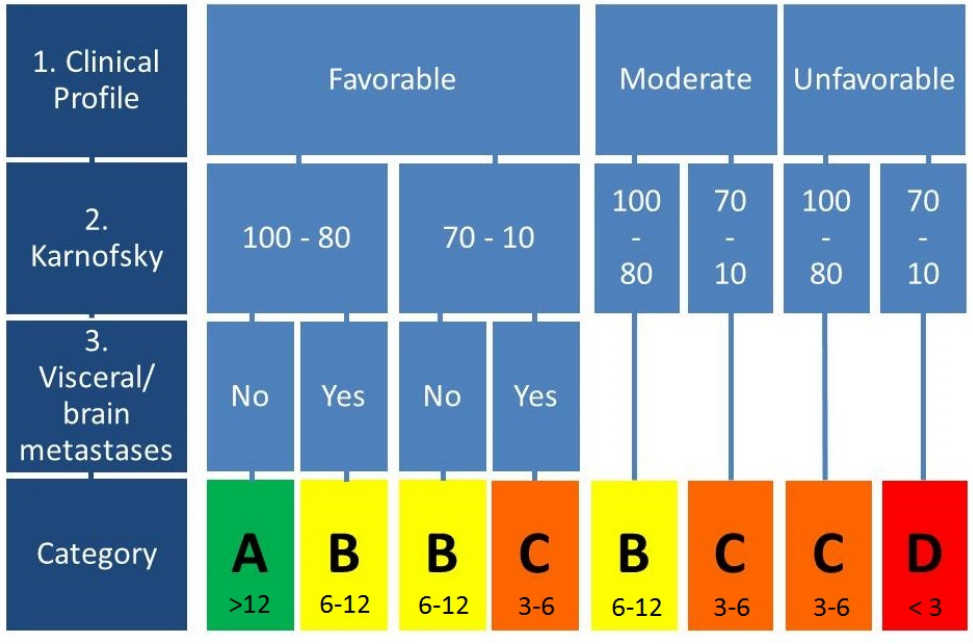

Figure 9.3 Prediction model for survival. Category (A-D) indicates expected survival in months. (Reprinted with permission from: Bollen L, van der Linden YM, Pondaag W, Fiocco M, Pattynama BPM, Marijnen CAM, et al. Prognostic factors associated with survival in patients with symptomatic spinal bone metastases: a retrospective cohort study of 1 043 patients. Neuro-Oncology. 2014 Jul; 16(7):991-8)

Surgery

Differing skeletal locations, life expectancies, patient characteristics (for example obesity) and types of fractures lead to variation in treatments. The planned procedure generally entails an intralesional approach. A more extensive procedure is unnecessary for oncologic control. An en-bloc resection is only indicated when there is vast destruction of bone or in the rare occasion of a curative intent of the procedure. In patients with actual fractures due to metastases of kidney and thyroid cancer, pre-operative embolisation of the metastasis is advised to prevent excessive peri-operative blood loss.[24] Surgery should be performed within 72 hours following embolisation.

For all pathologic fractures of the long bones, three principal surgical treatment options exist: intramedullary nail, plate, or (endo) prosthesis.

Intramedullary nails offer several advantages: they protect a long segment of bone, the necessary dissection is relatively small, blood supply to the

periosteum is preserved, and rigid fixation can be achieved by locking with proximal and distal interlocking screws, and/or by using bone cement surrounding the nail.[25] All intramedullary nails need distal locking to provide rotation stabilisation and prevent failure of fixation.[26] Proximal fixation can be achieved with standard screws or with an interlocking lag screw or helical blade, for both the femur and the humerus. The large lag screw or helical blade allows for a stronger construct due to the increased surface area contact. An intramedullary nail allows for immediate and unrestricted stability. With time, however, intramedullary nails without cement augmentation are at risk of failure, because they are load-sharing devices instead of load-bearing devices. Other disadvantages are the need for adequate bone stock at the site of the locking screw(s) and its inapplicability for lesions close to the joint.

Plate fixation offers several advantages: damage to the muscle cuff can be avoided, very distal fractures can also be adequately fixated, and a rigid fixation is possible with locking screws. In addition, the open approach provides good access and visualisation for curettage, fracture reduction and reposition, and application of adjuvant cement. The downsides of using a plate are the large incision needed, a longer surgical procedure and the lack of prophylactic fixation of the entire bone.

Prosthetic reconstructions (endoprosthesis, segmental prostheses, hemi- and total joint arthroplasty) provide immediate stability, independent of the degree of fracture healing, and the risk of local progression or implant failure is minimized.[27] The principal drawback of this method is the high risk of complications.[28] The surgery is extensive, muscles need detaching and reattaching, and it is associated with increased blood loss.[29] In addition, if post-operative radiotherapy is believed to be an important adjuvant treatment, endoprostheses should not be used due to radiotherapy-induced osteoporosis and impaired bone healing, leading to inadequate screw fixation.[30] The high costs of endoprostheses used to be a significant factor to take into account. However, manufacturers are developing cheaper endoprostheses indicated especially for metastatic disease so this has become a less decisive aspect.

Each region has its own options and treatment strategies, as shown in tables 9.2 and 9.3 for the femur and humerus, respectively. If the tibia, ulna, or radius is involved, treatment strategies for the humerus should be followed. Despite the extensive period of time during which bone metastases have been treated, no randomised controlled trials have been performed to evaluate the best surgical procedures for each setting.[31] Therefore, the recommended procedures are mostly based on retrospective observational studies and clinical experience.

Femur

Pathologic fractures of the proximal femur are most common in the femoral neck, followed by the sub and intertrochanteric regions, the diaphysis, and distal femur.32 The different treatment approaches are given in table 9.2.

In general, the treatment strategy of the femur depends on the involvement of the acetabulum. If the acetabulum is grossly affected, a (modular) total hip arthroplasty (THA) with cup augmentation is indicated. When placing a THA for metastatic disease a relatively high risk of dislocation should be acknowledged. The muscular cuff is very likely weak or insufficient due to previous systemic treatment, radiotherapy, or immobilisation. To minimize the risk of hip dislocation we recommend a dual-mobility cup. In cases with extensive involvement of the proximal femur and acetabulum and where long-term survival is expected, a hemi-pelvic endoprosthesis is more suitable. If the acetabulum is unaffected or marginally affected (less than one-third of the circumference), the strategy depends on the localisation.

For pathologic fractures of the femoral head and neck a (cemented) hemi-arthroplasty is recommended. The secondary degenerative changes associated with hemiarthroplasties will rarely present.[33] A long stem provides prophylactic stabilisation of the entire femur shaft, but is accompanied with higher risks of complications such as thrombo-embolic events.[34] It is unclear in literature whether a long stem should be routinely placed.[35]

The optimal treatment of pathologic fractures of the trochanteric region is a frequently discussed issue. The options consist of intramedullary reconstruction nails and prosthetic reconstruction, but there is poor evidence as to which serves patients better.[36] The decision is primarily based on the quality of bone stock. If the bone stock is sufficient to create a stable situation (i.e. a small or solitary lesion), an intramedullary reconstruction nail including femoral neck and head fixation is advised for both actual and impending fractures as for both patients with a short and long expected survival.[37] Cement can be considered to prevent mechanical failure, especially if the expected survival is long. If there is insufficient bone stock and doubt exists concerning the durability of the screw fixation in the femoral head, the choice of treatment needs more careful consideration. For patients with short-term survival, an intramedullary reconstruction nail with cement will provide sufficient stability, despite poor bone stock and irrelevant to the type of fracture. Patients with long-term expected survival and an actual fracture should be treated with a proximal femur modular tumour-prosthesis (PF-MTP) to provide an adequately durable situation (figure 9.4).[38] A PF-MTP can also be considered if patients with a long-term survival present with an impending fracture; however, it might not be necessary, and intramedullary nailing with cement can provide sufficient stabilisation.

Pathologic fractures of the diaphysis are commonly treated with intramedullary nails or plate osteosynthesis. If multiple lesions exist throughout the diaphysis, an intramedullary nail is recommended. Large lesions (>6cm) can be curetted prior to stabilisation and adjuvant cement will further stabilise the nail (figure 9.5). An intramedullary nail is also recommended for an impending fracture through a small or solitary lesion. However, if an actual fracture presents through a small lesion, open reduction and plate fixation with adjuvant cement is an adequate option, irrespective of the expected survival. In cases with a long survival and solitary metastases (for example, renal cell) or very large and destructive diaphyseal lesions, a segmental prosthesis of the diaphysis is an option.

The treatment of pathologic fractures of the distal femur generally consists of plating with adjuvant cement. However, if the condyles or metaphyses are largely affected the fixation of a plate is often impossible. In that case a distal femur modular tumour-prosthesis (DF-MTP) is recommended (figure 9.6). A DF-MTP should also be considered for patients with long-term survival and fractures due to distal or metaphyseal lesions. If there is no actual fracture yet and survival is short-term, cement injection only, or in combination with radio-frequency ablation, can be sufficient. However, if long-term survival is expected this might not provide sufficient prophylactic stabilization for an impending fracture, and an intramedullary nail with cement in the lesion or a DF—MTP should be considered.

Humerus

After the femur, the humerus is the second most commonly affected long bone by metastases.[39] The mainstay treatment is rigid surgical stabilisation because of a high incidence of nonunion and inadequate relief of pain with conservative treatment.[40] Although the upper extremities are not primarily weight-bearing, the proximal humerus is subject to rotational and bending forces due to the action of the rotator cuff, deltoid, pectoralis major and latissimus dorsi muscles. This demands great torsional strength of any kind of implant.[41] An overview of treatment options is given in table 9.3.

For the humeral head, options consist of plate fixation or a cemented hemi-arthroplasty. The latter should be considered for actual fractures in patients with long-term survival needing elaborate reconstruction due to inadequate

bone stock. However, if the expected survival is short, there is adequate bone stock, or there is only an impending fracture one should refrain from being too invasive. Lesions in the proximal humerus generally require curettage and augmentation to prevent rapid local progression and loosening of the osteosynthesis.[42] Therefore plate fixation is often the fixation method of choice. This gives immediate rigidity and allows for unrestricted function quickly post-operative.[43] Fixation with an ante-grade intramedullary nail and helical blade (or screws) strengthened with adjuvant cement is also possible; however, this is more appropriate in cases with extended involvement of the shaft than in cases with only proximal involvement. Total shoulder prostheses are not advised for bone metastases due to the high rate of complications, mainly recurring dislocations. If the glenoid is affected together with the proximal humerus, this can be filled up with cement.

Fractures affecting the humeral shaft can be treated with plate fixation or intramedullary fixation (figure 9.7a and b, respectively). In the region between 2-3 cm distal to the greater tuberosity and 5 cm proximal to the olecranon fossa, intramedullary nails achieve adequate stabilisation.[44] Depending on the lesion size, adjuvant cement might be required to provide adequate fixation. If an open approach is chosen for augmentation, a plate fixation can then also be chosen. Impending fractures of the shaft can always be treated with intramedullary nails. In patients with short expected survival or high surgical risks (ASA 4), percutaneous, photodynamic intramedullary stabilization systems can also be an option to examine.[45] The humeral diaphysis can also be treated with segmental prostheses according to the indications in the femur diaphysis.[46]

Bone metastases arising in the distal humerus are rare and present unique treatment challenges.[47] For actual fractures, intramedullary stabilisation will generally not provide sufficient stabilisation due to the anatomical localisation, thus plating with cement is advised. An impending fracture of the distal humerus can in most cases be treated with an intramedullary nail. Prosthetic reconstruction of the distal humerus rarely gives an adequate outcome and is associated with significant risks for complications and infections, and should not be pursued in a palliative setting.

Conclusion

The treatment of patients with impending or actual pathological fractures of the long bones requires multi-disciplinary teamwork. Treatment highly depends on the fracture risk in relation to expected survival. Further individual tailoring is

required to define the most optimal palliative strategy for each affected patient to maintain his or her quality of life.

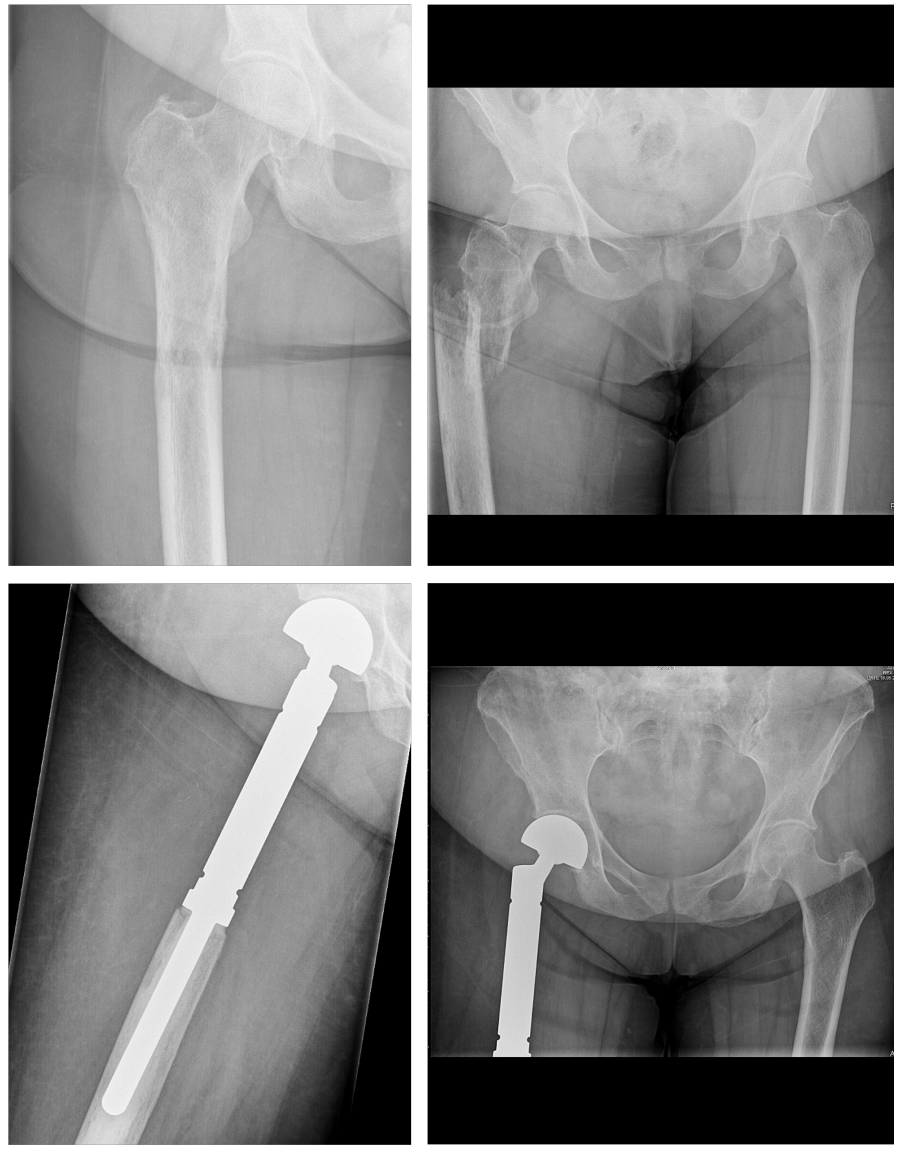

Figure 9.4 Patient with osseous and pulmonary metastases from breast cancer. Progression of the proximal femur lesion in one month with subtrochanteric pathologic fracture as result. Expected survival: > 6 months. A PF-MTP with cement was placed.

Figure 9.5 Patient with osseous and cerebral metastases from melanoma. Pathologic diaphyseal femur fracture after turning in bed. Expected survival < 6 months. Fracture stabilisation with intramedullary nail with curettage and augmentation of the lesion.

Figure 9.6 Patient with solitary bone metastasis from non small cell lung carcinoma (diagnosed and treated 4,5 years ago). Metastasis of distal femur with extensive destruction 1,5 year after radiotherapy for this lesion. Expected survival: > 6 months. Resection and reconstruction with DF-MTP.

Figure 9.7a Patient with osseous metastases from lung carcinoma. Pathologic fracture of proximal humerus diaphysis. Expected survival < 6 months. Plate fixation with cement.

Figure 9.7b Patient with osseous metastases from renal cell carcinoma. Pathologic fracture of proximal humerus diaphysis. Expected survival < 6 months. Pre-operative embolisation and intramedullary nail fixation with cement and helical blade.

Table 9.2 Surgical treatment of metastatic lesions of the femur

		Actual fracture		Impending fracture	
		Short-term survival (< 6 months)	Long-term survival (> 6 months)	Short-term survival (< 6 months)	Long-term survival (> 6 months)
Acetabulum largely affected		THP	THP or pAMP + C	THP	THP or pAMP+ C
Head/neck		Hemi + C	Hemi + C	Hemi + C	Hemi + C
Inter/sub trochanteric	Adequate bone stock (small / solitary*)	IMN	IMN	IMN	IMN
	Inadequate bone stock (large / multiple*)	IMN	PF-MTP + C	IMN	IMN or PF-MTP + C
Diaphysis	Small / solitary*	Plate# + C	Plate# + C or SP	Plate# + C or IMN	IMN or SP
	Large / multiple*	IMN	IMN or SP	IMN	IMN or SP
Metaphysis		Plate# + C	Plate# + C or DF-MTP	(Plate# +) C	IMN
Condyles	Small / solitary*	Plate#+ C	DF-MTP	(Plate# +) C	(Plate# +) cement or DF-MTP
	Large / multiple*	DF-MTP	DF-MTP	DF-MTP	DF-MTP

All types of treatments are intralesional. Adjuvant cement (C; polymethylmetacrylate) with intramedullary nails is indicated if expected survival is long or if the bone stock is inadequate. Treat sites with impaired strength with cement, i.e. at screw fixation through nail and at metastatic lesion.

#The use of locked plate-screw plate fixations generally makes double plating unnecessary. If conventional plates are used, double plating should be considered. *Number of metastases in the affected region. THP = total hip arthroplasty; Hemi = hemi hip arthroplasty; pAMP = peri-acetabular modular prosthesis; IMN = antegrade placed intramedullary nail (reconstruction type); PF-MTP = proximal femur modular tumour prosthesis; DF-MTP = distal femur modular tumour prosthesis; SG = segmental prosthesis.

Table 9.3 Surgical treatment of metastatic lesions of the humerus

		Actual fracture		Impending fracture	
		Short-term survival (< 6 months)	Long-term survival (> 6 months)	Short-term survival (< 6 months)	Long-term survival (> 6 months)
Proximal *humerus head*	Adequate bone stock	IMN + HB	IMN + HB	IMN + HB	IMN + HB
	Inadequate bone stock	Plate# + C	IMN + HB + C or HSP + C	IMN + HB	IMN + HB + C
glenoid		Cement	Cement	Cement	Cement
Shaft	Small / solitary*	Plate# + C or IMN	Plate #+ C or IMN or SP	IMN	IMN or SP
	Large / multiple*	IMN	IMN or SP	IMN	IMN or SP
Distal	All sizes	Plate# + C	Plate# + C	Plate# + C	Plate# + C

All types of treatments are intralesional. Adjuvant cement (C; polymethylmetacrylate) with intramedullary nails is indicated if expected survival is long or if the bone stock is inadequate. Treat sites with impaired strength with cement, i.e. at screw fixation through nail and at metastatic lesion.

#The use of locked plate-screw plate fixations generally makes double plating unnecessary. If conventional plates are used, double plating should be considered. *Number of metastases in the affected region. IMN = intramedullary nail; SP = segmental prosthesis; HB = helical blade. HSP = hemi shoulder prosthesis.

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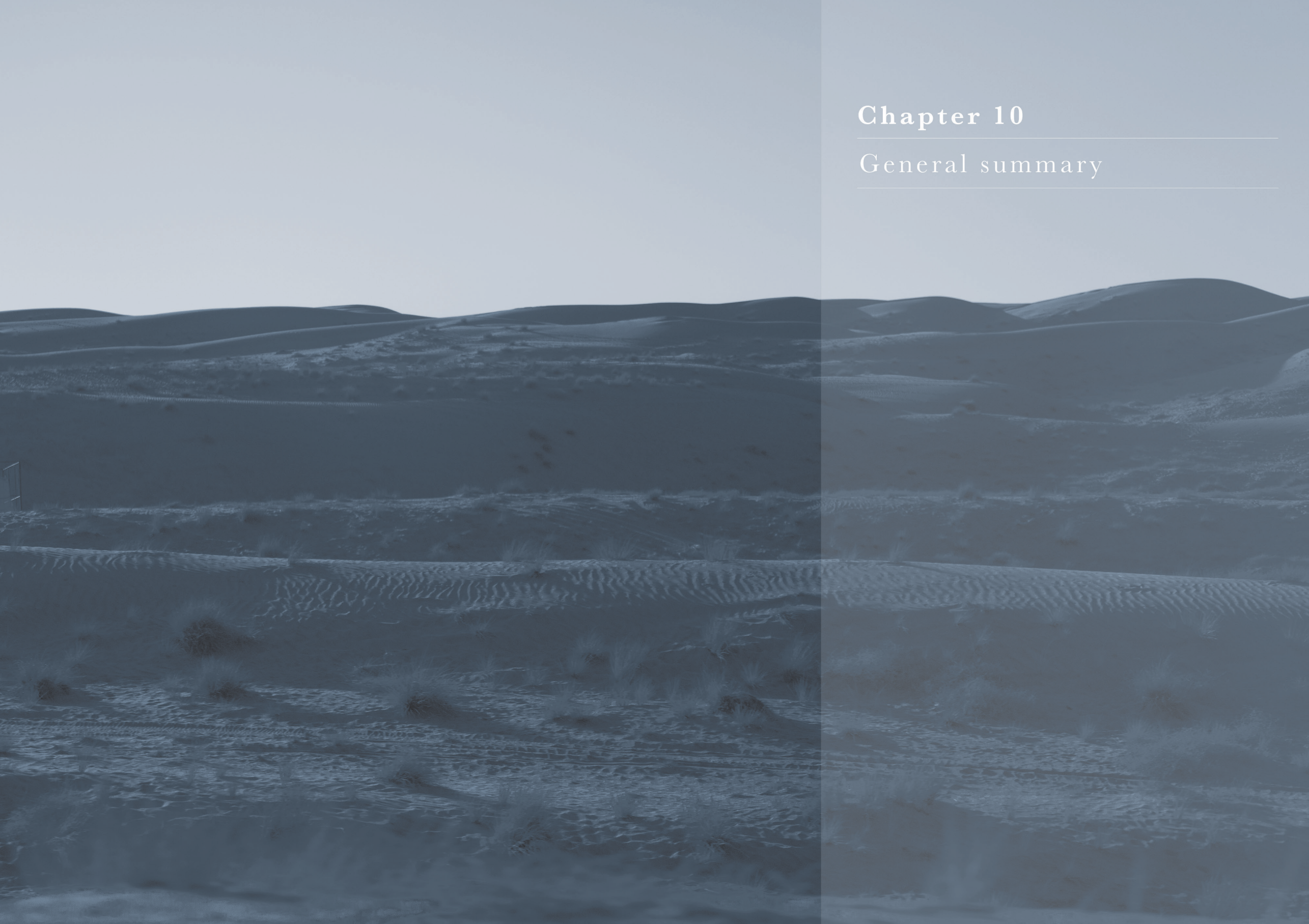


Chapter 10

General summary

Bone metastases of the long bones can cause pain and pathologic fractures. Local treatment consists of radiotherapy or surgical stabilisation. The most appropriate treatment depends on many factors, including the symptoms, the location and extent of the lesion, the wishes and expectations of the patient, and the expected remaining survival. This thesis aimed to develop a prognostic model for estimating survival in patients with cancer and symptomatic metastases of the long bones, evaluate current (surgical) treatment modalities and trends, and provide rationale for future prospective randomized trials. The first chapters of this thesis describe the developed model and how it is sustainable for future developments. The following chapters focussed on the evidence behind and outcomes of specific treatment modalities.

Survival estimation of patients with symptomatic long bone metastases is crucial to prevent over- and undertreatment. ***Chapter 2*** presented a simple, easy-to-use prognostic model for overall survival in patients with symptomatic long bone metastases. Based on a multicentre retrospective study of patients treated for symptomatic long bone metastases between 2000 and 2013 at several radiotherapy and/or orthopaedic departments (n=1520), the study shows that clinical profile (moderate: HR 1.8; 95%CI 1.5-2.1; unfavourable: HR 3.3; 95%CI 2.8-3.8), a Karnofsky Performance Score ≤70 (HR 2.0; 95%CI 1.8-2.3), and the presence of VBM (HR 1.4; 95%CI 1.2-1.5) were significantly associated with a higher risk of death. These factors were combined to create twelve categories with their own median overall survival. Subsequently a flowchart was designed to aid the stratification of patients (figure 10.1). The model leads to four clinically relevant categories (A-D): A (29%), B (19%), C (31%), D (21%) that represent the following median survival: 21.9 (95%CI 18.7-25.1), 10.5 (95%CI 7.9-13.1), 4.6 (95%CI 3.9-5.3) and 2.2 (95%CI 1.8-2.6) months, respectively. The discriminative ability was 0.70 with 12 categories and 0.69 with the final four categories. The model was validated with an external dataset of 250 patients. The application of the model to the external cohort shows similar results between observed and expected survival, suggesting that the model stratifies sufficiently in other datasets. The simplicity of the model should facilitate its use and result in an overall movement towards incorporating expected survival in the choice of the appropriate treatment.

One of the assets of the previously described model is its versatility. This is ensured by the dynamic aspect of the clinical profiles, which allows for adjustment of the classification of a primary tumour. The profiles encompass not only tumour growth speed, but also contributing factors such as the effectiveness of (future) evolving systemic treatments. The increase of targeted therapies will create sub-types of various primary tumours in the future and

thus flexibility in the categorization is of essence. The need for such flexibility is proven by the study described in ***chapter 3***. The study assesses whether mutations in the epidermal growth factor receptor (EGFR) and Kirsten rat sarcoma (kRAS) genes are associated with overall survival in patients who present with symptomatic bone metastases from non-small cell lung cancer (NSCLC), and whether mutation status should be incorporated into prognostic models. 139 patients with NSCLC treated between 2007 and 2014 for symptomatic bone metastases and whose mutation status was known were studied. Median overall survival was 3.9 months (95% confidence interval (CI) 2.1 to 5.7), but patients with EGFR (15%) mutations showed a median OS of 17.3 months (95% CI 12.7 to 22.0) while those with kRAS mutations (34%) showed a median OS of 1.8 months (95% CI 1.0 to 2.7). Compared with EGFR-positive patients, EGFR- negative patients had a 2.5 times higher risk of death (95% CI 1.5 to 4.2). The study subsequently re-evaluated the classification of primary tumours as presented in chapter 2. When NSCLC with an EGFR mutation was classified as 'moderate' instead of 'unfavourable', the discriminatory power of the model improved from 0.60 to 0.63, an increase of 5%.

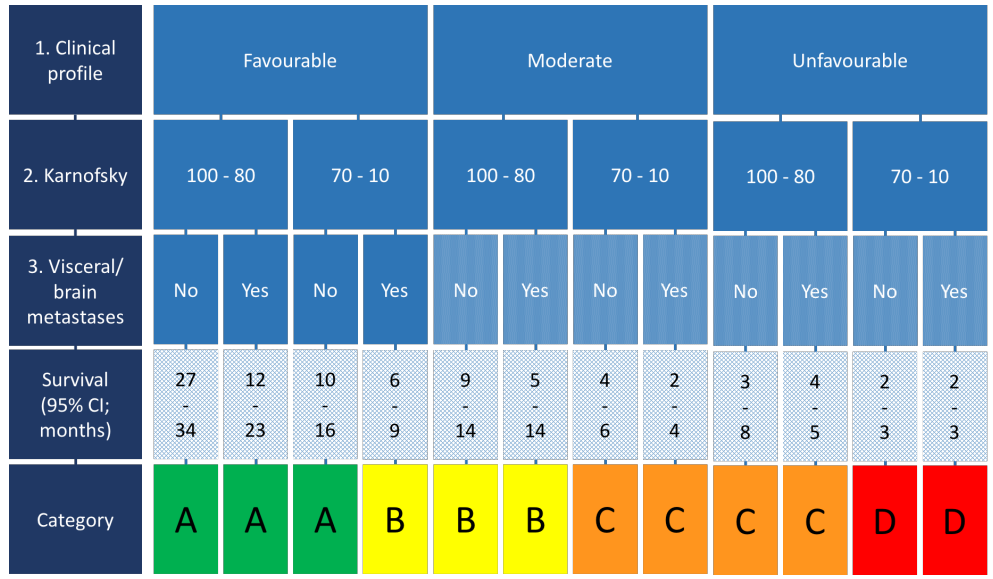


Figure 10.1 Stratification model for survival prognosis.

Postoperative radiotherapy is commonly advised as adjuvant treatment after internal fixation of an actual or impending pathologic fracture. The systematic review in ***chapter 4*** showed that substantial evidence for postoperative radiotherapy is lacking. Only two studies were included, and while they both

report a positive effect of postoperative radiotherapy regarding function, re-interventions, and survival, these results should be interpreted with caution because the studies are retrospective and thus subject to indication bias, based on small cohorts, did not use standard, validated outcome measures, and used insufficient statistical analyses. To determine whether postoperative radiotherapy has a beneficial effect or whether it is a redundant treatment, a large, multicentre, randomized study is required.

To evaluate the clinical practice, a questionnaire was sent to Dutch general orthopaedic surgeons and European oncological orthopaedic surgeons. The questionnaire aimed to assess the current trends in survival estimation and treatment preferences among national and international general and oncological orthopaedic surgeons, and to explore whether differences between the groups can identify areas of improvement in the care of patients with pathologic fractures. The results are described in ***chapter 5***. Ninety-six of the 948 approached members of the DOS (10.1%; groups 1 and 2) and 33 of the 182 approached members of the EMSOS (18.1%; group 3) replied. Overall, survival estimation was accurate by more than 50% of all three groups if expected survival was short (<3 months) or long (>12 months). Treatment preferences showed that general orthopaedic surgeons prefer an intramedullary nail for actual fractures of the humerus and femur, irrespective of the expected survival, tumour type and location. Oncological orthopaedic surgeons recommend prosthetic reconstruction in patients with an expected long survival. Based on these results, we can conclude that better identification of patients who require centralised care as opposed to those who can be adequately treated in a regional centre can improve the care of patients with pathologic fractures. This differentiation should be based on expected survival, fracture location, tumour type and extent.

Chapter 6 described the retrospective analysis of 228 intramedullary nails for actual (51%, n=117) or impending (49%, n=111) pathologic fractures of the femur. The results show that the cumulative incidence of local complications (8%), implant breakage (4%), and revisions (2.2%) is low, mostly as a result of the short survival of patients (median OS: 6 months). Independent factors associated with increased risk of implant breakage were an actual (as opposed to impending) fracture (cause-specific hazard ratio [HR_cs], 3.61; 95% CI, 1.23-10.53, p = 0.019) and previous radiotherapy (HR_cs, 2.97; 95% CI, 1.13-7.82, p = 0.027). The presence of an actual fracture was also independently associated with a higher risk of revision (HR_cs, 4.17; 95% CI, 0.08-0.82, p = 0.022), and use of cement was independently associated with a lower risk of revision (HR_cs, 0.25; 95% CI, 1.20-14.53, p = 0.025). Based on these results, surgeons should consider use of cement in patients with intramedullary nails with actual fractures and closer follow-up of patients after actual fractures and preoperative radiotherapy. Future, prospective studies should further analyse the effects of adjuvant therapies and surgery-related factors on the risk of implant breakage and revisions.

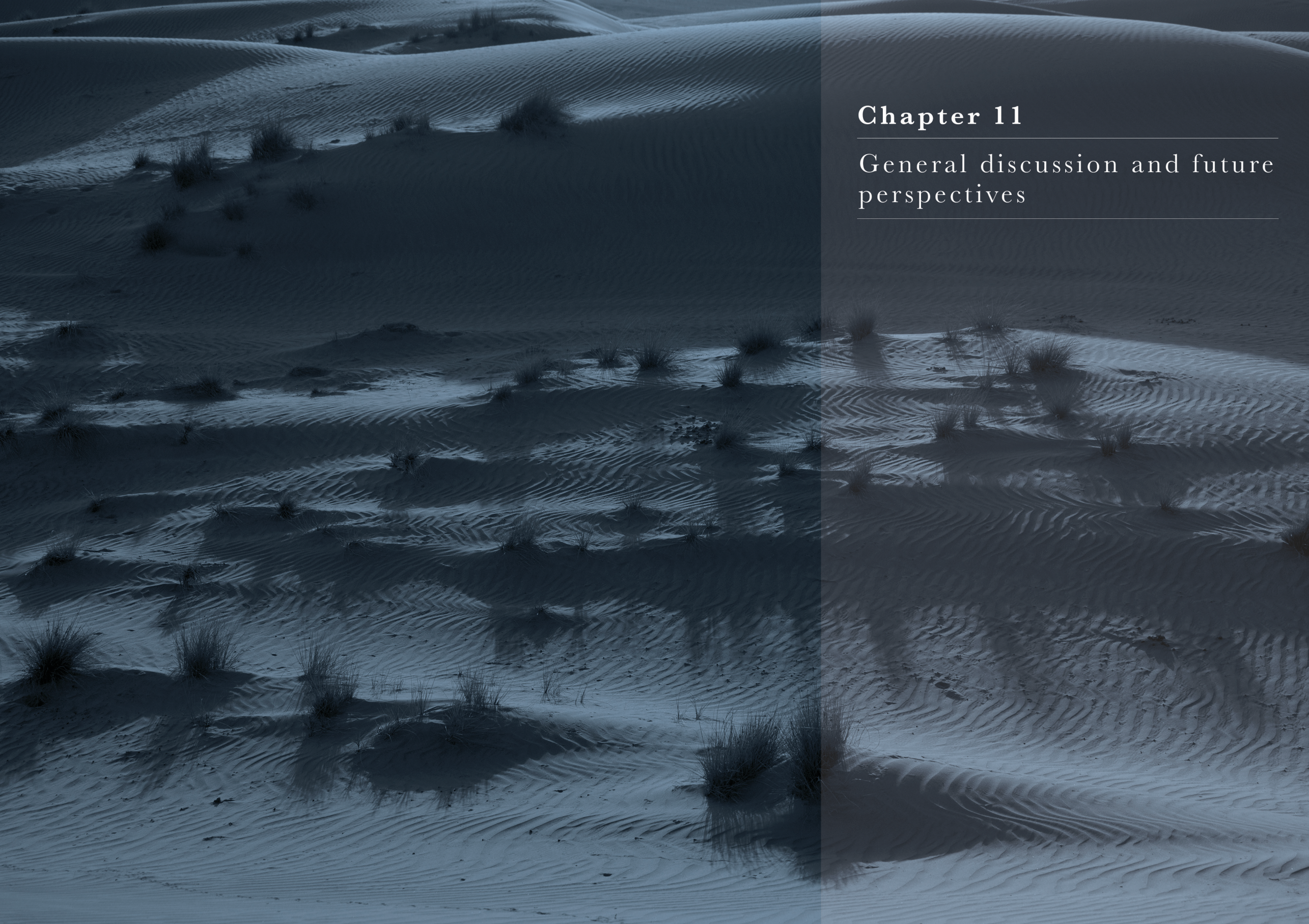
To evaluate whether the complications encountered in intramedullary nails of the femur are also found in the humerus, a similar study was performed with 182 intramedullary nails for actual (79%, n=143) and impending (21%, n=39) fractures of the humerus. The study aimed to to evaluate the cumulative incidence of and risk factors for failure. The results, as presented in ***chapter 7***, show the failure percentage is 12.6%. Thirteen failures had a predominant mechanical component (including (peri-)implant fracture, non-union, migration of nail or screw) whereas nine failures had a predominantly oncological cause (ranging from painful moderate tumour progression to massive recurrence). No risk factors for failure could be identified from this cohort. The prognostic factors for failure in the femur cohort (fracture and use of cement) were not significant in this humeral cohort, so no recommendations can be made about the use of adjuvant cement. Median overall survival (OS) was 5.7 months (95% CI 4.8 – 6.7). The median OS of patients treated for an impending fracture (8.6 [95% CI 5.5 – 11.7]) did not significantly differ from patients treated for actual fractures (5.3 [95% CI 4.2 – 6.4]) (p=0.112). While OS was expected to be shorter than in the femur cohort, the difference was less than expected (median OS 6.0 months [95% 4.4 – 7.3] for the femur IMN cohort as reported in chapter 6). Based on this study, we can conclude only that the numbers of failure of humeral IMNs is relatively high. Underestimation of the reported number of failures should be taken into account, due to lack of standardized follow-up and short overall survival. The choice for an intramedullary nail should be carefully weighed and discussed with the patient.

Chapter 8 was a systematic review on the treatment of pathologic fractures of the distal femur. Pathologic fractures of the distal femur are less common than those of the proximal femur, but also one of the most difficult pathologic fractures to stabilize. Only two studies qualified for the systematic review, but their quality was poor and no factors indicating the need for endoprosthetic reconstruction could be identified. Based on literature and expert opinion, indications for EPR in distal femur fractures are solitary metastases in patients with a long survival, a major affected joint surface, and insufficient bone stock for internal fixation. The paucity of results in this literature search and poor quality of the few included studies illustrate the issues that surgeons treating pathologic fractures are constantly confronted with: there is insufficient

adequate research on the treatment of pathologic fractures to answer relevant questions. International, prospective collaborations are needed to fill this void. Until results of such studies are published, all surgical treatments, for all locations, are predominantly based on retrospective studies, experience, and expert opinion.

Chapter 9 gave an overview of the surgical treatment of pathologic fractures. The treatment of patients with impending or actual pathological fractures of the long bones requires multi-disciplinary teamwork. Primary steps in the treatment are correct diagnosis of a metastasis. If a patient is not known with metastatic bone disease, a biopsy should be performed to prove the diagnosis of a metastatic lesion. In the back of ones' mind should always be the possibility of a primary bone tumour. After confirming a metastasis, further diagnostics should be undertaken to evaluate the dissemination status (CT thorax-abdomen for visceral metastases; PET-CT or radiographs of both humeri and femurs for bone metastases; CT-brain if any clinical indication for brain metastases), the general health of the patient (patient history [nutritional status, weight loss], blood tests [serum calcium and albumin]), and the local status of the affected bone including the extent of the lesion (bi-planar radiographs of the entire bone or CT scan of the lesion if radiograph is insufficient). The collected data is necessary to determine the most appropriate intervention, which depends on the expected survival, the location of the lesion and whether it concerns an actual fracture or there is a risk of fracture. A bone lesion with an axial cortical involvement of >30 mm has a high risk of fracturing and should be stabilised surgically. Radiotherapy is the primary treatment for symptomatic lesions without risk of fracturing. Main surgical treatment options consist of plate fixation, intramedullary nails and (endo) prosthesis. Adjuvant cement should be considered in large lesions for better stabilisation. Further individual tailoring is required to define the most optimal palliative strategy for each affected patient to maintain his or her quality of life.

The next chapter (***chapter 11***) discusses the conclusions and clinical implications of this thesis, as well as future perspectives for the treatment of pathologic fractures of the long bones. Finally, after the English summary in this chapter (***chapter 10***), the Dutch summary follows in the ***chapter 12***. In the appendices information is provided on the OPTIModel App and the prospective OPTIMAL study. In addition, the translation and validation of the Toronto Extremity Salvage Score (TESS) to Dutch is reported.



Chapter 11

General discussion and future perspectives

The care for patients with cancer and symptomatic bone metastases of the long bones is a broad topic made up of many different elements, including a range of symptoms and anatomical locations, survival and fracture prediction, and various treatment strategies. This thesis focused on some of these elements to provide reliable and solid data so that genuine steps forward can be taken regarding the care of this patient population. The current chapter places the results in a clinical perspective and evaluates whether some of the *Unknowns* as described in the introduction have become *Knowns.* These *Unknowns* referred to (1) estimating survival, (2) estimating fracture risk, and (3) faults and merits of specific treatment modalities. Not until we can label these aspects as *Knowns*, will we be able to determine the optimal treatment for each individual patient. As mentioned in the introduction, the second *Unknown*, regarding fracture risk estimation, is beyond the scope of this thesis.

Survival estimation

One of the primary aims of this thesis was to develop and validate a prognostic model for survival from the moment a patient presents with a symptomatic long bone metastasis (e.g. a painful lesion, an impending fracture or an actual pathologic fracture). The importance of estimating survival at the moment of a symptomatic long bone metastasis has been stressed many times throughout this thesis, because without adequate survival estimation the risk of overtreatment (e.g. resection and reconstruction in a patient with an expected survival of 3 months) or undertreatment (e.g. lack of surgical stabilisation of a pathologic fracture in a patient with an expected survival of 6 months) is significant. Such a risk does not comply with the palliative intent of the care for patients with symptomatic bone metastases. This 'palliative intent' means that the aim of local treatment is optimal symptom management, i.e. care as opposed to cure, in the light of the remaining survival. All treatments aim to keep a patient ambulant for as long as possible with the desired quality of life, preventing unnecessary treatments and hospital visits. Especially for impending and actual fractures, (surgical) treatment should be "once and for all", preventing failures and associated revisions on one hand, and too extensive interventions, recovery and rehabilitation times on the other hand. Survival estimation however, is difficult, as previously described by Chow et al. and White et al.,[1,2] and physicians tend to overestimate remaining survival. The results from ***chapter 5*** show that general orthopaedic surgeons mostly ask the referring medical specialist (e.g. medical oncologist, lung or urology specialist) to give an estimation. Despite the experience of medical specialists with predictions of survival in the adjuvant setting, e.g. when deciding on starting systemic therapies in breast cancer patients, we believe that patients with symptomatic

bone metastases form a different group than the mainstay of a referring medical specialists' patient population. This means that the prediction models that medical specialists use, in which the starting time point is the moment of diagnosis or treatment of the primary tumour,[3-5] are generally not applicable. For example, the referring lung oncologist might have a prediction model for overall survival for a patient with newly diagnosed advanced non-small cell lung cancer at time of diagnosis; say the patient has an expected survival of twelve months. If this patient sustains a symptomatic bone metastasis, e.g. an impending pathologic fracture seven months later, the initial prognosis of the referring lung oncologist is not applicable any more. Once a metastatic lesion becomes symptomatic (i.e. painful, fracture present or impending), a sudden, steeper decline in the survival curve of the patient can be expected than in the initially predicted curve because symptomatic bone metastases lead to impaired mobility, reduced quality of life, and increased mortality.[6,7] Undeniably, other factors than a bone metastasis becoming symptomatic also affect survival (e.g. pulmonary metastases), but that does not diminish the need for a new survival estimation with a specific model once a long bone metastasis becomes symptomatic.

Since the 1990's several specific prognostic models have been developed, but as the results in ***chapter 5*** show, only 10% of the orthopaedic surgeons participating in the questionnaire use such a model. The most recent and comprehensive are the updated model of Katagiri et al.[8] and model by Forsberg et al..[9] Katagiri et al. developed the first version of their model in 2005[10] and recently published an update to incorporate the development of effective targeted chemotherapeutic regimens.[8] In the updated model, not only the primary tumour, presence of visceral metastases, performance score, previous chemotherapy, and number of metastases are taken into account, but also several laboratory values: C-reactive protein, lactate dehydrogenase, serum albumin, serum calcium (corrected), platelet count, and total bilirubin. These are either classified as abnormal (CRP ≥ 0.4 mg/dl, LDH ≥ 250 IU/L, or serum albumin <3.7 g/dl) or as critical (platelet <100,000/µL, serum calcium ≥ 10.3 mg/dl, or total bilirubin ≥1.4). A strong aspect of this model is the differentiation within primary tumour types, depending on hormone-dependence (for breast and prostate cancer) or targeted treatment (for lung cancer), and thus the recognition that primary tumour types should not be regarded as single entities. Unfortunately, Katagiri et al. did not report a C-statistic or area under the curve, so no conclusions can be made about the discriminative ability of their model. A weakness of the model by Katagiri et al. however, is the large number of variables and especially the addition of laboratory values, because this makes it complicated for daily use. While blood-tests might be done pre-operatively, they

are invasive procedures for the patient and are rarely done before irradiation. Therefore, this model is less applicable for a large part of its target population. Moreover, the large number of variables and their weight in the total score, as well as the meaning of the total score, are difficult to remember. While this seems a futile argument, it is of relevance for the applicability of the model in daily practise. Amid the pressure of a busy out-patient clinic or hectic emergency department, a physician wants to fall back on an easy-to-use model that requires readily available and straight-forward input. In our opinion, the model by Forsberg et al. has slightly the same limitations. In their model, based on a machine-learned Bayesian belief network model (i.e. a probabilistic graphical model that explores the conditional, probabilistic relationships between a set of variables to estimate the likelihood of an outcome), predictive variables are categorised as first-degree (surgeon estimate, haemoglobin concentration, absolute lymphocyte count, completed pathologic fracture, and performance score) or second degree if related to one of the first-degree variables.[9] The first-degree factors for three-month survival were different to those for twelve-month survival. The predictive ability of this model is strong (mean area under the curve for 3-month survival: 0.85 [95% CI 0.80 – 0.93]; for 12-month survival: 0.83 [95% CI 0.77 – 0.90]) and the model has been validated in several (small) external cohorts. The limitations, however, again concern the elaborate number of variables required and the use of non-readily available variables (i.e. laboratory values). Forsberg et al. have made the model available for all through their website (www.pathfx.com). The fact that the statistics behind the model are so complicated that the model cannot be used without a website, is a downside. Not per se in daily practise, because use of digital aids is wide-spread, but more so because the user does not understand how the estimated survival is established. Thus while the design of the model is on one hand its strongest aspect, it is at the same time its weakest. We are convinced that physicians are most likely to use a clinical aid if (1) they recognise the aid is better than their own knowledge and (2) if the aid is easy and intuitive to use and understand. Creating awareness is the most important to convince physicians to use a prognostic model as opposed to their own, or the referring medical specialists', estimation. The second aspect, an easy-to-use model, lies predominantly in the design of the model and limited amount of prognostic factors. The latter was the essence of the OPTIModel, as described in ***chapter 2***. With only three variables and a clear flowchart, the model is straightforward to use. The two cases on the next pages show the necessity of such a model, as well as the easy applicability of the OPTIModel. These two examples are extremes in the spectrum of patients with symptomatic bone metastases, but throughout the entire spectrum it is relevant to estimate the remaining survival before

discussing treatment options with patients and their family. As part of shared decision-making, which might play an even greater role in the palliative setting than in other medical practises, it is important to explain and discuss the role of the expected survival on treatment choices.

> ***Case A*** *is a 64-year old woman who was treated for breast cancer (hormone receptor positive) 15 years earlier. She now presents at the outpatient clinic with pain in her left hip since several days. The pain is continuously present and non-opioid pain medication is insufficient. She was an active lady, but it now been home-bound due to the pain when mobilising. An x-ray shows a per-trochanteric fracture (figure 11.1). Given the history of cancer and lack of adequate trauma, the cause of the fracture is most likely pathologic and a biopsy confirms the diagnosis of a bone metastasis of the breast cancer. A CT scan shows no lung or liver metastases, but there are other bone metastases in the spine and one rib. The fracture is treated with a reconstruction type intramedullary nail and adjuvant radiotherapy (24 Gy in 6 fractions) five weeks postoperative. A year-and-a-half later, the same patient presents at the outpatient clinic, again with pain of the left hip. X-ray shows breakage of the nail at the junction with the collum screw, causing dislocation of the femur fragments. The broken nail is removed and replaced with a new nail with adjuvant cement around the collum screw. Six months later, the pain is still present in the left hip. A CT scan shows a pseudo-arthrosis of the fracture, lysis around the collum screw and collapse of the cranial part of the femur head. To prevent further collapse and lysis, cement is injected around the collum screw. Nonetheless, two months later, further lysis and migration of the collum screw is seen, causing perforation of the collum screw through the femur head. More than two years after primary presentation, the failed intramedullary nail is removed and a modular proximal femur reconstruction is placed. This gives good function and mobility until the patient's death (due to progressive disease) two years later.*

This case is a clear case of undertreatment caused by the lack of survival estimation at the first presentation. Application of the OPTIModel at presentation would have shown that the expected survival of the patient was more than 12 months: favourable clinical profile (breast cancer), Karnofsky performance score 90 ("an active woman"), and no visceral and/or brain metastases. According to the model the patient falls in category A, with a 95% confidence interval of survival between 27 and 34 months. Given the long expected survival, the failure of the intramedullary nail could have been anticipated, because an intramedullary nail is a load-sharing device, while it functions as a load-bearing device in a pathologic fracture; its lifetime is

therefore not very long. The treatment for this patient would have thus been more optimal, without all re-operations, if she had received a prosthetic reconstruction in the first place. Postoperative radiotherapy would then also have been redundant.

Figure 11.1 Per-trochanteric fracture.

Figure 11.2. Sub-trochanteric fracture.

Case B *is a 50-year-old man with deteriorating clinical condition who was diagnosed with disseminated non-small cell lung cancer shortly before presentation at the emergency department with acute onset of pain in the upper right leg after getting up out of bed. The patient is unable to bear weight on the leg. An x-ray shows a sub-trochanteric fracture (figure 11.2); its location corresponding to a hotspot on the PET-CT of a week earlier. The PET-CT had also shown multiple metastatic bone metastases and large nodules in both lungs. Although the general health of the patient was already poor and he required help for daily activities, he expressed the wish for surgery, because he would like to be able to walk around the house. Surgical stabilisation is required to enable mobilisation and a modular proximal femur reconstruction prosthesis is placed. Intensive physiotherapy is required during the postoperative phase to adequately mobilise. Three months postoperatively the patient passes away due to advanced disease.*

This case is in great contrast with case A, but again shows the importance of survival estimation when a patient presents with a pathologic fracture. Here, the patient would have fallen into category D (unfavourable clinical profile, Karnofsky performance score 50, visceral metastases present), with an expected survival of less than three months (95% confidence interval: 2-3 months). It is thus questionable whether such an extensive operation matched the short expected survival. Possibly, if survival had been estimated before surgery, a less invasive option would have been chosen, enabling earlier discharge, less risk of complications, and quicker return of function. The last phase of life of this patient would then have been spent more at home, surrounded by his family instead of focussing on rehabilitation.

The fact that we use as few variables as possible in the model could have an inverse effect on the discriminative ability (C-statistic 0.70). A model with a lot of detailed variables, might also be able to give more detailed results. However, survival estimation is used to make adequate treatment choices. There is no difference between the treatment choice of an estimated survival of 5.5 months or 6 months; therefore, it is not required to measure and estimate this difference in survival. In this setting, the predictive accuracy only has to be as much as the clinically relevant differences. One could also argue whether the included variables are truly as simple as we report.[11] To know whether visceral metastases are present, imaging diagnostics (PET-CT or CT scan of thorax and abdomen) are required. This is indeed true, but we have made the assumption that in countries with modern and well-developed healthcare systems dissemination examination is part of standard work-up of patients with metastatic disease. The need for considerable additional radiological imaging does make it questionable whether the model is applicable around the globe, especially in countries with less accessible and organised healthcare. We have chosen to use the Karnofsky Perfomance Score (KPS)[12] as measure for general health. Instructions for the application of this score are straightforward and it is therefore easy to use. During the development of our model, collecting the KPS retrospectively caused the greatest challenge, because it was not standard practise to report the score in the medical records. Lack of the performance score was therefore the largest cause of exclusion from the multivariate analysis. Also, in many cases the performance score was reported as Eastern Cooperative Oncology Group/World Health Organisation Score. Fortunately, the WHO score can be easily converted to a KPS score.[13] For daily use of the model, the incorporation of the performance score as KPS cannot be regarded as difficult; it merely requires an interpretation of the impression of general health a physician always makes of the patient. Patient reported outcome (PRO) and patient reported experience (PRE) measures are currently frequently used to

evaluate the quality of care. Although some might argue that these measures should be incorporated in survival models because they are patient driven, we do not think that incorporation of such measures would improve the model, as also shown by Westhoff et al..[14] Not only would it hinder the quick use of the model, but more importantly, PROMs and PREMs are not developed as reflection of the functioning or quality of life on its own; they are always associated with the health care or treatment a patient has received.

The OPTIModel is developed for all symptomatic long bone metastases requiring local treatment and is thus based on both irradiated and surgically treated patients. This enables multidisciplinary use of the model, as opposed to the previously mentioned models of Katagiri and Forsberg, which can be used only for patients with an indication for surgery as that is their reference population. Taking into regard that it is not uncommon for patients to receive radiotherapy and surgery for either the same or various different lesions, it is an asset that the treating radiation oncologists and surgeons can discuss the optimal treatment using the same model. One could argue that an important element of the treatment of bone metastases is left aside here: the medical oncologist and all systemic treatments that might affect survival. This is indeed true and deliberate; although it is not our intention to dismiss the important role of systemic treatments, the focus of the research was on local treatment. Whether the OPTIModel can be applied to patients receiving systemic treatment for symptomatic (long) bone metastases, remains to be investigated in future research.

The model presented in this thesis was validated with an external data set from Austria including surgically treated patients only. As the majority of patients with symptomatic bone metastases are treated with radiotherapy, further validation should be performed with a larger cohort, consisting of prospectively collected data and including both operated and irradiated patients. To ensure worldwide validation, cohorts from differing cultures and varying patient populations should be used.

As Katagiri et al. already recognised, primary tumours should in many cases not be regarded as a single entity.[8] This is also the message of ***chapter 3***, which shows that EGFR positive non-small cell lung cancer should be categorised more favourably than non-small cell lung cancer without the mutation. Bollen et al. showed an alike subcategorization of breast cancer in spinal metastases[15] and Ratasvuori et al. showed the preferential survival of solitary kidney metastases.[16] The clinical profile grouping in the OPTIModel has currently already taken these latter two aspects into account, even though the results of the referred two studies do not focus specifically on long bone metastases.

Analysis for these tumour types in long bone metastases is currently being performed in our centre with new data. Of course, there a many more primary tumour types that could be subdivided in this model, such as melanoma or thyroid cancer patients, since within these primaries, genetic alterations (e.g. BRAF mutations) lead to distinct survival patterns, based on the applicability of successful systemic treatments.[17,18] Unfortunately, we did not have sufficient number of patients to make subgroups for all these tumour types. Hopefully, international collaborations and future data collection will be able to provide more data, so more primary tumour types can be allocated with more precision to the correct clinical profile.

To ease the use of the OPTIModel as prognostic tool, we developed a web-based version of the flowchart (www.optimal-study.nl/tool), as well as an application for smartphones (as described in the appendix). Both are meant to be a supportive tool in making an estimation of survival. The app goes one step further and also provides treatment options, given the survival estimation, location and type of fracture, and details of the lesion. Both model and app are not a replacement of the experience and good clinical judgement of a multi-disciplinary team. As Jonathan Forsberg mentions in his thesis, “decision support models are designed to provide objective data on which an independent practitioner may base a decision”.[19] In other words, the models do not provide the decision itself; it is up to the physician to interpret the outcome of the model and make a decision. We agree with Forsbergs’ opinion that physicians should always maintain a healthy scepticism towards all supportive tools, including (- especially? -) those that are easily accessible throughout the web. Moreover, the fact that the app is easily accessible through app stores for all physicians, also makes it easily accessible for patients. We should look further into whether patients actually find and use the app, as it is not publicised beyond the medical environment, and whether this affects the conversation between physician and patient.

Beside guiding the physician through survival estimation and aspects relevant for treatment choices, the app we developed can be used as method to stratify patients between those patients that can be treated by a general orthopaedic surgeon in a regional hospital and patients who need referral to a specialised centre to receive less standard care. ***Chapter 5*** shows that general orthopaedic surgeons tend to treat all pathologic fractures with an intramedullary nail, while oncological orthopaedic surgeons consider a prosthetic reconstruction in patients with a long expected survival. Although the results are based on only a small fraction of all orthopaedic surgeons as the response percentages were relatively low, the results do confirm a trend we expected: the treatment a

patient receives is partly determined by the surgeon to whom he or she is referred. For a large part of all actual and impending pathologic fractures this is fine, because their optimal treatment would be an intramedullary nail. Specific patients however, who would benefit from other, possibly oncological, reconstructions, would not receive their most optimal treatment if not referred to a specialised centre. Complete centralisation of the treatment of pathologic fractures to centres specialised in oncological orthopaedics is not feasible due to the absolute number of pathologic fractures. In addition to accurate identification of patients who require referral, we would recommend all hospitals, or perhaps partnering hospitals, to assign "ownership" of pathological fracture treatment to one or several physicians. This will enable those specific physicians to become more familiar with the unique aspects of pathological fracture fixation, which will subsequently lead to improvement of care. Whether these designated physicians should treat all pathological fractures personally remains a logistical aspect, but they should at least be consulted before treatment decisions are made. We believe that centralisation of care on a local basis will lead to more individualised treatment and therefore better quality of life for patients. Additionally, creating such a local centre point for pathologic fractures will facilitate research.

Treatment

Insufficient knowledge on the faults and merits of specific treatment modalities was the final Unknown. Or more particularly, a collection of many Unknowns. These Unknowns concern the surgical treatment of pathological fractures. Regarding radiotherapy of bone metastases, more research, with higher levels of evidence, has been performed. A recent systematic review shows that 29 randomised trials have been performed aiming to define the optimal radiotherapy schedule comparing 8 Gy single dose fraction to multi-fraction schemes ranging from 20 Gy in 5 fraction, 24 Gy in 6 fractions, to 30-39 Gy in 10-13 fractions.[20] Response rates showed no significant differences between the single or multi-fraction regimens. The elaborate number of well-executed and large prospective studies regarding radiotherapy is in contrast with the limited number and quality of studies on the surgical treatment of long bone metastases. In part this is due to the fact that the number of patients receiving radiotherapy for bone metastases is larger than those receiving surgery, making research easier. Also, standardised data collection for research purposes might be more established among radiation oncologists than orthopaedic surgeons. Finally, the difference in amount of evidence is also caused by the fact that we cannot speak of "the surgical treatment of long bone metastases" as a single subject. Taking only the two large long bones into account (i.e. femur and humerus) and generalised treatment modalities (i.e. prosthesis, plate, nail), we are already looking at six categories, whilst ignoring other important factors such as location (i.e. proximal, shaft or distal) and type of fracture (i.e. actual or impending). For each of these categories it would be desirable to set indications based on evidence. Taking the number of subcategories into account, and within such subgroups endless more varieties (use of cement, estimated survival, primary tumour type, or level of activity, for example), striving to determine indications for all subcategories is ambitious to say the least. In this thesis we aimed to focus on three general subcategories: intramedullary nails for the femur, intramedullary nails for the humerus, and actual fractures of the distal femur. The latter was subject of a systematic review, while retrospective cohorts were studied for the prior two. We were unable to further specify characteristics of the study populations, because that would limit the number of eligible patients or studies.

The study in ***chapter 6*** reported of 245 intramedullary nails for actual or impending fractures in the femur over a fifteen-year period in five centres. Not all centres were able to submit data of patients over the entire study period, but nonetheless, this number gives insight into the relatively small numbers of patients we are dealing with when researching surgical treatments of long bone metastases. A fracture occurred in 8% of the nails and an actual fracture (as opposed to an impending fracture) and previous radiotherapy on the affected bone showed to be independent risk factors for such an implant fracture, both increasing the risk of breakage threefold. These risk factors show the importance of accurate fracture prediction. If a lesion erroneously gets classified as low risk for fracture, it is possible that the patient will get referred for radiotherapy, subsequently develops a pathologic fracture, and then has to undergo surgery burdened with both risk factors for complications. Accurate survival estimation also plays a role here, because of the aspect of time in both fracture prediction and the risk of developing a complication after intramedullary nailing.

The results in ***chapter 7*** showed that the treatment of actual and impending pathologic fractures of the humerus with intramedullary nails is not so simple as it seems. In the retrospective cohort containing 182 intramedullary nails, 12.6% failed. This percentage is probably an underestimation due to the lack of standardised follow-up and the short survival of the patients (median 5.7 months [95% CI 4.8 – 6.7]). Unfortunately, despite the large cohort, no risk factors for failure could be identified. Other studies on the surgical treatment of humeral pathologic fractures have neither led to risk factors for failure of

intramedullary nails.[21,22] Future research is thus required to identify treatment-related aspects that should be encouraged or avoided by surgeons.

Future directions

Throughout this thesis it has become clear that there are still pressing questions concerning the treatment of pathologic fractures; hence the previously mentioned 'Unknowns'. The primary conclusion from both systematic reviews (***chapter 4 and 8***) is that there is insufficient published literature to present any evidence based recommendations. The results in ***chapter 6 and 7*** provide interesting views on the use of intramedullary nails, but, like all retrospective cohort studies which have been published on this subject, the results are biased by indication. It is questionable whether we have been able to revolve the Unknowns of intramedullary nails for the femur and humerus into Knowns. While several national guidelines have been developed to improve the treatment of metastatic bone disease,[23,24] these are hardly based on reliable, unbiased, scientific data, because the latter is not available, as is also mentioned in the instructional review in ***chapter 9***. As briefly mentioned in the introduction, we believe there are several causes for the imbalance between the incidence of pathologic fractures and the amount of prospective studies. The heterogeneity of the patient population and therefore struggle to form a sufficiently large, comparable cohort is one of the causes. Additionally, we suspect that the palliative intent of the treatment generates less encouragement to start or participate in a study, from a physician and patient point of view, respectively. In line with the previous two factors, randomisation between two (standard) treatments could be regarded as unethical in certain cases, because all patients in this phase of life should receive the most tailored treatment, instead of being assigned to a study treatment protocol. Nonetheless, the care of patients with pathologic fractures should be converted from primarily experience based to predominantly evidence based. In order to achieve such a transformation, the prospective part of the OPTIMAL Study was designed. The aim of this study is to define optimal local treatment strategies (including radiotherapy and surgery) in relation to location, type of fracture and expected survival. This will enable a more personalised treatment that will lead to improvement of quality of life.

The prospective OPTIMAL Study (ClinicalTrials.gov identifier: NCT02705157) consists of a prospective, multicentre, multi-disciplinary cohort that provides subgroups for multiple embedded (randomised controlled) trials. This relatively new design, known as 'cohort multiple randomised controlled trial' (cmRCT), is an attempt to facilitate a more pragmatic approach to performing prospective studies as well as time- and resource efficiency.[25] In a cmRCT study, a

prospective cohort is the backbone of the study. From this cohort, subgroups can be selected that are eligible for a certain 'sub-study' (e.g., a RCT). The step-wised manner of informed consent is a unique asset of this study design. At inclusion in the prospective cohort patients are asked for informed consent for (i) the prospective cohort, and (ii) for randomisation if the patient is eligible for a certain sub-study that requires randomisation. If the patient agrees to (i) and (ii) and he is indeed eligible for a RCT in a subgroup, the patient is randomised. Only if randomised for the intervention group, will the patient be informed about the outcome of the randomisation. A third step of informed consent then follows, regarding consent for the subgroup RCT itself. If the patient is randomised for the control group, no further notice will follow and the patient will continue participation in the cohort without further notice. Details of the cmRCT design are published in appendix B in the summary of the treatment protocol. Primary outcome measures are patient-reported outcome measures (PROMs) regarding quality of life and pain after treatment. Using PROMs is a primary asset of the OPTIMAL Study. Previous studies on treatment of bone metastases have primarily focussed on radiological or physician-measured outcomes (e.g. implant failure, revision), while the palliative character of the treatment especially requires knowledge of whether treatments actually affect quality of life and lead to a pain-free and functional extremity. In the prospective OPTIMAL study, patients receive a number of questionnaires before treatment and at set moments after treatment, among others the Dutch version of the Toronto Extremity Salvage Score (TESS) of which our translation and validation study is reported in the appendix.[26] The prospective OPTIMAL cohort is currently active in seven centres in the Netherlands and including patients from both orthopaedic and radiotherapy departments.

The first embedded RCT has also launched: The PostOperative RadioTherapy (PORT) Study (ClinicalTrials.gov identifier: NCT02705183). Patients who participate in this RCT are thus also included in the OPTIMAL cohort. The PORT Study aims to answer the question that has remained after performing the systematic review in ***chapter 4***: "is postoperative radiotherapy required?" Based on the results of the review, we can conclude there is no evidence for or against postoperative radiotherapy. Sceptics of this prospective study question whether evidence is required for things that 'obviously' work. However, what is 'obviously working' in this setting? The effects of radiotherapy on oncologic control, and pain in case of bone metastases without signs of impending or actual pathological fractures, are indeed proven. Postoperatively though, its role is less clear. The role of postoperative radiotherapy needs clarification, not only to determine if it should be given, but also to establish the regimen type if it is required. Depending on the aim (i.e. to reduce pain or to provide oncologic

control) a single fraction or multi fraction regimen is effective. Pain is generally dealt with by the surgical stabilisation, so that should not be the reason for irradiation. What remains is the need for oncologic control (i.e. preventing tumour progression) and remineralisation, because it is thought this reduces the risk of implant failure. It is however questionable whether this aspect plays a role in a palliative treatment, when the mean overall survival is short (<6 months). We hypothesise that most patients do not develop implant failures because they die before these can occur, not because they receive postoperative radiotherapy. Moreover, in practise we see that many patients receive a single fraction postoperatively, which is effective for pain control, but it is questionable whether a single fraction is sufficient for oncologic control. If we could accurately select patients that do need postoperative radiotherapy (a long expected survival, for example), and appoint them a specific single or multi fraction regimen, many patients could avoid unnecessary time in hospital, and economic resources might be saved. All patients receiving surgery (nail, plate, or prosthesis) for a long bone metastasis are eligible to participate in the PORT Study. The study is a non-inferiority study between postoperative radiotherapy ('standard care') and no postoperative radiotherapy ('intervention'). Unfortunately, up to date the inclusion rate is very low. This is most probably due to the fact that surgeons are accustomed to referring a patient postoperatively to the radiation oncologist. Once the patient is at the radiotherapy outpatient clinic, he or she is not easily convinced anymore to participate in a study that possibly will not give them radiotherapy. Surgeons thus need to be more aware of the lack of evidence for postoperative radiotherapy and discuss with their patients that radiotherapy is possibly not needed. But, as seen more often, old habits die hard. Once the role of postoperative radiotherapy is defined, we should look further at the timing of this radiotherapy. Currently, patients receive their irradiation 3 to 6 weeks postoperatively to give the wounds time to heal. With minimal invasive treatments long wound healing is not required and postoperative radiotherapy, if required, could possibly already be given directly in the same hospital admission, or, maybe even preoperative.[27] Whether this is desirable and feasible requires further research.

Future studies planned within the cmRCT context of the OPTIMAL Study will focus on the treatment in more specific subgroups with regard to expected survival, fracture location and type. The IlluminOss study will aim to identify whether fixation of actual or impending pathologic fractures of the humerus in patients who qualify for an intramedullary fixation (i.e. short to mid-term expected survival, fractures of proximal humerus if sufficient bone stock in the head or of the humerus shaft) with an IlluminOss intramedullary fixation will

lead to the same levels of quality of life and pain reduction as a standard intramedullary nail. If this is the case, such an intramedullary fixation method, with a combination of balloons, light activated monomers, and flexible catheters, could be considered as substitution for conventional intramedullary nails, because they are reported to be less-invasive and quicker to insert.

The CarboFix study will focus on the subgroup of patients who qualify for intramedullary fixation of the femur (i.e. actual or impending fractures, short to mid-term expected survival, lesions located in the femur shaft, or if sufficient bone stock in the head in the proximal femur). These patients will be randomised between a standard intramedullary nail and a CarboFix intramedullary nail, the latter of which is made of material that is stronger than conventional nails. Aim of the study is to detect whether the quality of life and pain as reported by the patient is not worse than of the conventional nails, while leading to less implant failures due to the properties of the material.

What remains difficult in these intended studies, is that the choice for a specific implant is left to the surgeon. Although a framework is provided of which patients would be eligible for such an implant, no hard indications are set. This is a consequence of the pragmatic approach to research we are required to do in this patient population. Although numbers of patients are rising, pathologic fractures are still less common than traumatic fractures, and to be able to include sufficient number of patients in a study, a pragmatic approach is essential. In the planned studies, we are focussing on specific types of implants. Future studies however, also need to focus on the indications for certain implants. Again, that is where the ethical aspect plays a role, since in this palliative setting, it might be difficult to randomise a patient between two treatment modalities, when the surgeon has the feeling that one of either would be better for a patient due to the size of the lesion, the bone stock, the preference of the patient, or for any other reason. No study will be able to deduct such specific in- and exclusion criteria that all relevant factors are covered, and still be able to include sufficient number of patients. Some indication bias will thus always remain present in studies on treatments for patients with symptomatic bone metastases. A promising study has been initiated by colleagues in the Memorial Sloan Kettering Cancer Center in which patients with actual or impending fractures of the intertrochanteric, pertrochanteric or subtrochanteric region of the proximal femur are being randomised between long-stem cemented hemi-arthroplasties and intramedullary nails (ClinicalTrials.gov identifier: NCT02164019). Despite participation of multiple centres in the USA, recruitment of sufficient patients is difficult. This shows that international multicentre studies are necessary for

study completion within an acceptable period. We are planning to collaborate with our American colleagues in their study to hopefully answer this important question. Additionally, we plan to further develop our existing collaborations with centres in Europe to further optimise the treatment of patients with symptomatic long bone metastases.

The subject of this thesis has been the treatment of long bone metastases, but bone metastases occur throughout the entire skeleton. Our focus was predominantly on actual and impending fractures, which bring their own distinct problems and solutions. They cannot be compared with the consequences of spinal cord compression; both require their own approach. One group of metastatic bone lesions has up to now remained beyond the focus of researchers and studies: lesions in the pelvis. Future studies should not only focus on further perfecting and personalising treatment of long bone and spinal metastases, but also shine light on the lesions in the pelvis. Due to the unique anatomy of the pelvis, other treatment modalities than radiotherapy and surgery, such as cementplasty or radiofrequent ablation, could prove effective. Additionally, specific attention should be directed at identifying the best treatment in case of pelvic and long bone metastases combined.

To conclude, the current treatment of symptomatic metastases of the long bones is predominantly based on experience and low level evidence studies, while the treatment of patients with long bone metastases requires personalisation to provide adequate palliative care. To achieve adequate palliative care, answers to several Unknowns are required. This thesis has made a start to making the Unknowns known by developing a prognostic model that can provide adequate survival estimation. This thesis has also attempted to provide more detailed evidence on the faults and merits of certain treatment modalities. However, the prospective OPTIMAL study should provide further, less biased, answers regarding the outcome of treatment modalities. Accurate survival and fracture prediction, and specific pairing of treatment to patient, will enable individualised palliative care for patients with symptomatic metastases of the long bones, which will lead to optimisation of their quality of life.

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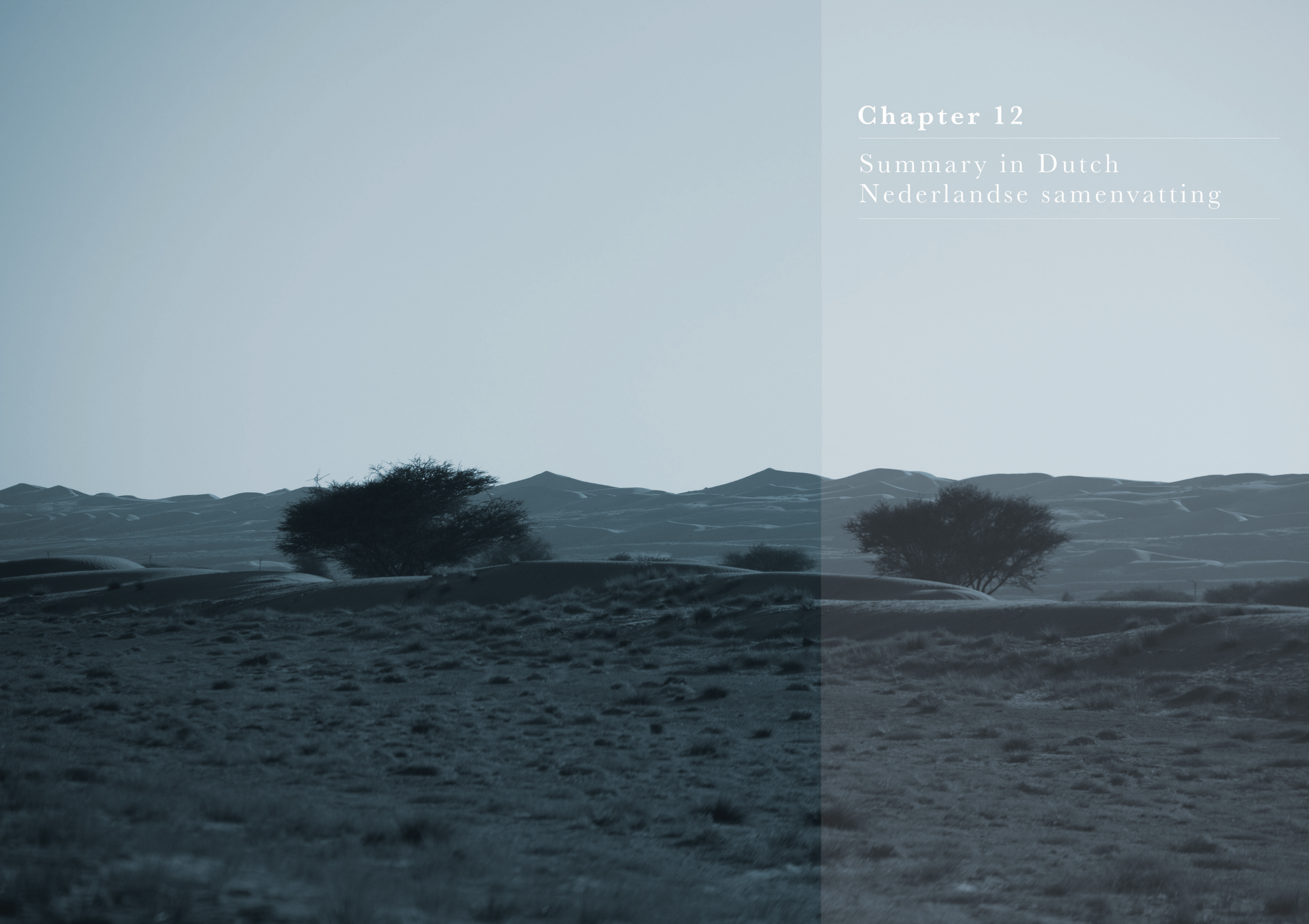
Chapter 12

Summary in Dutch
Nederlandse samenvatting



Botmetastasen van de lange pijpbeenderen kunnen pijn en pathologische fracturen veroorzaken. Lokale behandeling bestaat uit radiotherapie en/of chirurgische fixatie. De meest geschikte behandeling hangt af van verschillende factoren, waaronder de symptomen, de locatie en uitgebreidheid van de laesie, de wensen en verwachtingen van de patiënt, en de verwachte overleving. Doel van dit proefschrift was om een prognostisch model te ontwikkelen voor de inschatting van de overleving van patiënten met kanker en symptomatische botmetastasen van de lange pijpbeenderen, de huidige (chirurgische) behandelingen en ontwikkelingen te evalueren, en onderbouwing voor toekomstige gerandomiseerde studies te ontwikkelen. De eerste hoofdstukken van dit proefschrift beschrijven het ontwikkelde model en hoe dit model toekomst-bestendig is. De daaropvolgende hoofdstukken gaan over de onderbouwing en uitkomsten van verschillende behandelmodaliteiten.

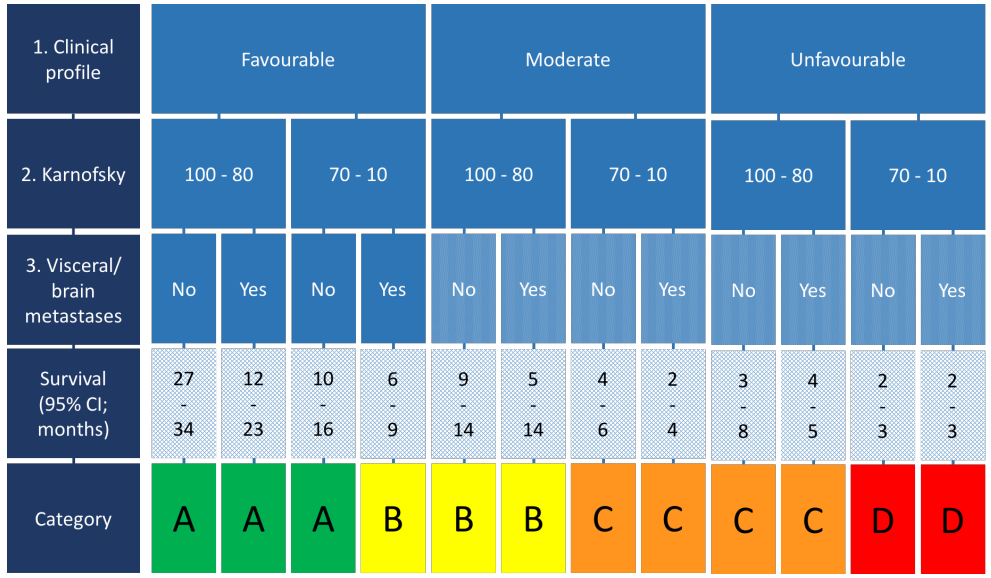
Het inschatten van de overleving van patiënten met symptomatische botmetastasen van de lange pijpbeenderen is cruciaal om over- en onderbehandeling te voorkomen. In ***hoofdstuk 2*** wordt een eenvoudig prognostisch model voor overleving in patiënten met symptomatische botmetastasen van de lange pijpbeenderen gepresenteerd. De studie, gebaseerd op een multicenter, retrospectief cohort van patiënten behandeld voor symptomatische botmetastasen van de lange pijpbeenderen tussen 2000 en 2013 bij verschillende radiotherapie dan wel orthopaedische afdelingen (n=1520), toont dat het klinisch profiel ("moderate"/matig: hazard ratio [HR] 1.8 [95% CI 1.5-2.1]; "unfavourable"/ongunstig: HR 3.3 [95% CI 2.8 - 3.8]), een Karnofsky Performance Score van 70 of lager (HR 2.0 [95% CI 1.8 - 2.3]), en de aanwezigheid van viscerale en/of hersenmetastasen (HR 1.4 [95% CI 1.2 - 1.5]) significant gerelateerd zijn met een hoger risico op overlijden. Deze factoren werden gecombineerd tot twaalf categorieën, met elk hun eigen mediane overleving. Vervolgens werd een stroomschema ontwikkeld om het gebruik van het model te vergemakkelijken (figuur 12.1). Het model leidt tot vier klinisch relevante overlevings-categorieën (A-D): A (29%), B (19%), C (31%), D (21%) die overeenkomen met de volgende mediane overleving: 21.9 (95% CI 18.7 - 25.1), 10.5 (95% CI 7.9 - 13.1), 4.6 (95% CI 3.9 - 5.3) en 2.2 (95% CI 1.8 - 2.6) maanden, respectievelijk. Het onderscheidende vermogen van het model was 0.70 met twaalf categorieën en 0.69 met de uiteindelijke vier categorieën. Het model werd gevalideerd met een externe dataset van 250 chirurgische patiënten. Toepassing van het model in het externe cohort toonde overeenkomstige resultaten tussen de geobserveerde en verwachte overleving op basis van het model. Dit toont dat het model ook voldoende patiënten kan stratificeren in andere datasets. De eenvoud van het model maakt het gemakkelijker in gebruik.

Dit zou ervoor moeten zorgen dat het meenemen van de verwachte overleving bij het maken van een behandelkeuze een algemene trend wordt.

Een van de unieke kenmerken van het hiervoor genoemde model, is het vermogen om aan te passen aan ontwikkelingen binnen de geneeskunde. Het dynamische aspect van de klinische profielen maakt het mogelijk dat de classificatie van een primaire tumor verandert. De indeling in de klinische profielen is niet alleen op basis van groeisnelheid van een tumor, maak ook afhankelijk van factoren zoals de effectiviteit van (toekomstige) ontwikkelende systemische behandelingen. De toename van doelgerichte therapieën zal er in de toekomst voor zorgen dat vele primaire tumoren onderverdeeld worden in subtypes. Flexibiliteit in de indeling van de klinische profielen is dus van groot belang, zoals getoond in ***hoofdstuk 3***. De studie beschreven in hoofdstuk 3 analyseert of mutaties in het 'epidermal growth factor receptor' (EGFR) gen en het 'Kirsten rat sarcoma' (kRAS) gen gerelateerd zijn met overlevingsduur in patiënten die zich presenteren met symptomatische botmetastasen op basis van een niet-kleincellig longcarcinoom (NKCLC) en of deze gen mutaties geïncorporeerd zouden moeten worden in prognostische modellen voor overleving. Honderdnegenendertig patiënten met NKCLC die tussen 2007 en 2014 behandeld waren voor een symptomatische bot metastase en van wie de mutatie status bekend was, werden bestudeerd. De mediane overleving was 3.9 maanden (95% betrouwbaarheidsinterval (CI) 2.1 - 5.7), maar patiënten met een EGFR-mutatie hadden een mediane overleving van 17.3 maanden (95% CI 12.7 - 22.0), terwijl patiënten met een kRAS-mutatie een mediane overleving van 1.8 maanden (95% CI 1.0 - 2.7) hadden. Vergeleken met EGFR-positieve patiënten hadden EGFR-negatieve patiënten een 2.5 hogere kans op overlijden (95% CI 1.5 - 4.2). De beschreven studie heeft vervolgens de classificatie van primaire tumoren, zoals beschreven in hoofdstuk 2, geëvalueerd. Als niet-kleincellig longcarcinoom met een EGFR-mutatie geclassificeerd wordt als "matig" (moderate) in plaats van "ongunstig" (unfavourable), verbetert het onderscheidend vermogen van 0.60 naar 0.63, een toename van 5%.

Postoperatieve radiotherapie wordt vaak voorgeschreven als adjuvante behandeling na chirurgische fixatie van een actuele of dreigende pathologische fractuur. De systematische review in ***hoofdstuk 4*** toont dat hier geen goed onderbouwd wetenschappelijk bewijs voor is. Slechts twee studies werden in de review geïncludeerd. Beide studies spreken van een voordelig effect van postoperatieve radiotherapie ten aanzien van functie, re-interventies en overleving, maar deze resultaten moeten worden geïnterpreteerd met enige terughoudendheid omdat de studies retrospectief zijn en er dus sprake is van indicatie bias, ze gebraseerd zijn op kleine cohorten, geen gebruik maakten van

gestandaardiseerde en gevalideerde uitkomstmaten, en inadequate statistische analyses gebruiken. Om te bepalen of postoperatieve radiotherapie een gunstige uitkomst heeft of dat het een overbodige behandeling is, moet worden onderzocht in een grote, multicenter, gerandomiseerde studie.



Figuur 12.1 Stroomschema voor verwachte overleving.

Om een overzicht te krijgen van de behandelingen van pathologische fracturen in de praktijk werd een enquête verstuurd naar alle leden van de Nederlandse Orthopedie Verenging (NOV) en Europese oncologische orthopaeden. Het doel van de enquête was om de huidige trends ten aanzien van de inschatting van overleving en behandelvoorkeuren onder nationale en internationale algemene en oncologische orthopaeden te inventariseren en te onderzoeken of er verschillen zijn tussen de groepen die tot verbetering van de zorg van patiënten met pathologische fracturen zou kunnen leiden. De resultaten van de enquête zijn beschreven in ***hoofdstuk 5***. Zesennegentig van de 948 benaderde leden van de NOV (10.1%, groepen 1 en 2) en 33 van de 182 benaderde leden van de Europese oncologisch orthopaeden (18.1%, groep 3) reageerden op de enquête. De inschatting van de overleving was accuraat in meer dan 50% van de respondenten in alle drie groepen als de verwachte overleving kort (<3 maanden) of lang (>12 maanden) was. Als de verwachte overleving tussen 3 en 12 maanden was, was er meer verdeeldheid onder de respondenten in alle groepen. De behandelvoorkeuren lieten zien dat algemeen orthopaedisch chirurgen de voorkeur hebben voor een intramedullaire pen ter behandeling

van een pathologische fractuur van femur en humerus, onafhankelijk van de verwachte overleving, tumor type en locatie. Oncologisch orthopaeden raden een reconstructie met prosthese aan in patiënten met een lange verwachte overleving. Op basis van deze resultaten zouden we kunnen concluderen dat een betere identificatie van patiënten die behandeling in een gespecialiseerd (gecentraliseerd) centrum nodig hebben ten opzichte van patiënten die adequate behandeling in een regionaal centrum kunnen krijgen, de gehele zorg van patiënten met een pathologische fractuur zou kunnen verbeteren. Deze differentiatie tussen patiënten zou gebaseerd moeten zijn op verwachte overleving, de locatie en uitgebreidheid van de laesie en het tumor type van de primaire tumor.

Hoofdstuk 6 beschrijft de retrospectieve analyse van 228 intramedullaire pennen voor actuele (51%, n=117) en dreigende (49%, n = 111) pathologische fracturen van het femur. De resultaten tonen dat de cumulatieve incidentie van lokale complicaties (8%), falen van het implantaat (4%), en revisie (2.2%) laag is. Dit komt vooral door de korte overleving van patiënten (mediane overleving 6 maanden). Een actuele (ten opzichte van een dreigende) fractuur (cause-specific hazard ratio [HR_cs], 3.61; 95% CI 1.23-10.53; p = 0.019) en eerdere radiotherapie (HR_cs, 2.97; 95% CI, 1.13-7.82, p = 0.027) waren onafhankelijke factoren gerelateerd aan een verhoogd risico op falen van het implantaat. De aanwezigheid van een actuele fractuur was ook onafhankelijk gerelateerd aan een hoger risico op revisie (HR_cs, 4.17; 95% CI, 0.08-0.82, p = 0.022), terwijl het gebruik van cement gerelateerd was met een lager risico op revisie (HR_cs, 0.25; 95% CI, 1.20-14.53, p = 0.025). Op basis van deze resultaten zouden chirurgen kunnen overwegen om cement te gebruiken bij een intramedullaire pen in patiënten met een actuele fractuur en betere follow-up van patiënten die behandeld worden voor een actuele fractuur na eerdere radiotherapie. In de toekomst moeten prospectieve studies verder uitwijzen wat de toegevoegde waarde van adjuvante behandelingen en implantaat-gerelateerde factoren is op het voorkomen van implantaat falen en revisie.

Een gelijksoortige studie werd uitgevoerd ten aanzien van intramedullaire pennen in de humerus, om te evalueren of de complicaties die gezien worden in het femur ook gezien worden in de humerus. Deze studie, zoals beschreven in ***hoofdstuk 7***, analyseerde 182 intramedullaire pennen voor actuele (79%, n=143) en dreigende (21%, n=39) pathologische fracturen van de humerus. Het doel van de studie was om de cumulatieve incidentie van en risico factoren voor falen te analyseren. De resultaten tonen een faalpercentage van 12.6%. In dertien gevallen was het falen veroorzaakt door een hoofdzakelijk mechanische component (o.a. [peri-] implantaat falen, pseudo-artrose, migratie van schroef

of pen) terwijl in de oorzaak in negen gevallen hoofdzakelijk oncologisch was. Op basis van dit cohort konden geen risico factoren voor falen geïdentificeerd worden. De factoren gerelateerd aan falen in het femur cohort (actuele fractuur en geen gebruik van cement) waren niet significant in dit cohort van humeri, dus er kunnen geen aanbevelingen worden gedaan ten aanzien van het gebruik van adjuvant cement in de humerus. De mediane overleving was 5.7 maanden (95% CI 4.8 – 6.7). Tussen patiënten met een actuele fractuur en een dreigende fractuur zat geen verschil in mediane overleving: 5.3 maanden (95% CI 4.2 – 6.4) versus 8.6 (95% CI 5.5 – 11.7) (p=0.112). Vooraf was verwacht dat de mediane overleving van het cohort van humerus pennen korter zou zijn dan van de femur pennen, dit verschil was echter minder dan verwacht (mediane overleving 6.0 maanden [95% 4.4 – 7.3] voor de femur pennen, zoals beschreven in hoofdstuk 6). Op basis van deze studie kunnen we slechts concluderen dat het aantal gefaalde pennen na fixatie in de humerus voor actuele of dreigende pathologische fracturen relatief hoog is. Daarbij moet rekening gehouden worden met het feit dat dit aantal gefaalde pennen zeer waarschijnlijk een onderrapportage is, gezien er geen gestandaardiseerde follow-up was en door de korte overleving van patiënten. De keuze voor een intramedullaire pen in de humerus moet derhalve goed worden overwogen en besproken met de patiënt.

Hoofdstuk 8 was een systematische review over de behandeling van pathologische fracturen van het distale deel van het femur. Pathologische fracturen van de distale femur komen minder vaak voor dan die van het proximale femur en zijn ook een van de meest ingewikkelde pathologische fracturen om te stabiliseren. Slechts twee studies voldeden aan de inclusiecriteria van de review, maar de kwaliteit van de studies was slecht en er konden geen factoren geïdentificeerd worden die als indicatie voor een endoprothese zouden gelden. Op basis van de literatuur en ervaringsdeskundigen zijn indicaties voor een endoprothese voor het distale femur: een solitaire metastase bij patiënten met een lang verwachte overleving, een uitgebreid aangetast gewrichtsoppervlak, en onvoldoende bot kwaliteit voor interne fixatie van schroeven in het distale femur. De schaarste aan resultaten in de literatuur en de slechte kwaliteit van de paar geïncludeerde studies illustreren de kwesties waar chirurgen die pathologische fracturen behandelen constant tegenaan lopen: er is onvoldoende adequaat onderzoek over de behandeling van pathologische fracturen om relevante vragen te beantwoorden. Internationale, prospectieve samenwerking is nodig om deze lacune te vullen. Tot de resultaten van zulke studies gepubliceerd zijn, zullen alle chirurgische behandelingen, voor alle locaties, vooral gebaseerd zijn op retrospectieve studies en klinische ervaring.

Hoofdstuk 9 gaf tenslotte een overzicht van de chirurgische behandeling van pathologische fracturen. De behandeling van patiënten met actuele of dreigende pathologische fracturen van de lange pijpbeenderen vergt multidisciplinaire samenwerking. De eerste stappen in de behandeling zijn een correcte diagnose van een metastase. Als een patiënt niet bekend is met gemetastaseerde ziekte, moet een biopt altijd afgenomen worden uit de laesie om de diagnose van een metastase te bevestigen. In de differentiaaldiagnose moet immers altijd een primaire bottumor staan. Na de bevestiging van een metastase, is verdere diagnostiek nodig ten aanzien van de disseminatie status van de patiënt (CT thorax-abdomen voor viscerale metastasen; PET-CT of röntgenfoto's van beide humeri en femora voor botmetastasen; CT-hersenen als er klinische verdenking op hersenmetastasen bestaat), de algemene gezondheid van de patiënt (voorgeschiedenis [voedingsstatus, gewichtsverlies], bloedonderzoek [serum calcium en albumine]), en de lokale status van het aangedane bot, inclusief de uitgebreidheid van de laesie (röntgenfoto's van het gehele bot in twee richtingen of een CT-scan van de laesie indien de röntgenfoto's onvoldoende zijn). De verzamelde data is nodig om de meest geschikte behandeling te bepalen, welke afhangt van de verwachte overleving, de locatie van de laesie, en of het een actuele of dreigende fractuur betreft. Een laesie met een axiale corticale aantasting van >30 mm heeft een hoog risico op fractuur en moet profylactisch gestabiliseerd worden. Radiotherapie is de primaire behandelmodaliteit bij symptomatische (pijnlijke) laesies zonder hoog risico op fractuur. Primaire chirurgische opties zijn onder andere plaat fixatie, intramedullaire pen fixatie en endoprothese. Adjuvant cement moet worden overwogen bij grote laesies voor een betere stabilisatie. Verder personalisatie van iedere behandeling is nodig om de optimale palliatieve strategie te bepalen en voor elke patiënt de kwaliteit van leven zo goed mogelijk te behouden.

Uit alle hoofdstukken en de discussie kan geconcludeerd worden dat de huidige behandeling van symptomatische metastasen van de lange pijpbeenderen vooral gebaseerd is op ervaring en studies van lage kwaliteit, terwijl de behandeling van deze patiënten gepersonaliseerd moet worden om adequate palliatieve zorg te kunnen bieden. De resultaten uit dit proefschrift hebben daarvoor de basis gelegd, echter verdere, onafhankelijke resultaten uit de prospectieve OPTIMAL-studie zijn nodig om beter onderbouwde conclusies te kunnen trekken. Precieze inschatting van zowel de overleving als het fractuurrisico en specifieke koppeling van behandeling aan patiënt, zullen het mogelijk maken om gepersonaliseerde zorg te kunnen leveren. Daarmee zal de kwaliteit van leven van patiënten met symptomatisch metastasen van de lange pijpbeenderen geoptimaliseerd kunnen worden.

Appendices

A. OPTIModel App

B. Study protocol for The OPTIMAL Study - a cmRCT

C. Validation and cross - cultural adaptation of the Toronto Extremity Salvage Score to Dutch

Appendix A.
OPTIModel App
A digital and online application

The OPTIModel application is designed to aid clinicians in the decision-making of any patient presenting with long bone metastases. The content of the application is based on the prognostic model as described in ***chapter 2*** and treatment recommendations as described in ***chapter 9***.

First, users are guided through a flowchart to estimate the remaining survival as shown in the screenshots in figure A.1.

Subsequently, users are guided through a second flowchart to receive a recommendation for local treatment, based on the initial survival estimation and the location, extent, and presentation of the metastasis as shown in the screenshots in figure A.2.

This application does not serve as treatment protocol and no rights may be derived from this information by physicians or patients.

The application can also be used on the following website: www.optimal-study.nl/tool (figure A.3).

The application can be downloaded (free of charge) in the Apple App Store and Google Play Store.

Apple App Store:

Google Play Store:

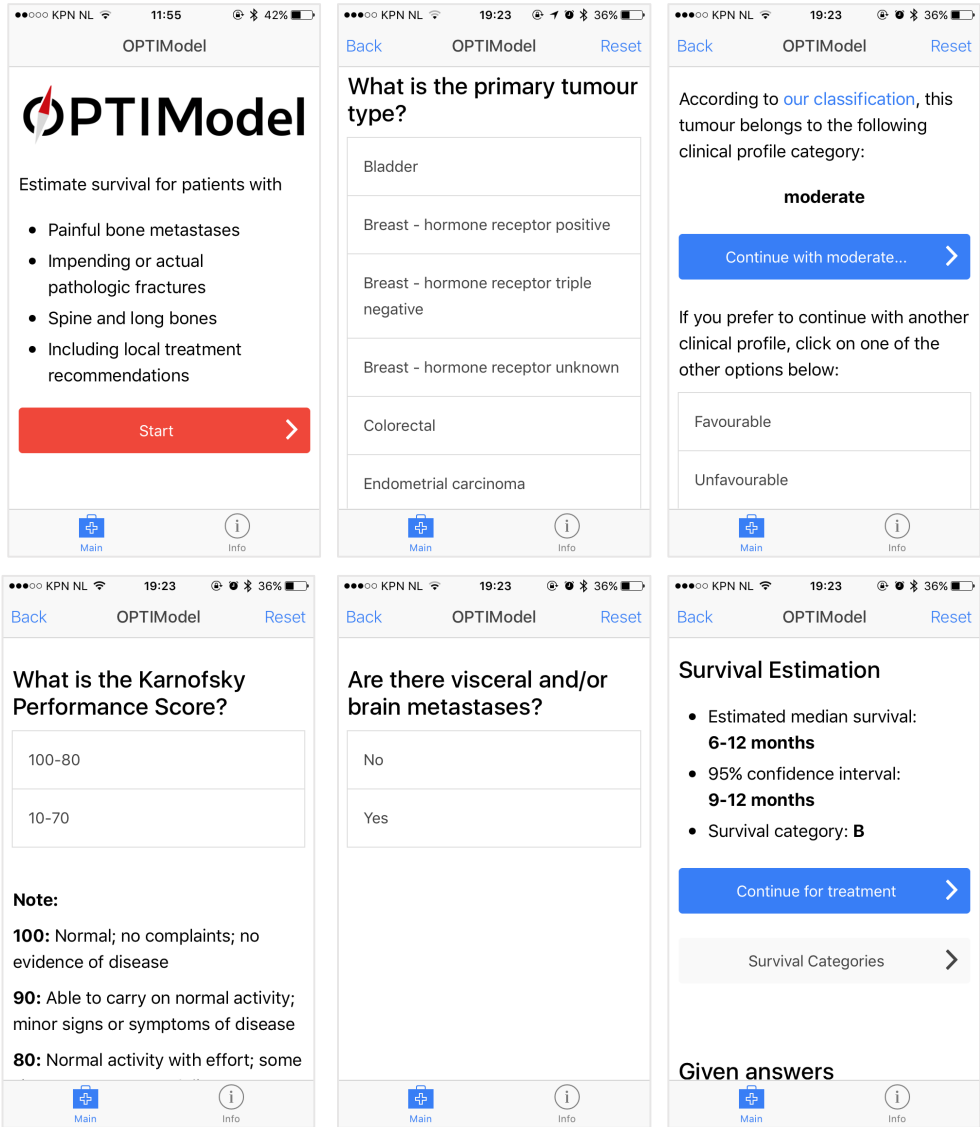


Figure A.1 Screenshots of the steps of the first part of the OPTIModel to estimate the remaining survival. As shown in the example in the last screenshot, the outcome is presented as estimated median survival (with 95% confidence interval) and the corresponding survival category according to the Optimal prognostic model (OPTIModel) as reported in chapter 2.

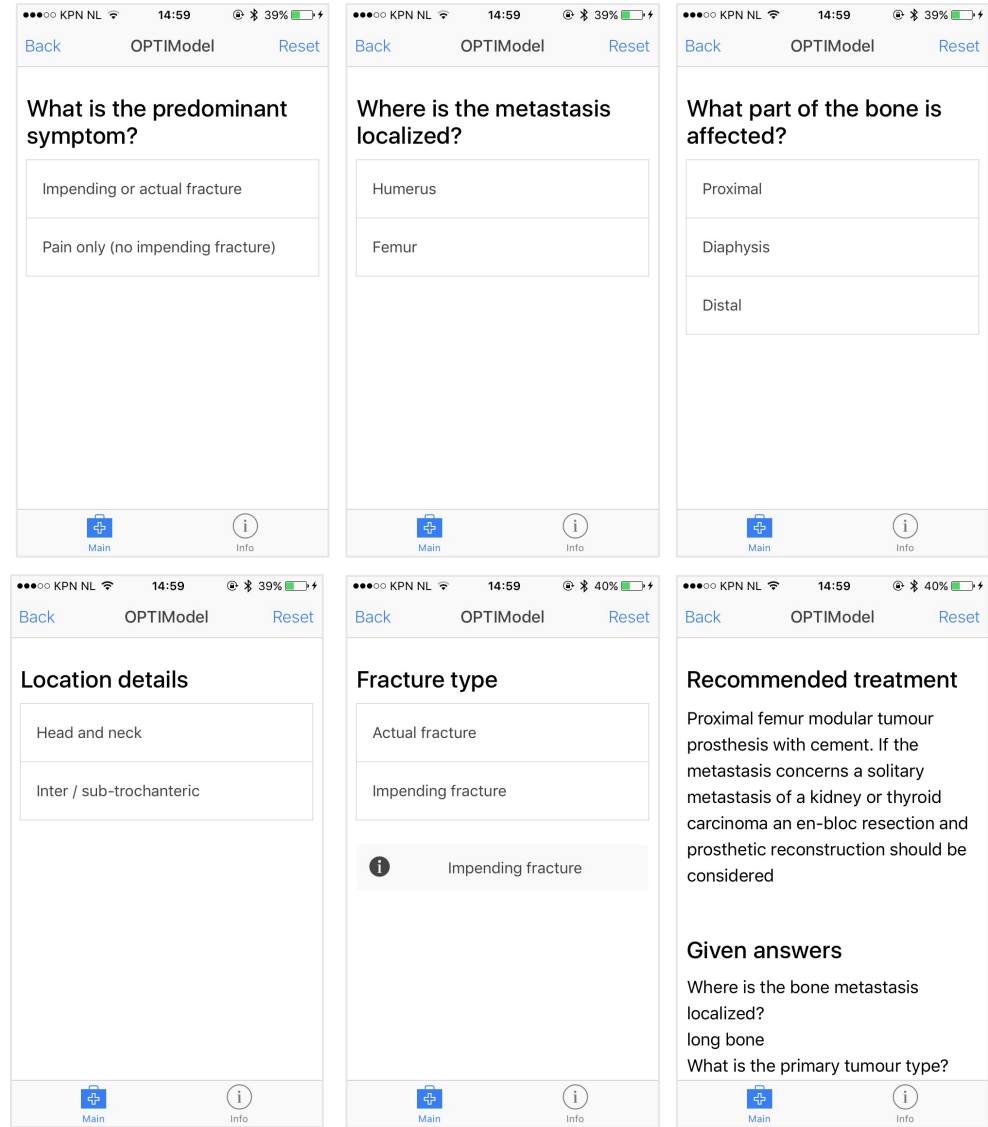


Figure A.2 Screenshots of the some of the steps of the second part of the OPTIModel that result in an advice for treatment (both radiotherapy or surgery) for symptomatic bone metastases of the humerus and femur.

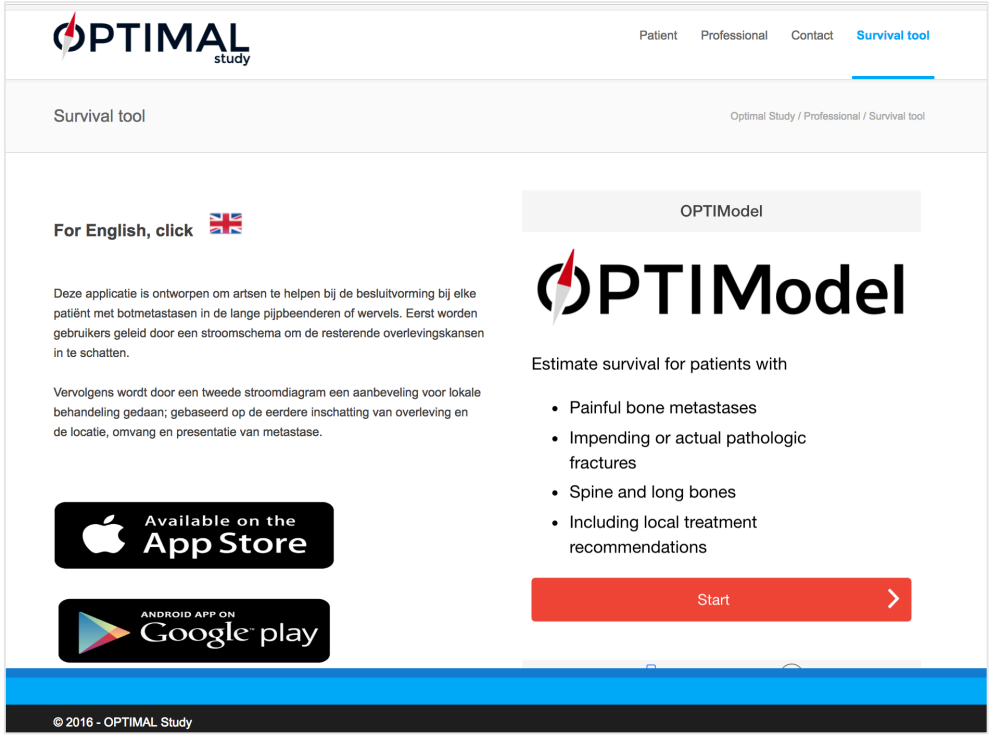


Figure A.3 Screenshot of the webpage www.optimal-study.nl/tool to use the OPTIModel online. The model can also be used on the site if the app is not downloaded (right part of the screen).

Appendix B. Study protocol for The OPTIMAL Study – a cmRCT

The following description of the prospective OPTIMAL Study is a shortened version of the study protocol as reviewed and approved by the medical ethical committee of the Leiden University Medical Center. The full protocol can be found online at https://clinicaltrials.gov (NCT02705157). The version below focusses on the cohort multiple randomised controlled trial (cmRCT) and why we chose to use this study design for the prospective OPTIMAL Study. Details on data collection, analysis, registration of (serious) adverse events, and data storage can be found in the full protocol.

Cohort multiple randomised controlled trial (cmRCT)

The following paragraphs will portray the difficulties with randomised controlled trials, describe the cmRCT design, discuss our reasons for choosing this design, and explain how we plan to adopt and adjust this design to be applicable in the study population we wish to study and to be feasible as a multicentre study.

Difficulties with RCTs in the palliative setting

Although Randomised Controlled Trials (RCT) are considered to provide high-grade evidence, the classical RCT poses several challenges, especially in pragmatic cancer research. Recruiting sufficient numbers of patients is known to be extremely difficult, not in the least due to cumbersome and time consuming procedures of informed consent, randomization, and inclusion.[1] Furthermore, the mandatory elaborate informed consent for all eligible patients, which is regarded as ethical requirement, is often a barrier for patients to join trials. The abundance of complicated information given combined with the uncertainty of randomization often leads to rejection of participation.[2] Moreover, the recruited (trial) population is often unrepresentative of the reference population, thus leading to poor external validity. It is also possible that patients withdraw from a trial when they do not get the experimental intervention, or exhibit disappointment bias when reporting outcomes. In the

field of oncology, there are often multiple treatments for the same disease, leading to multiple trials for the same population. These all have heterogeneous outcomes and are thus difficult to compare. Finally, modern technology has often surpassed the investigated intervention before the trial has ended.[3]

In the field of palliative medicine, the previously described difficulties become yet more evident. This is not only our personal experience from earlier trials we have performed in the Netherlands, but has also been described in the ZonMw report entitled "Successful inclusion in the palliative setting" (in Dutch: "Succesvol includeren in de palliatieve zorg").[4] This research was performed in response to the observed inclusion problems of studies in the palliative setting. Physical and emotional frailty are two major factors limiting inclusion. Due to physical frailty patients might deny participation; a lack of energy to fill out questionnaires or physically demanding visits at outpatient clinics can be reasons to refuse participation. Emotional frailty is possibly a more important reason for denial of participation, or earlier drop out. The partaking in a research forces a patient to think about his illness in some way or another. This can be extremely confronting, especially if patients have problems coping with their situation. Furthermore, it is plausible that this emotionally unstable situation influences patients in their decision-making. Many patients remain in a state of doubt and have difficulty drawing up the balance, thus being given the choice of participating in randomised research can be very demanding.

Mirroring this emotion is the reserve treating physicians feel to ask their patients to join a study. The physician often does not want to burden the patient any further than the illness already does. The often long and intensive relation between physician and patient further increases this protective attitude.

A more logistical problem with research of patients in the palliative setting is that they are often out of reach of the researchers. The majority of the patients in this phase receives care from their general practitioner or the local hospital, and does generally not visit an academic hospital unless necessary.

The ZonMw report looked into 13 research projects (total budget 2.8 million euro) aimed at improving quality of life and pain of patients in the palliative phase.[4] Four of these studies have been completed, 1 has been discontinued due to inclusion problems, and 1 did not start because the needed sample size was not considered feasible. One of the four completed studies did so on time, 2 were delayed, and 1 changed the aims because the number of patients included could not answer the primary question. All research projects reported problems with inclusion, mainly because too many eligible patients are missed at inclusion. Half of the studies had problems with the inclusion itself, for

example due to certain extra measurements (laboratory analysis) needed for the study or because patients were too ill to think about participation in a trial.

It is thus clear that inclusion in the palliative phase is difficult and although the majority of these limiting factors cannot be changed, they are aspects that need to be taken into account when setting up a new study. The 'cohort multiple randomised controlled trial' design has characteristics that will lessen the burden for the patient and ease the inclusion for the study. Only by employing such a design, will it be possible to answer several pending questions concerning the treatment of patients with bone metastases of the long bones.

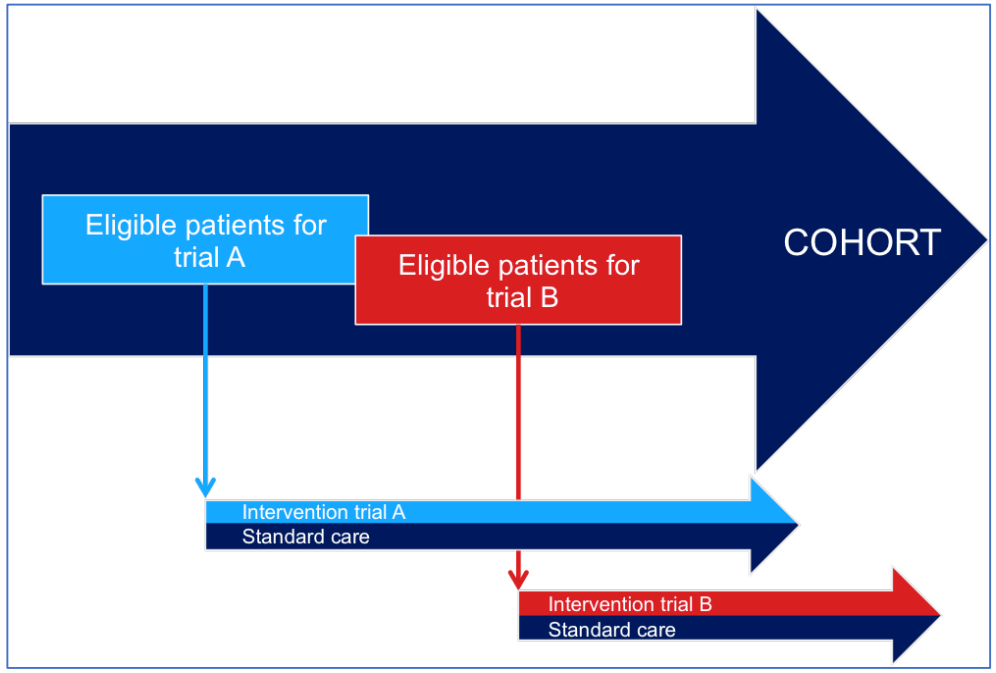


Figure B.1 Cohort multiple randomised controlled trial design.

Cohort multiple randomised controlled trial

In 2010 a new research design, the 'cohort multiple Randmised Controlled Trial' (cmRCT) was developed by Relton et al. in which several solutions are offered for the problems associated with classical RCTs.[5] The backbone of this design is an observational prospective cohort in which patients with the condition of interest (i.e. bone metastases of the long bones) are included (dark blue arrow in figure B.1). These patients are treated according to usual care and baseline data are registered. Secondly, all patients in the cohort are asked to periodically complete questionnaires on the quality of life and pain. Thirdly, patients are

asked for consent to be informed about possible trials in the future. This consent entails permission for random selection if the patient is eligible for a certain trial. For each trial, a random sample is selected from the group of consenting and eligible patients (light blue box in figure B.1), who will be offered the intervention treatment (light blue half of arrow in figure B.1). Only this group will be notified about the trial. After notification follows a second informed consent for participation in the specific trial. If patients do not wish to participate, they will cross over into the 'control group', compromising all patients not randomly selected, and receive standard usual care. The patients who were consenting and eligible but not randomly selected receive standard care as usual without being informed about the trial (dark blue half of the arrow in figure B.1).

Reasons for using this design

With the cmRCT design, patients are not randomized between treatments, but between whether or not they are invited for the intervention arm of a trial. This enables 'patient centred' informed consent: only those patients selected for the intervention arm are offered information about the trial. Thus only these patients are confronted with the possibly difficult choice of participating in a specific trial. Their choice however is a lot clearer than it would normally be, because this group knows that if they consent, they will surely receive the intervention. Likewise, those patients that have not been selected receive straightforward information regarding the standard care only, without any possibly confusing information about a trial.

This aims to replicate 'real world' routine health care, in which patients are only informed about treatments for which they are eligible. This is the keystone aspect of the study design and is of great importance for our potential trial participants who are under substantial emotional stress associated with the end-of-life stage.

It is important to realise that this design is not the same as a Zelen design. The Zelen design randomises patients before a single form of consent has been given. The Zelen design has for that reason been subject to ethical criticisms and is not often applied. In the design we propose, patients are informed on beforehand of the possibility of random selection (when they are eligible for a certain trial), and this will only be performed if the patient consents to that. Patients are clearly informed about the If the patient does not consent, he will receive standard care, i.e. the same care he would have received had there not been a trial.

For the research questions posed in our OPTIMAL study and in the setting we propose to perform our study, there is little room for setting up a traditional RCT. An alternative approach seems to be more appropriate and the outline of the cmRCT design is most suitable. Keystones are the 'patient centred' informed consent and the possibility for multiple prospective trials at the same time. Also, trials will be better comparable and a shorter period of time will be needed for including sufficient amount of patients, thus lowering the costs. Especially in a fragile patient population, such as patients with symptomatic bone metastases, the cmRCT design is uttermost suitable.

Although the clinical experience with cmRTC model is limited, it is currently being used in several studies in the UK, Canada, and The Netherlands [6-8] after ethical approval of respective ethical review committees. In The Netherlands, the University Medical Centre Utrecht (UMCU) is active in the field of further developing the cmRCT design. At their radiotherapy department they currently have 3 cohorts, with each one or more active trials. Their numbers of inclusion into the cohorts, informed consent for notification about trials, and inclusion into trials are promising. Recently, Young-Afat et al. wrote a brief report about their experiences with this new design.[9] They stated that the cmRCT design avoids prerandomization and actively engages participants in the research process during cohort participation. All preparations to employ the cmRCT design in the OPTIMAL Study have been in close collaboration with our colleagues at the UMCU.

Adjustment to the design

There are multiple research questions we wish to investigate and the study design for each trial will differ according to the research question. Therefore, in addition to only performing randomized controlled trials within the cmRCT design, we plan to use different designs, best suitable for each new study. Reasoning for the specific design will be extensively addressed in each separate study protocol.

This small adjustment is necessary, especially, in trials where two or more surgical techniques are going to be compared. Whereas very few eligible patients will be treated in a single year, even the cmRCT design and the multicentre setting can't address this sufficiently.

Thus, some trials will be comparative cohort trials, others pragmatic cluster randomized trials, and some with a cmRCT design. For this reason, we renamed the design: cohort multiple (randomized controlled) trial.

In conclusion, current knowledge concerning adequate, personalized treatment of metastatic lesions of the long bones is insufficient. Several factors of great importance are generally acknowledged: the aim of treatment should be maintaining or improving the quality of life; expected survival is an important factor to bear in mind; and current literature on local treatment modalities is inconclusive. For this reason, it is of upmost importance to explore whether other (innovative) treatments can be an alternative or addition to the current standard treatment options. The OPTIMAL Study, a cohort multiple (Randomised Controlled) Trial accounts for differing life expectancies and focusses on quality of life outcomes. The study will provide high-grade evidence as to which treatment is superior to others.

Objectives

The OPTIMAL Study in its entirety aims to provide a more personalized treatment for metastases in the long bones based on expected survival and impending fracture risk in order to improve functioning and the quality of life for the remaining lifetime in patients with disseminated cancer. The OPTIMAL Study will provide the infrastructure for a prospective cohort (OPTIMAL cohort) and multiple independent trials according to the cm(RC)T design. The specific aims of the cohort are discussed in this protocol.

The primary aim of the cohort is to describe the quality of life and pain perception of patients after local treatment (radiotherapy and/or surgery) of metastases of the long bones, for both the entire cohort as well as for specific treatments separately.

Secondary aims are to describe the complication rate and survival of patients after local treatment (radiotherapy and/or surgery) of metastases of the long bones.

The specific aims of further future individual trials within the cm(RC)T design will be described in separate protocols and submitted to the medical research ethics committee (METC) independently. In general, however, all trials will be pragmatic research trials in search of answers to which treatment (radiotherapy or surgery) fits specific patients (categorised by metastasis location, expected survival and fracture risk) best.

Study design

The OPTIMAL Study encompasses the OPTIMAL cohort and multiple independent trials. The cohort is primarily aimed at collecting patient reported outcomes, but will also provide the facility to select eligible patients for specific

trials according to the cm(RC)T design. This offers the possibility to perform multiple trials at the same time in the same patient population, as shown in figure B.1. Currently one trial is ongoing (the PORT study), the details of which are discussed in a separate protocol. Future trials will also be described in separate protocols, which will be submitted to the medical research ethics committee (METC) independently.

The OPTIMAL cohort

The OPTIMAL cohort is the backbone of the OPTIMAL Study. The cohort will be prospectively collected and multicentre, including all consecutive patients with BMLB who have signed informed consent. These patients will be followed prospectively, and data concerning patient and treatment characteristics as well as patient reported outcomes on quality of life will be collected. Baseline data will be collected by the physician and entered into the OPTIMAL database. These baseline data match the information that is obtained for standard care. For the assessment of patient reported outcomes a set of internationally and nationally validated questionnaires will be used. Further details are discussed in chapter 5. The OPTIMAL cohort will additionally serve as facility for efficient, systematic and simultaneous evaluation of new and existing interventions for bone metastases.

Informed consent

Informed consent will consist of the following three steps.

(1) Participation in the cohort (use and registration of routinely collected clinical data and (possibly) contacting the general practitioner or other physicians involved).
(2) Prospective registration of patient reported outcome measures (quality of life, pain).
(3) Approval to be approached for participating in future (intervention) studies.

Informed consent is signed after full oral and written information has been provided. Consent for step 1 (use and registration of routinely collected clinical data) is mandatory for participation in the OPTIMAL Study. Step 2 is a straight-forward consent for receiving and completing questionnaires about patient-reported outcomes. Step 3 is the crux for the 'patient-centred' informed consent. Patients who sign step 3 can be invited to participate in one or more of the studies within the OPTIMAL Study if they meet the inclusion criteria of a certain study and in case of a randomized trial, at random selection, as explained below in figure B.2.

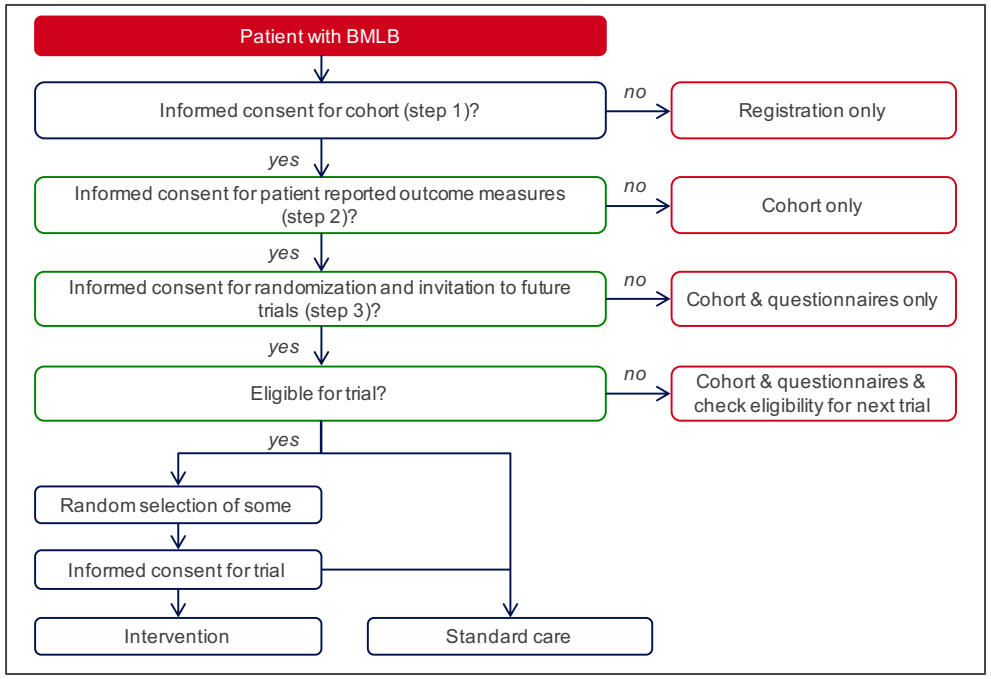


Figure B.2 Flowchart of informed consent.

For a new study, all consenting and eligible (i.e. according to study specific inclusion and exclusion criteria) patients are identified. From this sub-group, in case of a randomized trial, a random selection is made of patients who are invited to participate in the intervention arm. All patients (randomly) selected for the innovative treatment, will receive detailed information about the intervention and the study. Subsequently they may accept or refuse participation (figure B.3).

Those eligible patients who are not randomly selected will receive standard care as usual, without being informed about the randomized trial; this is the essence of 'patient-centred' informed consent.

Consenting to step 3 thus implies permission for being randomly selected to receive information about and be invited for a randomized trial on one hand, and for the use of clinical and self-reported data if patients are eligible but not selected for the intervention arm of a trial on the other hand. Patients are clearly informed that, if they are selected for and invited to the intervention arm of a trial, they are free to refuse it, in which case they will receive standard care. Patients are also informed that if they are not selected, they will be part of the control-arm, and that they therefore may be (temporarily) ineligible for some

future trials. In no case however, will patients be withheld from evidence based standard treatments.

Also, patients participating in in the OPTIMAL Study are permitted to participate in other research (e.g., a 'classic' RCT) outside the OPTIMAL Study.

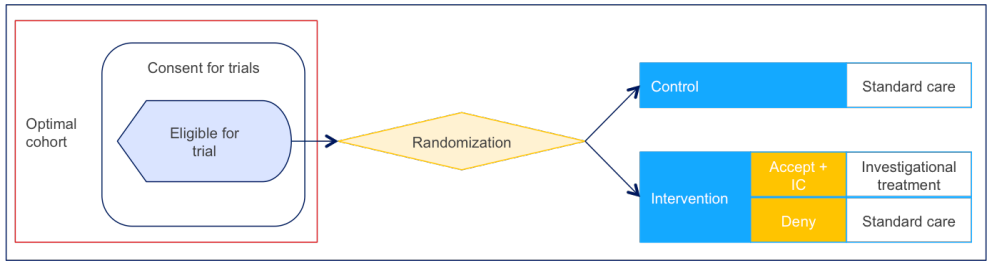


Figure B.3 Schematic overview of process from cohort to trial.

Study population

Population (base)

All patients visiting the radiation oncologist or the orthopaedic surgeon of participating centres, for possible local treatment of a symptomatic BMLB or impending fracture, will be registered in the OPTIMAL registry. This includes patients with newly diagnosed metastatic bone disease as well as patients undergoing re-treatment of the same lesion or patients who have received previous treatment for other lesions.

Inclusion criteria

To participate in the cohort, the patient must meet all of the following criteria:

- Aged 18 or older
- Symptomatic bone metastasis deriving from the bones of the extremities (humerus/femur and further distal) requiring pain medication or intervention with radiotherapy or surgery, or, non-symptomatic bone metastasis with an expected high risk of fracturing requiring treatment
- Radiographic or histologic proof of metastatic bone disease, originating from a solid tumour or primary bone tumour
- Histologic diagnosis of the primary tumour or – if the primary tumour is unknown - at least adequate diagnostic investigations into the origin of the metastasis (e.g. dissemination imaging, histology, biopsy)

Exclusion criteria

A potential patient will be excluded from participation in the cohort if any of the following criteria are met:

- Communication with patient is hampered (e.g. language barrier, severe cognitive impairment, dementia)
- The symptomatic lesion originates from multiple myeloma, solitary plasmacytoma or lymphoma of bone

Note: Previous treatment for metastatic bone disease at the present location is *not* an exclusion criterion.

Methods

Study parameters

At moment of inclusion baseline patient data will be collected for the OPTIMAL cohort, which will also be used for all other studies nested within the OPTIMAL Study. Data will comprehend information concerning demographics (date of birth, gender), medical history (primary tumour, dissemination status), clinical status (systemic treatment) and functioning (Karnofsky performance score, pain score, pain medication). Details concerning the treatment(s) will be reported when relevant.

Patient reported outcome measures

Patients will be invited to fill out questionnaires about pain, quality of life (QoL), and functioning at baseline (pre-treatment; if possible), and 4, 8, 12, and 24 weeks after initial treatment, then every six months for minimal two years or until death. All subsequently or concomitantly symptomatic metastases will be registered (including treatment and follow-up), but a new course of questionnaires will generally not be initiated. These outcome measures will be applied in the entire OPTIMAL cohort. The outcome measures and time-points are the same for all trials within the OPTIMAL Study.

(1) ***Pain*** has been chosen as primary endpoint because it can act as a proxy for mechanical complications (i.e. loosening). Mechanical complications are only relevant for these patients if they give clinical complaints needing treatment.
To measure the primary endpoint patients will be asked to score the worst pain in the past 24 hours on a NRS from 0-10. In addition, patients will be asked to list their usual pain medication and the escape medication they used the previous 24 hours. These questions are derived from the Brief Pain Intervention (BPI) score, which is advised by the International Consensus Statement for Bone Metastasis Research[10]. The BPI is a pain assessment tool for use with cancer patients developed by the Pain Research Group of the WHO Collaborating Centre for Symptom Evaluation in Cancer Care and is also available in Dutch. However, multiple questions are similar to questions in the EORTC QLQ15-PAL and EORTC QLQBM-22 (described below). Thus to spare patients answering the same questions twice, we have selected only 2 questions from the BPI.

(2) ***Quality of life;*** For longitudinal assessment of quality of life after treatment, we will use nationally and internationally used, validated and recommended questionnaires: European Organization for Research and Treatment of Cancer (EORTC) QLQ-C15-PAL[11] and EORTC QLQ-BM22.[12,13] In addition, the EQ-5D questionnaire will be conducted. The EORTC is currently developing a utility scoring instrument for the EORTC QLQ-C30 (from which the QLQ-C15-PAL originates). We expect this scoring instrument will also be applicable for the QLQ-C15-PAL. After validation of this scoring instrument has taken place, we plan to apply it to our data. This would make the addition of the EQ-5D questionnaire redundant and it will then be withdrawn.

(3) ***Function;*** For assessing improvements in functional outcomes after treatment, the Toronto Extremity Salvage Score (TESS) for upper and lower extremities will be used.[14]

Observational clinical data

Observational clinical data will be collected at baseline (pre-treatment; if possible) and at first, and possibly second, post-operative follow-up (generally, patients are subsequently only seen if there are complications or new complaints):

(1) ***Complications;*** For complication rate, the Henderson classification of complications will be applied.[15] This classification identifies five primary modes of endoprosthetic failure: soft tissue failure (type 1), aseptic loosening (type 2), structural failure (type 3), infection (type 4), and tumour progression (type 5). Wound complications with clinical consequences will be registered separately. Re-operations due to complications will be registered as such in the treatment field as a new operation.

(2) ***Radiological status;*** Progression of BMLB will be monitored with conventional radiography and on indication with CT scan. This is according to usual care, generally at six weeks and 3 months. No additional outpatient visits or imaging will be requested for study purposes only. The radiological images will be used to place the subjective reports of pain (as reported by the NRS) into perspective.

(3) S***urvival***; Dates of death will be derived from the Hospital Electronic Patient Registry (in Dutch: Ziekenhuis Informatie Systeem, ZIS), which is linked to the Municipal Personal Records Database (in Dutch: *Gemeentelijke Basisadministratie*, GBA). If this is not possible or not up to date, data will be derived from the general practitioner. The utmost will be tried to prevent sending questionnaires to deceased patients.

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Appendix C. Cross-cultural adaptation, translation, and validation of the Toronto Extremity Salvage Score for extremity bone and soft tissue tumour patients in The Netherlands

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Sarcoma 2017 Jul; 17

Abstract

Purpose

The aim of this study was to translate and culturally adapt the Toronto Extremity Salvage Score (TESS) to Dutch and to validate the translated version.

Methods

The TESS lower and upper extremity versions (LE and UE) were translated to Dutch according to international guidelines. The translated version was validated in 98 patients with surgically treated bone or soft tissue tumors of the LE or UE. To assess test-retest reliability, participants were asked to fill in a second questionnaire after one week. Construct validity was determined by computing Spearman rank correlations with the Short Form- (SF-) 36.

Results

The internal consistency (0.957 and 0.938 for LE and UE, respectively) and test-retest reliability (intraclass correlation coefficients 0.963 and 0.969 for LE and UE, respectively) were good for both questionnaires. The Dutch LE and UE TESS versions correlated most strongly with the SF-36 physical function dimension (r = 0.737 for LE, 0.726 for UE) and the physical component summary score (r = 0.811 and 0.797 for LE and UE).

Interpretation

The Dutch TESS questionnaire for lower and upper extremities is a consistent, reliable and valid instrument to measure patient-reported physical function in surgically treated patients with a soft tissue or bone tumor.

Introduction

The preferred treatment of bone and soft tissue tumors of the extremities is limb-sparing surgery. Measuring physical function after surgery is of the utmost importance to determine the success of treatment and to improve patient care. Patient-reported outcome measures enable the surgeon and the patient to objectively evaluate the patients' pain and function in order to optimize clinical care.

The Toronto Extremity Salvage Score (TESS)[1] is a valid and reliable disease-specific measure developed to evaluate physical disability in patients treated for extremity sarcoma. Different questionnaires are available for the upper and lower extremities. The TESS was originally developed in English and has currently been translated and validated in five other languages (Japanese,[2,3] Korean,[4] Chinese,[5] Danish,[6] Portuguese[7]).

While the TESS is commonly used in the Netherlands, it has not been translated or validated for use in the Dutch language using standardized and methodologically sound procedures. The current study aims to translate and culturally adapt the TESS (for upper and lower extremities) to Dutch and to validate the translated version among patients with surgically treated bone or soft tissue tumors of the extremities.

Methods

This research was reviewed and approved by the Medical Ethical Committee of the Leiden University Medical Center. A waiver for informed consent was provided based on the law for medical research on humans in the Netherlands (April 2016; P16.060).

Translation and cross-cultural adaptation

The methodology used for translation and adaption concerns a well-established process, based on published guidelines for the cross-cultural adaptation of self-reported measures by Beaton et al.[8] and Guillemin et al..[9] During the course of translation, adaptation, and validation the TESS questionnaires for the lower extremity (LE) and upper extremity (UE) were handled separately. Forward translation from the English TESS into Dutch was performed by three bilingual translators, with Dutch as mother tongue (JJW, CWPGvdW, JB). One of these translators (JB) was unaware of the concepts addressed and without a medical background. This led to a first Dutch consensus version. Two independent, bilingual translators with English as mother tongue and without medical background subsequently translated the Dutch version back to English (MH, TT).

The expert committee, compromising a methodologist (TVV), the principal investigator (MAJvdS), and four translators (JJW, CWPGvdW, JB, TT) reviewed all versions and components of the original questionnaire and the translations to reach consensus on the final wording to be used in the Dutch version of the TESS.

Patients

Consecutive eligible patients who visited the outpatient clinic between July and September 2016 (regarding LE) or February 2017 (regarding UE) for follow-up of previous surgery for bone or soft tissue tumors of the extremities were invited to complete the translated and adapted TESS. Eligible patients were identified by checking the electronic medical records of patients scheduled for follow-up. Inclusion criteria were: (i) aged 18 or older, (ii) a minimum of 3 months since surgical treatment for an aggressive benign or malignant bone tumor or soft tissue sarcoma, and (iii) no sign of local or systemic recurrent disease. Patients with whom communication was impaired or who could not complete questionnaires unaided were not asked to complete the questionnaires. Baseline characteristics of the participating patients, including age, gender, primary tumor, location of primary tumor, and time since primary surgery were collected.

Instruments

The TESS is a self-administered questionnaire that includes 30 items regarding activity limitations in daily life, such as restrictions in body movement, mobility, self-care and performance of daily tasks and routine. The degree of physical disability is rated from 0 (not possible) to 5 (without any problem). The raw score is converted to a score ranging from 0 to 100 points, with higher scores indicating less functional limitations. Patients are able to answer questions concerning activities they do not perform in daily life with “not applicable”. These questions are deducted from the calculation of the total score.

The SF-36 is a widely used questionnaire to survey health-related quality of life.[10] The SF-36 has been validated for the Dutch population[11] and is administered as part of standard-care protocol in our hospital. The questionnaire measures eight dimensions of health and reports a score (from 0 (worst) to 100 (best)) for each category.[10] The scores from the eight categories can also be grouped into two summary scores: the physical and mental component summary scores (PCS and MCS). These summary scores were standardized using normative data from the Dutch general population with a mean score of 50 and standard deviation of 10.[11] The scores give an indication of the functioning of the patient population in comparison with the general population.

Assessments

Eligible patients were invited to participate in the study by a research assistant when presenting at the outpatient clinic. The questionnaires were provided on paper. The first questionnaire was to be completed while waiting for the outpatient appointment. The second questionnaire (with a stamped return envelope) was handed out at the outpatient clinic together with the first questionnaire and patients were asked to complete the questionnaire one week later at home and send return by post. The questionnaires were paired by a code, to enable test-retest analysis.

Once patients agreed to participate in the study, their name was recorded. Patient identifying information was however not coupled to the questionnaire number, thus ensuring anonymity of the questionnaire.

Analyses

Prior to analysis, patients who answered 80% or more of the questions of the first TESS questionnaire with “not applicable” were excluded. For calculation of mean scores and analyses of difficult or “not applicable” questions, the first completed questionnaire of each patient was used.

Reliability

Internal consistency measures the homogeneity of all parts of the instrument, and was evaluated by means of calculation of Cronbach’s alpha.[12] Cronbach's alpha provides a measurement of the strength of the relationship among the items of the questionnaire, with a value of >0.80 generally being considered as acceptable for scaling of the measure.[13] Test-retest variability concerns the ability of an instrument to create reproducible results when no real change has occurred for a subject. For this purpose, the intraclass correlation coefficient (ICC) was estimated between the responses to the first (test) and the second (retest) questionnaire for each item and for the total score. Bland-Altman plots were computed to visualize the absolute differences between the two assessments against the mean of the two tests to show the limits of agreement.[14]

Validity

Construct validity measures the extent to which the scores of an instrument relate to other widely accepted measures of the same construct. For this study,

construct validity of the TESS was determined by calculating the Spearman rank correlation-coefficient between the TESS and the SF-36 dimension and summary scale scores.

All statistical analyses were performed with IBM SPSS version 23.0 (Armonk, NY, USA). The strength of agreement for the correlation coefficients and the ICC was defined as strong (≥0.70), moderate (>0.50 to <0.70), and weak (≤0.50).[15] A *p*-value of <0.05 was considered statistically significant.

Results

Translation process

The translators and expert committee encountered no major linguistic or cross-cultural challenges during the translation and cross-cultural adaptation phase of the TESS-LE and TESS-UE questionnaires. The translation and adaptation process finally resulted in a Dutch TESS-LE and TESS-UE questionnaire, which can be found online.

(https://www.hindawi.com/journals/sarcoma/2017/6197525/sup/)

Patients

Ninety-eight patients (49% male) with a mean age of 48.7 years (range 18.1–83.8) were included (figure C.1). The characteristics of the patients and their TESS and SF-36 scores are presented in Table C.1 and C.2.

Dutch TESS LE and UE questionnaire results

Overall, the mean score of the TESS questionnaire was 77.5 (standard deviation (SD) 19.8) for the lower extremities and 90.2 (SD 14.9) for the upper extremities (table C.2). Getting up from kneeling was regarded the most difficult of all activities (mean score 3.21) in the LE questionnaire. Lifting a box to an overhead shelf was regarded the most difficult of all activities (mean score 3.94) in the UE questionnaire. Five patients (10.0%) scored a maximum score (100) on the TESS-LE, versus 19 patients (39.6%) on the TESS-UE. On the TESS-LE patients answered a median of 1 question with "not applicable" (range 0–17 questions). The questions concerning getting in and out of bath (n=11, 22%), driving a car (n=9, 18%) and sexual activities (n=9, 18%) were most frequently answered as "not applicable". Regarding the TESS-UE, the median number of questions answered with "not applicable" was 0 (range 0–7 questions) The most common "not applicable" UE-activities were those about working the usual number of hours (n=5, 10%) and tying a tie or bow at the neck of a blouse (n=5, 10%).

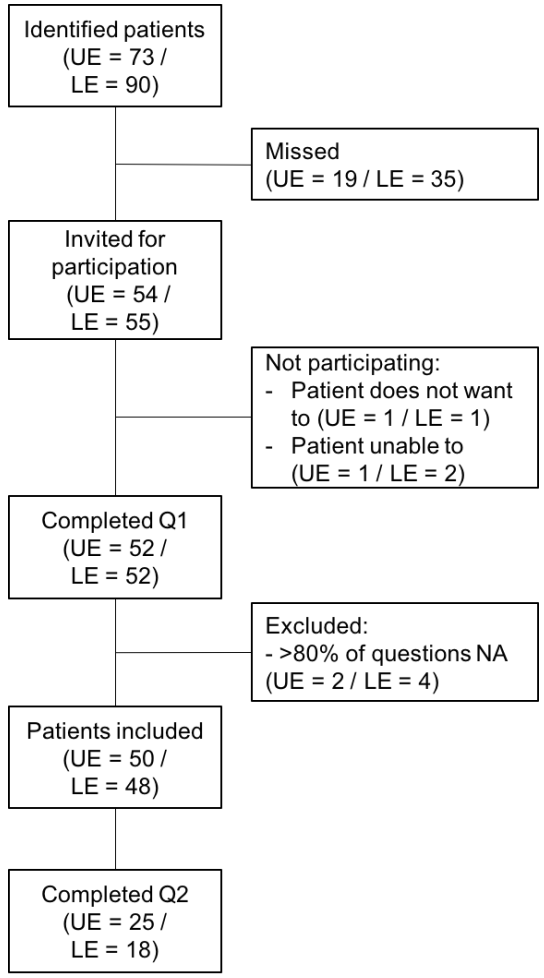

Figure C.1 Flowchart of participating patients.

Reliability

The internal consistency was good with Cronbach's alpha of R = 0.957 for the TESS-LE and R = 0.938 for the TESS-UE. The Spearman rank correlation coefficients between one item and the total score (excluding that item) ranged from 0.955–0.958 per item for the TESS-LE and from 0.933–0.939 per item for the TESS-UE. Twenty-five and eighteen of the LE (50%) and UE patients (38%) completed the "retest" questionnaire, respectively. The test-retest reliability was strong with ICCs of 0.963 (95% confidence interval (CI) 0.916–0.984) and 0.969 (95%CI 0.914–0.989) for the TESS-LE and TESS-UE, respectively.

Table C.1 Patient and tumor characteristics of patients with benign and malignant bone and soft tissue tumors who completed the TESS questionnaire

	TESS LE	*TESS UE*
N	50	48
Age: mean (range)	48.9 (18.6 – 74.9)	48.5 (18.1 – 83.8)
Gender: % male	47	52
Time since surgery in years: mean (range)	3.5 (0.03 – 18.8)	3.0 (0.03 – 17.8)
Location n (%)		
Shoulder	0	1 (2)
Humerus	0	21 (44)
Upper arm (soft tissue)	0	6 (13)
Radius	0	2 (4)
Metacarpals	0	9 (19)
Digits	0	7 (15)
Femur	22 (44)	0
Upper leg (soft tissue)	1 (2)	0
Knee	2 (4)	0
Tibia	12 (24)	0
Fibula	1 (2)	0
Lower leg (soft tissue)	3 (6)	0
Foot	2 (4)	0
Missing data*	7 (14)	2 (4)
Primary tumor n (%)		
Atypical cartilaginous tumor	10 (20)	22 (46)
Chondrosarcoma grade 2/3	5 (10)	4 (8)
Osteosarcoma	6 (12)	3 (6)
Soft tissue sarcoma	4 (8)	5 (10)
(Tenosynovial) Giant cell tumor	6 (12)	2 (4)
Osteochondroma	2 (4)	0
Fibromatosis	1 (2)	1 (2)
Cartilagenous tumour - benign	2 (2)	2 (4)
Bone other - malignant	2 (4)	1 (2)
Soft tissue other - benign	2 (4)	3 (6)
Bone other - benign	3 (6)	3 (6)
Missing data*	7 (14)	2 (4)

*Baseline characteristics were unavailable for 11 patients (7 LE and 2 UE) because they had not been recorded correctly.

Table C.2 Mean and median scores of TESS and SF-36 for the lower and upper extremities

	Lower extremity		*Upper extremity*	
	Mean (SD)	Median (range)	Mean (SD)	Median (range)
TESS	77.5 (19.8)	80.2 (13.3 – 100)	90.2 (14.9)	96.3 (21.6 – 100)
SF-36				
Physical functioning	60.5 (26.2)	65.0 (10.0 – 100.0)	80.4 (22.4)	85.0 (10.0 – 100.0)
Role limitations: physical	47.5 (43.2)	25.0 (0.0 – 100.0)	62.0 (42.5)	75.0 (0.0 – 100.0)
Social functioning	72.8 (25.3)	75.0 (0.0 – 100.0)	82.8 (22.6)	87.5 (12.5 – 100.0)
Role limitations: emotional	82.7 (33.8)	100.0 (0.0 – 100.0)	80.6 (36.2)	100.0 (0.0 – 100.0)
Mental health	72.9 (19.8)	80.0 (28.0 – 96.0)	78.2 (18.1)	80.0 (36.0 – 100.0)
Vitality	61.5 (22.6)	65.0 (15.0 – 100.0)	62.5 (22.3)	70.0 (15.0 – 100.0)
Bodily pain	62.1 (27.3)	57.1 (0.0 – 100.0)	72.9 (26.2)	73.5 (0.0 – 100.0)
General health perceptions	60.8 (25.5)	67.0 (10.0 – 100.0)	62.7 (19.9)	65.0 (15.0 – 100.0)
Physical component score	40.5 (11.2)	39.0 (16.5 – 58.6)	46.7 (9.9)	48.4 (23.4 – 61.9)
Mental component score	50.6 (10.9)	54.2 (14. 0 – 67.9)	50.2 (9.8)	53.7 (20.5 – 62.8)

The Bland-Altman plots for both questionnaires showed there were no signs of systematic bias (figures C.2 and C.3). The mean difference between the first and second questionnaire was 1.65 (SD 8.55) for the TESS-LE and -1.01 (SD 3.51) for the TESS-UE.

Validity

The mean scores for the eight SF-36 dimensions of the patients in the study and the physical and mental component scores (PSC/MSC) are shown in table C.2. The correlation was strong between the TESS-LE and the SF-36 dimensions: physical functioning, role physical, social functioning, vitality, bodily pain, PSC (table C.3). There was a moderate correlation between the TESS-LE and the SF-36 dimensions: role emotional, mental health, and general health perceptions. The correlation with the MSC was poor. For the TESS-UE the dimensions physical functioning, role physical, bodily pain, and PSC strongly correlated, while the correlation was moderate for the dimensions social functioning, role emotional, and vitality. Mental health, general health perceptions, and MSC were poorly correlated.

Table C.3 Construct validity. Spearman rank correlations of the TESS (upper and lower extremities) with the SF-36 dimensions

Spearman	*Lower extremity*	*Upper extremity*
Physical functioning	0.737	0.726
Role limitations: physical	0.766	0.766
Social functioning	0.810	0.585
Role limitations: emotional	0.511	0.525
Mental health	0.505	0.383
Vitality	0.704	0.586
Bodily pain	0.777	0.766
General health perceptions	0.540	0.465
Physical component score	0.811	0.797
Mental component score	0.429	0.347

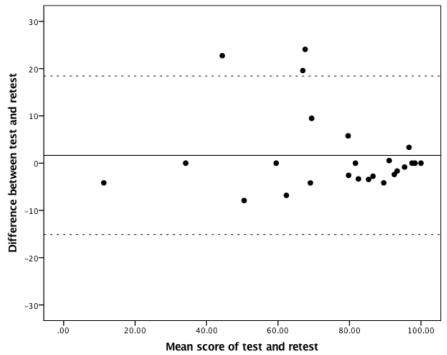

Figure C.2 Bland-Altman plot of the test-retest reliability of the Dutch TESS-LE. The solid line shows the mean difference of the two tests (1.65) and the dashed lines show the 95% limits of agreement (-15.11; 18.41).

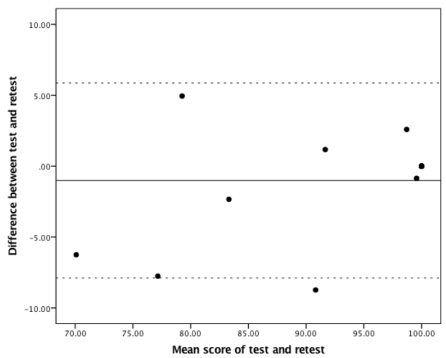

Figure C.3 Bland-Altman plot of the test-retest reliability of the Dutch TESS-UE. The solid line shows the mean difference of the two tests (-1.01) and the dashed lines show the 95% limits of agreement (-7.89; 5.86). The dot with 0 difference between test and retest and a 100 mean score represents ten patients.

Discussion

The TESS questionnaires for both the lower and upper extremities (LE and UE) are commonly used patient-reported outcome measures for functioning after the treatment of bone or soft tissue tumors in the Netherlands. However, there is currently no validated Dutch version. This study translated and culturally adapted a Dutch variant of both versions (LE and UE) of the TESS questionnaire.

The cultural adaption was limited to a minimum, which might be due to the similarities regarding the performance of daily activities between the Canadian and the Dutch societies.

Six questionnaires were excluded from the analysis because too many (>80%) questions had been answered with “not applicable”. For both the LE and UE versions, there was one questionnaire that was completely answered with “not applicable”, of which no score could be computed. In the other four questionnaires, the number of “not applicable” answers ranged from 24-29. Although the summary score excludes the “not applicable” answers, a score based on only one or several items did not appear trustworthy to the authors. In the original TESS publication, no advice is given as to dealing with such outcomes. Neither do previous articles validating the TESS questionnaire report of questionnaires with this amount of “not applicable” answers. Reasons for the high incidence of “incomplete” questionnaires are unclear; however, the TESS was the second questionnaire to fill in, after the SF-36, and it is possible that patients ran out of patience after the first 36 questions.

The internal consistencies and test-retest reliabilities of the Dutch TESS-LE and TESS-UE were comparable with the original version of the TESS[1] and with other translated and validated versions.[3-6] As in all other versions, the test-retest reliability was slightly higher of the UE version than the LE version.

In the TESS-UE 19 patients (39.6%) scored the maximum score. This ceiling effect reduces the possibility of measuring improvement and makes discrimination in patients who are doing well difficult. In the validation of the Japanese translation of the LE-TESS a ceiling effect for 17% of the participants was registered. None of the other translation and validation studies report the presence of absence of a ceiling effect. Therefore, it is difficult to place the current result in context; was the testing group too good or is the TESS-UE really not sensitive enough to discriminate patients with good function of the upper extremity? It is however important to take this result into account when interpreting questionnaire results of individual patients with a good function.

While the original[1] and most other language versions[3-5] test the validity with the MusculoSkeletal Tumor Society (MSTS) score[16], this study tested the validity with the SF-36. The SF-36 was used as comparison with the TESS because it is standard procedure for patients to fill out the questionnaire at the outpatient clinic. Moreover, as opposed to the MSTS questionnaire which is designed as a physician-reported outcome measure, the SF-36 is designed as patient-reported outcome. From that point of view, the SF-36 is suitable to compare with the TESS, which is also patient reported. An additional comparison with the MSTS questionnaire would have brought further information, because that is a disease-specific questionnaire, but this was not possible because the MSTS questionnaire is not regularly completed by the physicians in the outpatient clinic. The correlation between the Dutch TESS (both LE and UE) and SF-36 was strong in the expected dimensions: physical component summary, physical functioning, role physical, and bodily pain. In both questionnaires the correlation with the mental component summary was poor, as was to be expected because the TESS is developed to measure physical functioning only.

This study is limited by several factors. Although the total population is sufficiently large, the subpopulations for the lower and upper extremities are small. The number of patients included in the current study was based on previous studies validating the TESS. The TESS was validated in other languages in cohorts ranging from 22 to 126 patients, thus a total of 98 patients in the current study seems reasonable. The TESS-LE was previously tested in cohorts ranging from 16 to 102 (mean 60, median 48)[3-6], so the LE cohort in this study was of average size. The TESS-UE has been validated in four other languages with small cohorts (6, 23, 43, 56 patients). The current validation in 48 patients is thus one of the larger cohorts.

The proportion of patients returning the second questionnaire ranged between 38% and 50% which left a small group for the test-retest validity. There are no clear reasons why the return-rate was low. However, as the second questionnaire had to be filled in from home and sent by post, it is conceivable that people simply forgot. It would have been interesting to analyze whether there was a selection in the patients returning the second questionnaire. However, due to the anonymity of the questionnaires, this could not be retrieved.

The comprehension of the questions was not tested in separate questions. However, patients received verbal instructions to report any unclear questions or issues concerning the interpretation of questions to the researcher handing out the questionnaires at the outpatient clinic. Although some patients

commented on the amount of questions, no issues were raised concerning the content or meaning of the questions.

The study did not test the Dutch responsiveness to the questionnaire. For use in clinical practice, especially for follow-up in the direct post-operative phase, it would have been useful to know the ability of the questionnaire to accurately detect change when this occurs. However, to test the reliability in the current validation study the population of interest was the group that was longer post-operative and with a stable situation.

To conclude, the Dutch TESS questionnaire for UE and LE is a reliable and valid instrument to measure patient-reported physical function for patients undergoing limb salvage surgery for benign and malignant bone and soft tissue tumors. The Dutch version of the TESS can be used for future cross-cultural international studies of orthopedic oncology.

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List of publications

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Curriculum vitae

Julie Johanneke Willeumier was born on October 23rd 1988 in Rotterdam, the Netherlands. After spending her childhood abroad (Genova, Italy; Atlanta, USA; London, UK) she graduated from the Maerlant Lyceum in The Hague in 2006. That same year she started medical school at Leiden University (LUMC). Before starting her clinical rotations in 2012, she moved to London for a clinical internship with Prof. Mafulli, orthopaedic surgeon at the Barts and London School of Medicine, and a research internship with Mr. W. Aston, orthopaedic surgeon at the Royal National Orthopaedic Hospital, Stanmore. The latter research was the foundation of a large, international collaboration on the treatment of soft tissue sarcomas led by dr. M.A.J. van de Sande, orthopaedic surgeon at the LUMC. During her clinical rotations in Leiden and The Hague she continued her research within this field.

After graduating from medical school in 2014, she pursued her scientific work at the orthopaedic department of the LUMC with the research project on bone metastases of the long bones (Prof. P.D.S. Dijkstra and dr. Y.M. van der Linden), which forms the basis of this thesis. As part of the research project she was in the lead to design and implement a multidisciplinary, multicentre prospective study encompassing a cohort of patients with long bone metastases with multiple randomised studies to evaluate treatments. Additionally, she developed the OPTIModel application for smart phones to assist in survival estimation in clinical practise and was co-author to a chapter for the book *Management of bone metastases – a multidisciplinary guide* (Springer 2018). During her PhD research she presented her research at multiple national and international scientific meetings. At the annual meeting of the European Musculoskeletal Oncology Society Meeting in May 2016, she won the EMSOS Best Innovation Oral Presentation Award.

In August 2017 she started working as resident not-in-training in general surgery at the St Antonius Ziekenhuis in Nieuwegein/Utrecht. She will start her orthopaedic residency in 2019.