Optimising the treatment of patients with long bone metastases

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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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