Optimising the treatment of patients with long bone metastases

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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.

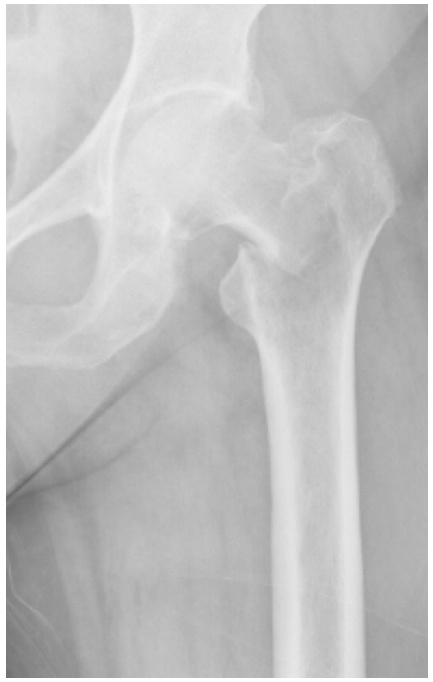

Figure 11.1 Per-trochanteric fracture.

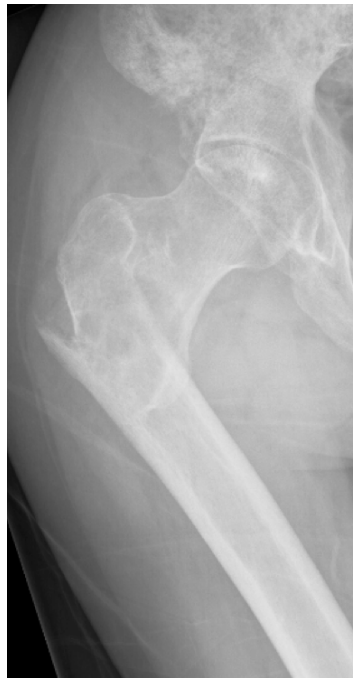

Figure 11.2. Sub-trochanteric fracture.

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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