Optimising the treatment of patients with long bone metastases

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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%.

1. Clinical profile	Favourable		Moderate		Unfavourable	
2. Karnofsky	100 - 80	70 - 10	100 - 80	70 - 10	100 - 80	70 - 10
3. Visceral/ brain metastases	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Survival (95% CI; months)	27 - 34	12 - 23	10 - 16	6 - 9	9 - 14	5 - 14	4 - 6	2 - 4	3 - 8	4 - 5	2 - 3	2 - 3
Category	A	A	A	B	B	B	C	C	C	C	D	D

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.