Surgical decision-making for long bone metastases

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Publication date
2018

Document Version
Other version

License
Other

CHAPTER 12

Summary

Appendicular bone metastastases are most frequent in the femur and the humerus. These lesions can weaken the bone and often lead to pathological fractures. An increase in the number of patients living with bone metastatic disease will most likely result in a larger number of patients developing pathological fractures. Pathological fractures negatively impact quality of life, physical function, and survival. Surgical intervention is often indicated to treat a pathological fracture in a long bone and aims to optimize quality of life by providing a stable construct that outlives the patient. The purpose of this PhD thesis is to: develop tools for better patient selection for surgery, improve implant selection based on patient- and tumor characteristics, identify risk factors for adverse outcomes, and evaluate outcome after treatment for patients with long bone metastases.

PART I: METASTATIC FEMORAL LESIONS

This part starts with a retrospective study (**Chapter 2**) comparing outcomes after surgical management of pathological and impending fractures of the proximal femur using data from two affiliated orthopaedic oncology centers. This study included 417 consecutive patients with proximal femoral metastases that were treated by intramedullary nailing, endoprosthetic reconstruction, and open reduction internal fixation. Overall reoperation rate did not differ significantly between these strategies and were 5.3% after intramedullary nailing, 11% after endoprosthetic reconstruction, and 13% after open reduction and internal fixation. However, we did find differences in reoperation rates when focusing on specific reasons for reoperation: fixation failure and deep infection. The fixation failure rate was highest after open reduction internal fixation (13%), followed by intramedullary nailing (3%), and none after endoprosthetic reconstruction. The deep infection rate also differed and was highest after endoprosthetic reconstruction (8.6%), followed by intramedullary nailing (2%), and none after open reduction internal fixation. Deep infections occur in the first months after surgery, while fixation failure accumulates over time. Overall, 30-day systemic complication rates (9.6%) and 30-day survival (93%) did not differ between surgical strategies. Intraoperative blood loss was almost twice as high and anesthesia time was about 40 minutes longer for endoprosthetic reconstruction when compared with intramedullary nailing and open reduction internal fixation.

The subsequent systematic review (**Chapter 3**) puts these findings into perspective and included 40 studies describing endoprosthetic reconstruction (n=1,461), intramedullary nailing (n=1,054), and open reduction internal fixation (n=233) for proximal femoral metastases. Breast (35%), lung (15%), prostate (10%), and renal cell (8.2%) are the most common primary cancers. Oneyear survival ranged from 0 to 62%; variation in baseline (e.g. primary tumor type) explains the substantial variation in oneyear survival. The pooled overall reoperation rate differed significantly between surgical strategies and was 5.2% after endoprostheses, 4.2% after intramedullary nailing, and 14% after open reduction internal fixation. Again, when focusing on reasons for reoperation, we noticed a difference. The pooled fixation failure rate was 0.4% after endoprostheses, 2.8% after intramedullary nailing, and 10% after open reduction internal fixation. The pooled deep infection rate was 0.68% for endoprostheses, 0.04% for intramedullary nailing, and none for open reduction internal fixation. We were not able to pool and compare functional outcome and systemic complications between surgical strategies due to varying definitions and heterogeneity in reporting; functional outcome has been scarcely reported.

Subsequently, we established which patient reported outcome questionnaire was the most useful –in terms of effectiveness, reliability, and efficiency– when measuring physical function in patients with lower extremity bone metastases (**Chapter 4**). One hundred of 115 invited patients with lower extremity metastases participated in this prospective study and completed five questionnaires in random order: PROMIS-CAT Physical Function Cancer, PROMIS-CAT Neuro-QoL Mobility, Toronto Extremity Salvage Score (TESS), Lower Extremity Function Score (LEFS), and Musculoskeletal Tumor Society score (MSTS). All questionnaires measured the same concept; this was demonstrated by substantial correlation of every questionnaire with the underlying trait (factor scores >0.7) and by high interquestionnaire correlations (>0.7). Floor effect (i.e. score at lowest limit of questionnaire) was absent, while ceiling effect (i.e. score at upper limit of questionnaire) was present in all, but highest for the PROMIS Neuro-QoL Mobility (7%) indicating poor coverage. The standard error of measurement (i.e. a measure of precision of a questionnaire) was below the threshold –indicating reliability– over a wide range of ability levels for the PROMIS Physical Function Cancer, TESS, and LEFS. Completion time differed between questionnaires, and was shortest for the two PROMIS questionnaires. The PROMIS Physical Function Cancer questionnaire is the most useful questionnaire to measure physical function in patients with lower extremity bone metastases due to its reliability over a wide range of ability levels, validity, brevity, and good coverage.

Finally, we introduced and tested an algorithm to establish fracture risk in lytic femoral metastases using CT scans (**Chapter 5**). The algorithm uses attenuation measurements of metastases (measured in Hounsfield units) in CT scans compared to the unaffected contralateral side. We tested this method by comparing the cumulative Hounsfield units and the geometric distribution of the Hounsfield units between femora with metastatic lesions that fractured and femora with metastatic lesions that did not fracture nor underwent prophylactic fixation. We found no difference between these two groups when analyzing all tissue –trabecular and cortical bone, and tumor tissue–. However, when including cortical bone only, we found that the femora that fractured had lower cumulative Hounsfield units as compared to those that did not fracture. The diagnostic accuracy of this method was expressed by an area under the curve (AUC) of 0.69; a threshold of <87% resulted in a sensitivity of 89% and a specificity of 48%. Our findings can be useful for predicting the development of a pathological fracture.

PART II: METASTATIC HUMERAL LESIONS

This part starts with an overview of the current literature (systematic review) on outcomes after surgical treatment of metastatic humeral fractures (**Chapter 6**). Breast (30%), multiple myeloma (15%), lung (15%), and renal cell (13%) are the most common metastatic humeral lesions. The average postoperative survival of the patients was poor and varied from 4 to 23 months; variation in baseline (e.g. primary tumor type) explains the substantial variation in average survival. We found that –among 23 studies including 909 patients– overall reoperation rates were 4.4% after intramedullary nailing (range: 0 to 10%), 9.3% after plate-screw fixation (range: 5 to 14%), 2.5% after endoprosthetic reconstruction (range: 0 to 6%), and 15% after diaphysis prosthesis (range: 14 to 16%). Although indications for these surgical strategies vary and preclude comparison, the presented findings can be used to inform patients and their caregivers. In addition, we found that the quality of reporting was poor, definitions of systemic complications varied or were not described, and patient reported outcome data were scarce.

Subsequently, we reviewed reoperations and systemic complications after surgical treatment of 295 metastatic humeral lesions from two large affiliated orthopaedic oncology centers (**Chapter 7**). The median postoperative survival was 11 months. We found that the reoperation rates were 6.7% after intramedullary nailing, 10% after plate-screw fixation, and 11% after endoprosthetic reconstruction. Deep infection, nonunion, peri-implant fracture, and tumor progression were the most common reasons for reoperation. No patient or tumor characteristics were associated with the risk of undergoing reoperation; however, we did find that the proportion of patients who underwent reoperation increased considerably with longer survival from 2.6% at 1 month up to 19% at 2 years. In addition, we found a postoperative systemic complication rate of 5.8%, and demonstrated that a worse modified Bauer score (an indicator of survival prognosis that combines cancer type and degree of dissemination) was associated with a higher risk of developing systemic complications.

Finally, we surveyed 161 orthopaedic surgeons and assessed how they would treat metastatic humeral lesions in a cross-sectional survey study (**Chapter 8**). We created 24 fictional case scenarios by combining: tumor type, life expectancy, fracture type, and anatomical location of the lesion. For every case, all 161 participants (78 orthopaedic oncologists, 83 trauma / general orthopaedic surgeons) answered the question "What treatment would you recommend?". Orthopaedic oncologists were more likely to recommend endoprosthetic reconstruction and plate-screw fixation and less likely to recommend intramedullary nailing compared to other subspecialty surgeons. Recommendation for nonoperative management did not differ. In addition, we found that recommendation for specific treatments differed based on tumor type, life expectancy, and anatomical location, but not fracture type. In some cases, surgeons agreed about the treatment strategy, while in other cases, there was substantial variability.

PART III: SURVIVAL

This part starts with a comparison of resection strategies for bone metastases from renal cell carcinoma (**Chapter 9**). It remains unclear how different types of tumor resection affect oncological outcome –survival and tumor recurrence–. We assessed differences in local tumor recurrence/progression, reoperation, and survival between three different surgical strategies: metastasectomy, intralesional curettage, and stabilization only in this retrospective study. Secondarily, we assessed whether the margin status affected outcomes. We included 183 patients from two affiliated orthopaedic oncology centers: 48% underwent metastasectomy (margins: 72% negative; 23% positive; 5% unclear), 30% intralesional curettage (margins: 100% positive), and 22% stabilization only (margins: 100% positive). The local recurrence/progression rate differed between surgical strategies and was highest after stabilization only (39%), followed by intralesional curettage (22%), and metastasectomy (12%). However, reoperation rates were comparable between surgical strategies. Survival was best in patients who underwent metastasectomy; however, this difference did not hold when stratifying patients based on metastatic load. Local recurrence/progression rate was lower in patients who had a negative margin (5%) compared to those who had a positive margin (26%). However, we found no difference in overall reoperation rate based on margin status. Survival was best in patients who had negative margins.

The next chapter (**Chapter 10**) aims to develop an algorithm to estimate survival in patients with long bone metastases. We assessed what factors were independently associated with decreased survival, and used these risk factors to build three algorithms: a classic scoring system, a nomogram, and a boosting algorithm. After construction of each algorithm, we compared their accuracies at predicting 30-, 90-, and 365-day survival. This retrospective study included 927 patients who underwent surgery for a metastatic long bone lesion. We found that the following factors are independently associated with decreased survival: older age (hazard ratio [HR]: 1.02), additional comorbidity (HR: 1.2), body mass index less than 18.5 kg/m^2 (HR: 2.0), tumor type with poor prognosis (HR: 1.8), presence of multiple bone metastases (HR: 1.3), presence of visceral metastases (HR: 1.6), and low hemoglobin level (HR: 0.91). Survival estimates by the nomogram were moderately accurate for predicting 30-day (area under the curve [AUC], 0.72), 90-day (AUC, 0.75), and 365-day (AUC, 0.73) survival, and remained stable after correcting for optimism through fivefold cross validation. Boosting algorithms were better predictors of survival on the training datasets, but decreased to a performance level comparable to that of the nomogram when applied on testing datasets for all three timepoints. Accuracy of the classic scoring system was lowest for all prediction periods. Comorbidity status and body mass index are newly identified risk factors associated with survival, and should be accounted for when estimating survival. We recommend use of the nomogram due to its simplicity.

Finally, we studied the impact of perioperative blood transfusion on survival in patients who undergo surgery for long bone metastases (**Chapter 11**). Several studies demonstrate that perioperative allogeneic blood transfusions increase the risk of tumor recurrence and decrease survival after surgery for primary cancers. It is unclear if this association exists in patients who undergo surgery for long bone metastases. We included 789 patients who underwent surgery for a long bone metastatic lesion in this retrospective study. We assessed exposure versus no exposure as well as a dose-response relationship per unit of blood transfused and its association to survival while controlling for possible confounding variables. Exposure to blood transfusion (HR: 1.06) was not associated with worse survival; however, we did find a dose-response relationship with an increased risk of death per unit of blood transfused (HR: 1.07). Our sample size might have been insufficient to demonstrate an effect of exposure versus no exposure. Perioperative blood transfusion in patients who undergo surgery for long bone metastases might negatively influence survival, although the effect is small.

SUMMARIZED ANSWERS TO PRIMARY STUDY QUESTIONS

Part I: Metastatic Femoral Lesions

Is there a difference in outcome –physical function, reoperations, and complications– between endoprosthetic reconstruction, intramedullary nailing, and open reduction internal fixation for proximal femoral metastasis?

- Overall reoperation rates are comparable for endoprosthetic reconstruction and intramedullary nailing, but is higher after open reduction internal fixation (**Chapter 3**).
- Fixation failure leading to reoperation is more common after open reduction internal fixation and intramedullary nailing, while deep infection leading to reoperation occurs more often after endoprosthetic reconstruction (**Chapter 2 & 3**).
- Systemic complication rates do not differ between surgical strategies (**Chapter 2**).
- All three surgical strategies result in reasonable function on average. However, wide ranges indicate that both poor and good functional levels are obtained. In addition, functional outcome was only scarcely reported and difference in their use preclude pooling of results and comparison between surgical strategies (**Chapter 3**).

What questionnaire is most useful for measurement of physical function in patients with lower extremity bone metastasis?

- The PROMIS Physical Function Cancer questionnaire is the most useful questionnaire due to its reliability over a wide range of ability levels, validity, brevity, and good coverage (**Chapter 4**).

Can a CT-scan based algorithm predict occurrence of a pathological fracture through a metastatic femoral lesion?

- An attenuation coefficients (Hounsfield units) based algorithm can predict occurrence of a pathological fracture when focusing on cortical bone. However, the accuracy of this method is moderate and comparable to radiographic measurements and symptoms (**Chapter 5**).

Part II: Metastatic Humeral Lesions

What outcome –physical function, reoperations, and complications– can be expected after surgical treatment of humeral metastasis?

- In our systematic review, reoperation rates were 0 to 10% after intramedullary nailing, 5 to 14% after plate-screw fixation, 0 to 6% after endoprosthetic reconstruction, and 14 to 16% after diaphysis prosthesis (**Chapter 6**). In our cohort study, we found reoperation rates of 6.7% after intramedullary nailing, 10% after plate-screw fixation, and 11% after endoprosthetic reconstruction. Deep infection, nonunion, peri-implant fracture, and tumor progression are the most common reasons for reoperation (**Chapter 7**).
- In our systematic review, definitions of systemic complications varied substantially among studies or were poorly reported (**Chapter 6**). In our cohort study, we found a systemic complication rate of 5.8% (**Chapter 7**).
- In our systematic review, we found that patient reported outcome measures such as physical function have not been reported (**Chapter 6**).

What factors are associated with reoperations and systemic complications after surgical treatment of humeral metastasis?

- No factors are independently associated with reoperation. However, the probability of undergoing reoperation increases considerably with longer survival (**Chapter 7**).
- A prognostic survival score (the modified Bauer score, including tumor type and degree of tumor dissemination) is an independent predictor of developing postoperative systemic complications (**Chapter 7**).

Is there a difference in surgical decision making for humeral metastasis based on physician, patient, or tumor characteristics?

- Orthopaedic oncologists are more likely to recommend endoprosthetic reconstruction and plate-screw fixation, and less likely to recommend intramedullary nailing compared to other subspecialty surgeons (**Chapter 8**).
- Recommendation for specific implants differ based on tumor type, life expectancy, and anatomical location, but does not differ based on fracture type (**Chapter 8**).

Part III: Survival

Is there a difference in local tumor recurrence, reoperation, and survival between metastasectomy, intralesional resection, and stabilization only for renal cell metastasis?

- The local recurrence rate differs between types of treatment and is highest after stabilization only, followed by intralesional curettage, and lowest after metastasectomy (**Chapter 9**).
- Reoperation rates do not differ between stabilization only, intralesional curettage, and metastasectomy (**Chapter 9**).
- Survival is best in patients who underwent metastasectomy, when compared to stabilization only and intralesional curettage; however, this difference does not hold when stratifying patients based on metastatic load (**Chapter 9**).

What factors are associated with worse survival among patients who underwent surgery for long bone metastases?

- Older age, comorbidity, low body mass index, tumor type with poor prognosis, presence of multiple bone metastases, presence of visceral metastases, and low hemoglobin level are independently associated with worse survival (**Chapter 10**).

What type of algorithm is most accurate for predicting survival probability after surgery for long bone metastases?

- The nomogram is moderately accurate for predicting 30-day, 90-day, and 365-day survival (**Chapter 10**).

Are allogeneic blood transfusions associated with worse survival after surgery for long bone metastases?

- Exposure to blood transfusion is not associated with worse survival; however, we did find a dose-response relationship with an increased risk of death per unit of blood transfused (**Chapter 11**).