Surgical decision-making for long bone metastases

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CHAPTER 7

Complications After Surgery For Metastatic Humeral Lesions

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ABSTRACT

Objectives

To establish surgical outcome after treatment of humeral metastases.

Design

Retrospective cohort study.

Setting

Two tertiary care referral centers for orthopaedic oncology.

Participants

295 consecutive patients with humeral metastases who underwent surgery between 1998 and 2013.

Interventions

Proximal lesions were treated by intramedullary nailing (43%, n = 57), endoprosthetic reconstruction (34%, n = 46), open reduction and internal fixation using plate and screws (22%, n = 30), and a combination (n = 1). Diaphyseal lesions were treated by intramedullary nailing (69%, n = 91), and open reduction and internal fixation using plate and screws (30%, n = 39), and a combination (n = 1). Distal lesions were treated by open reduction and internal fixation using plate and screws (97%, n = 29) and intramedullary nailing (3.3%, n = 1).

Outcome Measures

Primary outcome measures were reoperations and 30-day systemic complications. Secondary outcome measures were total estimated blood loss, anesthesia time, duration of hospital admission, and 30-day survival.

Results

We found 25 (8.5%) reoperations and 17 (5.8%) patients had 18 systemic complications; pneumonia (3.7%, n = 11), pulmonary embolism (1.3%, n = 4), sepsis (0.68%, n = 2), and fat embolism (0.34%, n = 1). No factors were independently associated with reoperation. Logistic regression analysis demonstrated that favorable cancer status (i.e. a higher modified Bauer score: OR 0.48, 95% CI: 0.29 – 0.80, $p = 0.005$) was independently associated with a decreased systemic complication rate.

Conclusion

Poor cancer status is an independent predictor of postoperative systemic complications. This could help inform the patient and anticipate postoperative problems.

INTRODUCTION

Indications for surgery of a metastasis, myeloma, or lymphoma lesion of the humerus vary from a completed pathological fracture, through a lesion at risk for fracture (i.e. impending fracture), to a solitary lesion. The decision for surgery is not always clear and many factors are considered including expected survival, systemic load, anatomical location, tumor type, size of the lesion, fracture risk, and expected outcome.[1-4] Several criteria are proposed to assess the fracture risk, of which the Mirels classification is most commonly used.[5] Metastasectomy is occasionally warranted in patients with a solitary metastasis as some studies suggest that this improves survival in patients with renal cell carcinoma;[6,7] however, this finding is contradicted by others.[8,9] Surgical treatment for metastatic humerus lesions is often palliative and aims to stabilize the bone for the remaining lifetime of the patient to preserve quality of life while minimizing the risk of complications.[2,4,10] Most previous studies are relatively small and focus on a single surgical technique.[2,11,12]

This study aims to assess the outcome –reoperation and 30-day systemic complication rate– of surgery in a larger cohort of patients with metastatic humerus lesions treated in various ways. Our null hypothesis was that there are no factors associated with reoperation and complications among patients surgically treated for metastatic humerus lesions. Additionally, we assessed differences in estimated blood loss, anaesthesia time, duration of hospital admission, and 30-day survival among surgical strategies. Knowledge of complication rate and its predictors can help inform the patient and aid surgical decision making.

METHODS

Study Design

We assessed reoperations and 30-day systemic complications, and risk factors for these outcomes, in patients who underwent surgery for metastatic humerus lesions. Medical record data was obtained of patients who had an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for a metastatic fracture (code: 733.11) or a Current Procedural Terminology (CPT) code (code: 24391 and 24498) for prophylactic fixation of the humerus between 1998 and 2013 at two tertiary care referral centers for orthopaedic oncology. We reviewed all medical records of identified patients to assess eligibility. A final consecutive series of 295 patients with a metastatic humerus lesion –impending or pathological fractures– was included. We included only the first surgery per patient if patients had bilateral lesions (12 patients) so as to not violate the assumption of independence.[13] Inclusion criteria were patients older than 18 years who underwent intramedullary nailing, open reduction and internal fixation with plate and screws, endoprosthetic reconstruction, or a combination. No patients underwent distal or intercalary endoprosthetic reconstruction. We included patients regardless of followup duration as we considered all reoperations, short-term and long-term, to be relevant. We included metastases from solid tumors, multiple myeloma, and lymphoma. We excluded patients who underwent only revision surgery at our institutions or who underwent fixation with non-interlocking nails (4 patients were treated with Rush rods).

Surgical Strategies

The surgeon, together with the patient, decided for surgery and selected the surgical strategy on the basis of life expectancy, systemic load, tumor type, location, and size of the lesion. Orthopaedic oncologists performed 286 of the 295 (97%) surgeries, the remainder were performed by trauma surgeons.

There were 237 (80%) pathological fractures and 58 (20%) impending fractures. Proximal lesions without significant involvement of the humeral head were treated by intramedullary nailing (43%, 57 of 134 cases; 45 pathological and 12 impending fractures), plate-screw fixation (22%, 30 of 134 cases; 23 pathological and 7 impending fractures), or a combination of these techniques (0.75%, 1 of 134 cases; 1 pathological fracture). Cement was used in 7 of 57 intramedullary nailing cases (12%): in 1 cases after curettage of the tumor and in 6 cases to create a strong construct for the proximal interlocking screws in the humeral head. Cement was used in 25 of 30 plate-screw fixations (83%), an osteoarticular allograft was used in combination with plate-screw fixation after proximal humerus resection in one patient with renal cell carcinoma (3.3%, 1 of 30 cases). Endoprosthetic reconstruction was used for 46 (34%, 46 of 134 cases; 43 pathological and 3 impending fractures) proximal humeral lesions after resection of the humeral head (17 humeral head hemiarthroplasties) or proximal humerus (29 modular tumor prostheses). Five of the 17 (29%) humeral head replacements were combined with a proximal intercalary allograft (3 renal cell, 2 breast carcinomas). Cement was used in 43 of 46 (93%) endoprosthetic reconstruction cases.

Diaphyseal lesions were treated by non-cemented intramedullary nailing (69%, 91 of 131 cases; 70 pathological and 21 impending fractures), plate-screw fixation (30%, 39 of 131; cases 28 pathological and 11 impending fractures), or a combination of these techniques (0.76%, 1 of 131 cases; 1 impending fracture). Cement was used in 19 of 39 (49%) plate-screw fixation cases. Six patients (2 renal cell, 1 breast, 1 lung carcinoma, and 2 multiple myeloma) underwent a segmental resection of the humeral shaft followed by intercalary allograft placement and plate screw fixation (15%, 6 of 39 cases).

Distal lesions were mainly treated by plate-screw fixation (97%, 29 of 30 cases; 26 pathological and 3 impending fractures); cement was used in 24 cases (83%). The remaining case (3.3%; 1 pathological fracture) was treated with an non-cemented intramedullary nail.

The type of operation, as outlined above, varied on the basis of the location of the lesion ($p < 0.001$, by Fisher exact test) and the type of fracture ($p = 0.037$, by Fisher exact test).

All intramedullary nails were interlocking and inserted in an antegrade fashion. Postoperative care and rehabilitation varied among patients depending on their health status.

Outcome Measures

Our primary outcome was reoperation in one of the two hospitals. Only the first reoperation was taken into account. Two research fellows (S.J., M.v.D.) independently screened all reports of subsequent procedures to identify reoperations.

The secondary outcome was non pre-existing systemic complications –pneumonia, pulmonary embolism, fat/cement embolism, myocardial infarction, and sepsis– within 30 days after index surgery. These systemic complications were identified through disease specific ICD-9-CM codes (Appendix 1). Medical records of patients with one of these codes were reviewed independently by two research fellows (S.J., M.v.D.) to assess if the complication fulfilled the predefined criteria: (1) pneumonia was defined as symptoms clinically consistent with pneumonia and a positive sputum culture or empirical start of antibiotics; (2) the diagnosis pulmonary, fat or cement embolism was based on computed tomography or ventilation/perfusion scan; (3) the diagnosis myocardial infarction was based on electrocardiography or echocardiography; and (4) sepsis was defined as Systemic Inflammatory Response Syndrome requiring intensive care unit admission with a positive culture. Any discordant judgments were resolved by consensus discussion.

We obtained data on the following variables through chart review: age, body mass index, sex, comorbidities, cancer status, tumor type, systemic load, type of fracture (pathological or impending), location of the lesion, preoperative local radiation and systemic therapy, postoperative local radiation and systemic therapy, type of operation, allograft use, reaming, cementation, concomitant procedures (e.g. femoral fixation during same surgery), white blood cell count (in K/uL), duration of hospital admission, anesthesia time, and estimated blood loss.

We scored bone metastatic lesions using Mirels' classification to demonstrate the fracture risk of the impending fractures. The total score, based on 4 aspects of the bone lesion (site of the lesion [all upper extremity], pain, lesion type, and lesion size), varies from 4 to 12; 4 being at low risk of fracture, and 12 being at high risk of fracture.[5] According to Mirels, a score of 8 and above is suggestive of an impending fracture.[5,14,15] We reviewed radiographs to establish the lesion type (blastic/mixed/lytic) and size (<1/3, 1/3-2/3, >2/3).[5,14,15] Description of pain level in the medical record was used to assess if the pain was mild (including "no pain", "mild pain", or a pain score below 4 [numeric pain rating scale: 0-10]), moderate (including "moderate pain" or a pain score between 4 and 8), or functional (including "severe pain", "significant pain", a pain score of 8 and higher, or any pain that increased with loading).[5,14,15]

The modified Charlson Comorbidity Index was used to assess comorbidity status and determined through an algorithm based on ICD-9-CM codes given prior to surgery (Appendix 2). The Modified Charlson Comorbidity Index is based on 12 comorbidities and the score ranges from 0 to 24 with a higher score indicating more severe comorbidity status.[16-18]

We used the modified Bauer score as a surrogate marker for cancer status.[1,19] The modified Bauer score is most commonly used to estimate survival and is a summary score of four prognostic factors: (1) no visceral metastases, (2) no lung cancer, (3) breast, renal cell, multiple myeloma, or lymphoma as primary tumor type, and (4) a solitary skeletal metastasis.[1,19] The score ranges from 0 to 4 with a lower score indicating worse prognosis.[1,19] A patient with breast cancer with a single bone metastatic lesion and no visceral metastases is assigned a score of 4 (indicating relatively good prognosis).

We categorized tumor type into thyroid, renal cell, and other; as the former two are relative radioresistant tumors and have a relatively good prognosis and are therefore potentially more likely to recur leading to failure of the fixation mandating reoperation.[4,20]

Followup

The median followup was 4 months (interquartile range [IQR] 1 to 14 months, range 0 months to 10 years). One hundred and sixty-four (56%) patients were alive at followup after 3 months, 79 (27%) were deceased and 52 (18%) were lost to followup. After 6 months; 130 (44%) patients were still in followup, 116 (39%) deceased, and 49 (17%) were lost to followup. One year after surgery, 85 (29%) were still in followup, 150 (51%) patients were deceased, and 60 (20%) were lost to followup.

Statistical Analysis

Variables were presented with frequencies and percentages for categorical variables and as mean with standard deviation (SD) for continuous variables. Cases were not included in the respective analyses that had missing values for one of these variables: body mass index (18%, 54 of 295 cases), estimated blood loss (11%, 31 of 295 cases), white blood cell count (9.5%, 28 of 295 cases), duration of hospital admission (0.68%, 2 of 295 cases), and anesthesia time (26%, 77 of 295 cases).

The association between the response variable "reoperation" and explanatory variables was assessed using univariate Cox regression analysis. Unadjusted hazard ratios (HR) with 95% confidence intervals (CI) –indicating the relative likelihood of reoperation in one group as compared to another group– are presented to quantify the association of explanatory variables with reoperation. Multivariable Cox regression analysis –including all variables marginally associated with reoperation (i.e. $p < 0.10$) in bivariate analysis– was used to assess if variables were independently associated with reoperation. Cox regression analysis accounts for variable lengths of followup and survival. We used Kaplan-Meier curves to plot probability of survival and reoperation in our cohort. Testing the Schoenfeld residuals indicated no violation of the proportional hazard assumption.

The association between the response variable "30-day systemic complication" and explanatory variables was demonstrated using unadjusted odds ratios (OR) with 95% confidence intervals derived from logistic regression analysis. Multivariable logistic regression analysis –including all variables with a *p* value below 0.10 in bivariate analysis– was used to assess if variables were independently associated with systemic complications. Postoperative adjuvant treatment was not included in these analyses as it is often given after the 30-day period.

Variation in blood loss, anesthesia time, and duration of hospital admission between surgical strategies was tested using one-way analysis of variance (ANOVA). Difference in 30-day survival was tested using the Fisher exact test.

All statistical analyses were performed using Stata® 13.0 (StataCorp LP, College Station, TX, USA). A two-tailed p value less than 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

Among the 295 cases, 143 were men (48%) and the mean age was 63 years (Table 1). Of the 58 cases with an impending fracture; 1 (1.7%) had a Mirels score of five, 3 (5.2%) had a score of seven, 11 (19%) had a score of eight, 28 (48%) a score of nine, and 13 (22%) a score of ten. Establishing the Mirels score was not possible in two cases (3.4%, 2 of 58 cases) due to missing radiographs. Most bone metastases included lung (24%), breast (17%) and renal cell carcinoma (15%) (Table 2).

Reoperations

We found 25 reoperations (8.5%, 25 of 295 cases) (Table 3). Primary reasons for the 25 reoperation in our cohort were: deep infection (2.0% [6 of 295 cases]), nonunion (2.0% [6 of 295 cases]), peri-implant fracture (1.4% [4 of 295 cases]), allograft nonunion (1.0% [3 of 295 cases]), massive hematoma (0.68% [2 of 295 cases]), tumor progression (0.68% [2 of 295 cases]), compartment syndrome (0.34% [1 of 295 cases]), and early plate loosening in an intercalary allograft construct (0.34% [1 of 295 cases]). There were 5 local progressions (3 renal cell, 1 lung, and 1 colorectal metastasis) of which 3 coincided with other reasons for reoperation (Table 3).

Acknowledging the variation in indications among the surgical strategies, we found that 5 of the 46 (11%) patients who underwent endoprosthetic reconstruction required reoperation; 3 cases for deep infection and 2 cases for massive hematoma. The reoperation

Table 1: Demographics and baseline characteristics

	n = 295
	Mean (± Standard Deviation)
Age (in years)	63 (±12)
Body mass index*	28 (±6.0)
Modified Charlson Comorbidity Index	6.5 (±2.1)
Modified Bauer score	2.1 (±1.1)
White blood cell count (in K/uL)*	9.4 (±5.0)
Estimated blood loss (in mL)*	323 (±438)
Duration of hospital admission (in days)*	6.4 (±5.9)
Anesthesia time (in minutes)*	209 (±70)
	n (%)
Men	143 (48)
Visceral metastases	124 (42)
Multiple bone metastases	222 (75)
Pathological fracture	237 (80)
Anatomical location	
Proximal humerus	134 (45)
Diaphyseal humerus	131 (44)
Distal humerus	30 (10)
Previous local radiotherapy	64 (22)
Previous systemic therapy	177 (60)
Operation	
Intramedullary nailing	149 (51)
Plate-screw fixation	98 (33)
Proximal endoprosthetic reconstruction	46 (16)
Intramedullary nailing + plate screw fixation	2 (0.68)
Allograft	12 (4.1)
Reaming	121 (41)
Cement	119 (40)
Concomitant other surgery†	22 (7.5)

* Body mass index was available in 241 (82%) cases, white blood cell count in 267 (91%), estimated blood loss in 264 (89%), duration of hospital admission in 293 (99%), and anesthesia time in 218 (74%).
† 20 patients underwent concomitant fixation of a femur metastatic lesion, 1 for a tibia metastatic lesion, and 1 patient underwent concomitant fixation of a femur metastatic lesion and decompression of the L3 nerve root due to spine metastases.

rate was 10% (10 of 98 cases) for patients who underwent plate-screw fixation and 6.7% (10 of 149) for those who underwent intramedullary nailing.

Table 2: Tumor distribution

	n = 295
Bone metastases:	**n (%)**
Lung	70 (24)
Breast	50 (17)
Renal cell	43 (15)
Unknown	17 (5.8)
Prostate	14 (4.7)
Thyroid	10 (3.4)
Esophageal	6 (2)
Melanoma	6 (2)
Colorectal	4 (1.4)
Adenocarcinoma of unknown origin	3 (1.02)
Bladder	2 (0.68)
Hepatocellular	2 (0.68)
Pancreatic	2 (0.68)
Gastric	1 (0.34)
Primary bone tumors:	**n (%)**
Myeloma	54 (18)
Lymphoma	11 (3.7)

The proportion of patients who required reoperation increased considerably with time from 2.6% at 1 month up to 19% at two years (Figure 1). Survival is longer in patients who underwent a reoperation (median: 60 months, IQR 22 to 110 months) compared with those who did not (median: 9 months, IQR 3 to 36 months; $p = 0.002$, by log-rank test), indicating that longer survival is associated with a higher risk of reoperation.

We found that higher white blood cell count (HR 1.11, 95% CI: 1.02 to 1.20, $p = 0.010$), higher body mass index (HR 1.06, 95% CI: 1.00 to 1.13, $p = 0.078$), and longer anesthesia time (HR 1.01, 95% CI: 1.00 to 1.01, $p = 0.057$) were marginally associated with a higher risk of reoperation in bivariate analyses (Appendix 3). None of the other explanatory variables (e.g. sex, age) were associated with reoperation (Appendix 3). Multivariable Cox regression analysis –including white blood cell count, body mass index, and anesthesia time– demonstrated that none of the factors were independently associated with the outcome reoperation: white blood cell count ($p = 0.73$), body mass index ($p = 0.21$), and anesthesia time ($p = 0.35$).

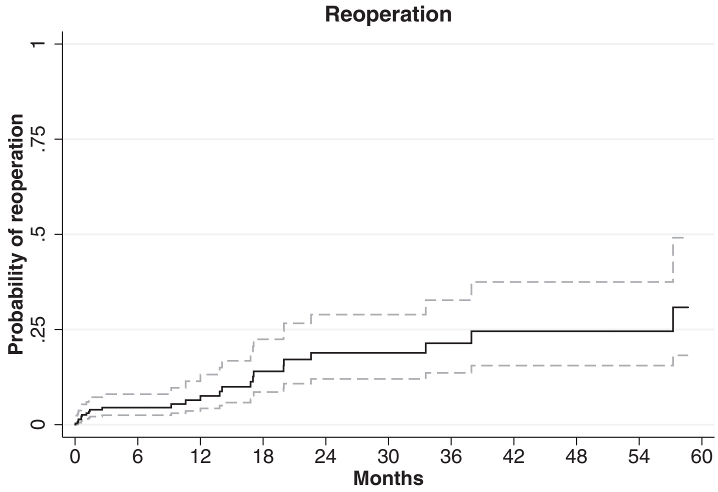
Table 3: Reoperations

Sex, age	Fracture type	Humerus Location	Tumor type	Operation	Implant type	Reason for reoperation	Months, Reoperation
Male, 65	Pathological	Proximal	Prostate	IMN	Interlocking nail	Deep infection	0, Debridement
Male, 68	Pathological	Diaphysis	Lymphoma	IMN	Interlocking nail	Peri-implant fracture	1, Additional plate fixation with 2 plates
Female, 58	Pathological	Proximal	Lung	IMN	Interlocking nail	Compartment syndrome	1, Fasciotomy
Female, 42	Pathological	Proximal	Breast	IMN	Interlocking nail	Nonunion	9, Plate fixation and bone graft
Male, 61	Pathological	Diaphysis	Renal cell	IMN	Interlocking nail	Nonunion, tumor recurrence	10, Tumor resection and placement modular prosthesis
Female, 69	Pathological	Diaphysis	Breast	IMN	Interlocking nail	Nonunion	14, Nail replacement and bone grafting
Female, 78	Pathological	Proximal	Breast	IMN	Interlocking nail	Nonunion	17, Nail removal and bone grafting
Female, 62	Pathological	Proximal	Lung	IMN	Interlocking nail	Peri-implant fracture	20, Additional plate fixation and bone graft
Female, 61	Pathological	Diaphysis	Lung	IMN	Interlocking nail	Nonunion and nail loosening	34, Nail removal, plate fixation with bone graft
Male, 72	Pathological	Proximal	Renal cell	IMN	Interlocking nail	Tumor recurrence	58, Tumor resection and allograft with head prosthesis
Male, 29	Pathological	Proximal	Myeloma	Prox EPR	Modular prosthesis	Hematoma, compartment syndrome	0, Debridement
Female, 52	Pathological	Proximal	Breast	Prox EPR	Humeral head prosthesis	Hematoma, followed by deep infection	0, Debridement
Female, 53	Pathological	Proximal	Lymphoma	Prox EPR	Humeral head prosthesis	Deep infection	1, Debridement
Female, 66	Pathological	Proximal	Breast	Prox EPR	Humeral head prosthesis	Deep infection	17, Debridement, prosthesis removal, placement spacer
Male, 72	Pathological	Proximal	Myeloma	Prox EPR	Modular prosthesis	Deep infection	38, Debridement, and replacement prosthesis
Female, 44	Pathological	Proximal	Lung	PSF	1 plate	Peri-implant fracture	0, Plate removal and placement of modular prosthesis

Table 3: Reoperations (*continued*)

Sex, age	Fracture type	Humerus Location	Tumor type	Operation	Implant type	Reason for reoperation	Months, Reoperation
Male, 62	Pathological	Proximal	Breast	PSF	1 plate	Deep infection	1, Debridement
Male, 79	Pathological	Diaphysis	Renal cell	PSF	1 plate + intercalary allograft	Hardware loosening distal allograft	1, Refixation with 2 new plates distally
Female, 93	Pathological	Distal	Lymphoma	PSF	1 plate	Peri-implant fracture	1, Refixation with additional plate
Female, 49	Impending	Proximal	Colorectal	PSF	2 plates	Deep infection, tumor recurrence	3, Debridement and removal of hardware
Female, 77	Pathological	Distal	Breast	PSF	1 plate	Nonunion	12, Hardware removal, refixation 2 plates and bone graft
Male, 57	Pathological	Proximal	Renal cell	PSF	1 plate + osteoarticular allograft	Allograft nonunion	14, Humeral head prosthesis with new allograft
Female, 54	Impending	Proximal	Renal cell	PSF	1 plate + intercalary allograft	Allograft nonunion, tumor recurrence	17, Allograft and tumor resection, new allograft + 1 plate
Female, 43	Pathological	Proximal	Breast	PSF	1 plate + intercalary allograft	Allograft nonunion and broken plate	20, Revision plate fixation with bone graft
Male, 80	Pathological	Diaphysis	Lung	PSF	1 plate	Plate loosening, tumor recurrence	23, Curettage, plate refixation and cement

Prox EPR = proximal endoprosthetic reconstruction, IMN = intramedullary nailing, PSF = plate-screw fixation



N at risk: 295 129 85 61 46 37 28 19 17 14 9

Figure 1: Kaplan-Meier failure plot demonstrating the probability of reoperation among all patients (solid black line) with 95% Confidence interval (CI) (gray dashed line). The probability of reoperation was 2.6% at 1 month (95% CI: 1.3% to 5.4%), 4.5% at 3 months and 6 months (95% CI: 2.5 to 8.1%), 7.6% at one year (95% CI: 4.3% to 13%), and 19% at two years (95% CI: 12% to 29%).

Systemic Complications

Seventeen patients (5.8%) had 18 postoperative systemic complications: pneumonia (3.7% [11 of 295]), pulmonary embolism (1.3% [4 of 295]), sepsis (0.68% [2 of 295]), and fat embolism (0.34% [1 of 295]) (Appendix 4). There was no case of myocardial infarction and no patient died intraoperatively. The fat embolism occurred while reaming the humeral shaft for intramedullary nailing resulting in a transient drop in saturation and blood pressure (Appendix 4).

Bivariate analysis demonstrated that poor cancer status (modified Bauer score: OR 0.47, 95% CI: 0.29 to 0.75, $p = 0.001$) and longer duration of hospital admission (OR 1.08, 95% CI: 1.02 to 1.14, $p = 0.008$) were associated with an increased systemic complication rate. The complication rate was lower among patients who underwent plate-screw fixation as compared to those who underwent intramedullary nailing (OR 0.22, 95% CI: 0.05 to 0.99, $p = 0.048$). None of the other included variables were associated with complications in bivariate analyses. However, when controlling for possible confounding in a multivariable logistic regression analysis we only found the modified Bauer score to be independently associated with the outcome systemic complications (OR 0.48, 95% CI: 0.29 to 0.80, $p = 0.005$) (plate-screw fixation as compared to intramedullary nailing [$p = 0.47$], hospital duration [$p = 0.11$], and use of cement [$p = 0.26$]). This means that having a relatively poor prognosis –as indicated by a lower Bauer score– is associated with a higher rate of systemic complications.

The complication rate per modified Bauer score category was 18% (5 of 28) for score zero, 8.6% (5 of 58) for score one, 5.8% (5 of 86) for score two, 2.1% (2 of 95) for score three, and 0% (0 of 28) for score four. This further explains its association with complications.

Additional outcomes

The mean estimated blood loss differed between treatment types and was 165mL (SD: 174) after intramedullary nailing, 472mL (SD: 530) after plate screw fixation, and 600mL (SD: 640) after endoprosthetic reconstruction ($p < 0.001$). The mean anesthesia time did not differ between treatments ($p = 0.32$) and was 201 (SD: 68) minutes after intramedullary nailing, 212 (SD: 71) minutes after plate-screw fixation, and 227 (SD: 70) minutes after endoprosthetic reconstruction. The mean duration of hospital admission did not differ between treatments ($p = 0.07$): 6.4 (SD: 6.5) days after intramedullary nailing, 5.6 (SD: 4.5) days after plate-screw fixation, and 8.0 (SD: 6.5) after endoprosthetic reconstruction.

By the last moment of followup, 220 (75%) patients were deceased; the median survival was 11 months (IQR: 3 to 40 months) (Figure 2). The 30-day survival was 92% and did not differ between surgical strategies ($p = 0.99$): 92% after intramedullary nailing, 92% after plate-screw fixation, and 93% after endoprosthetic reconstruction.

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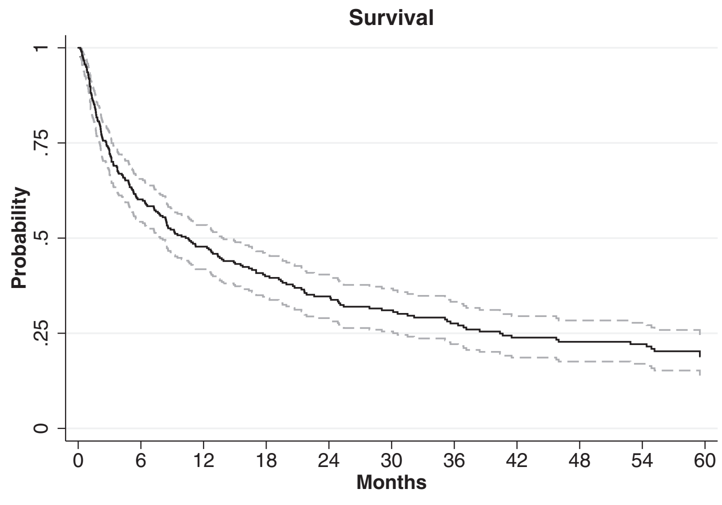

N at risk: 295 168 127 94 77 66 52 45 41 36 27

Figure 2: Kaplan-Meier survival plot demonstrating probability of survival (solid black line) with 95% Confidence interval (CI) (gray dashed line). Median survival is 321 days (95% CI: 239 to 423), with an interquartile range from 82 (95% CI: 62 to 97) to 1228 (95% CI: 930 to 1810) days.

DISCUSSION

Understanding outcomes after surgical treatment of metastatic humerus lesions could help inform the patient and aid surgical decision-making. Previous studies are limited by their relatively small sample size. We aimed to assess reoperation and systemic complication rates and assessed factors associated with these outcomes in a relatively large cohort of patients from two institutions. We found an overall reoperation rate of 8.5%, and a systemic complication rate of 5.8%. None of the included variables were found to be independently associated with the outcome reoperation. We found that a lower modified Bauer score –indicating relatively poor prognosis– was independently associated with postoperative systemic complications.

There were several limitations. First, there were no uniform criteria for surgical treatment owing to the retrospective study design (i.e. selection bias). Decision for surgical strategy depends on many factors, and could have differed among surgeons or changed over time and might therefore have influenced the occurrence of reoperations. Second, reoperations and complications would have been missed if a patient went to a different hospital or deceased outside of the hospital because of a complication. The complication rates found in our study might therefore be an underestimation of the true complication rate. Third, the relatively low number of reoperations (n = 25 and systemic complications (18 in 17 patients) limited the number of variables we could include in the multivariable analyses. Therefore it was not possible to account for all potential confounders. Furthermore, a larger sample size might have resulted in more statistical power to detect subtle but relevant risk factors (type II error). For example, bivariate analysis demonstrated a trend towards a higher reoperation rate (HR 3.15, 95% CI: 0.74 to 13.42, $p = 0.12$) in patients with a pathological fracture as compared to those with an impending fracture; a larger sample size might have identified a difference. Fourth, followup and survival varied substantially among patients due to the severity of the underlying disease. We accounted for this by using time-dependent Cox regression analysis for reoperations and using a relatively short timeframe (30-days) for systemic complications.

The overall reoperation rate found in our study (8.5%) is comparable with reoperation rates reported in previous studies (ranging from 0 to 9%).[2] A study by Wedin et al. presented a large cohort of 214 surgically treated metastatic humerus lesions and found a reoperation rate (6.1%) after intramedullary nailing comparable to ours (6.7%).[21] However, we found a higher reoperation rate (11% vs. 6%) with endoprosthetic reconstruction and a lower rate with plate-screw fixation (10% vs. 14%).[21] Our reoperation rate (10%) after plate-screw fixation is comparable to the rate (11%) found in a large study by Weiss et al. focusing on plate-screw fixation (n = 63) for metastatic humerus disease.[12] Differences in reoperation rates might be explained by different indications for surgery and variation in technique. Consistent with previous studies we found that the proportion of patients who require reoperation increased considerably with time (Figure 3).[12] The finding that reoperations occur more often in patients who live longer emphasizes the importance of estimating life expectancy in these patients.[1,3,22]

In further exploring reasons for reoperation, it seems that nonunion is the main reason for late reoperation (6 months after the index surgery); about two-thirds (64%, 9 of 14 cases) of the late reoperations in our cohort were performed for nonunion, comparable to the results presented by Wedin et al. (67%, 6 of 9 late reoperations).[21] Peri-implant fractures and deep infections were more evenly distributed among early and late reoperations, while massive hematoma and compartment syndrome only occurred in the early postoperative period.[21] These findings might help the surgeon to anticipate these local complications.

The association of high white blood cell count with reoperation in bivariate analysis did not hold when accounting for potential confounding in multivariable analysis. We found no independent predictors of reoperation. This could be a result of the variation in reasons for reoperation (e.g. peri-implant fracture, nonunion, deep infection), which might have other underlying causes and corresponding risk factors. The study by Wedin et al. studied predictors of reoperations and found a higher rate among distal humerus lesions and tumors originating from the prostate.[21]

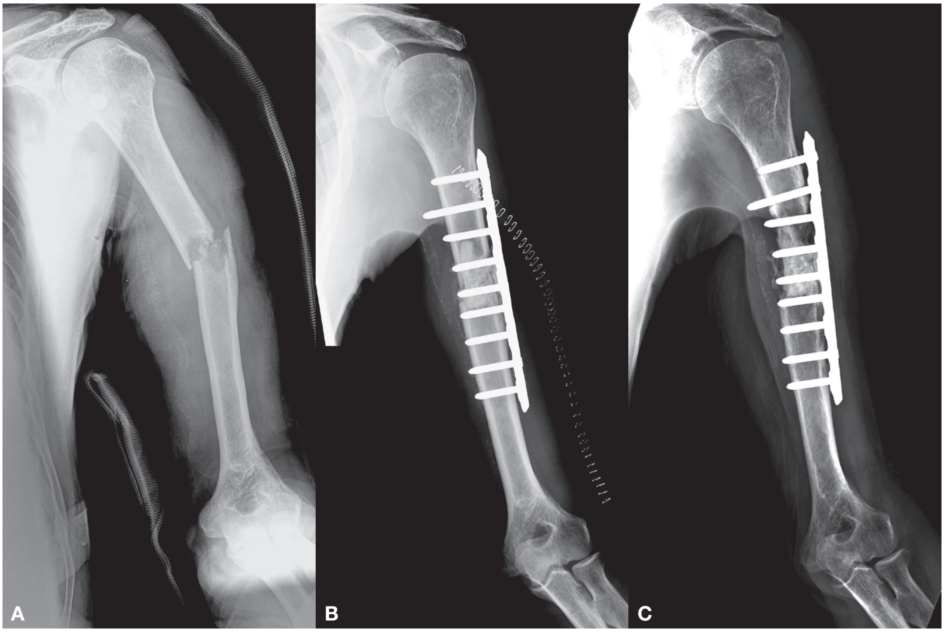

Figure 3: An 80 year old man presented with this (Figure 3A) pathological humerus fracture after lifting an object from the floor. Work-up revealed a non-small-cell lung carcinoma. Open reduction internal fixation was done using plate-screw fixation with cement augmentation after curettage of gross tumor (Figure 3B). The patient presented 2 years later with progressive arm pain, imaging demonstrated tumor recurrence and screw loosening (Figure 3C).

The systemic complication rate found in our study (5.8%) is also in line with previously published studies (0 to 26%).[2] Difference in the definition of systemic complication probably explains the substantial variation in reported rates. No intraoperative death occurred, which is in line with previous studies.[2] One patient had a transient intraoperative saturation and blood pressure drop during reaming of the humeral shaft; this was ascribed to a fat embolism. This potentially severe complication has been reported during fixation of metastatic femoral lesions;[23,24] however, it is very rare in treatment of metastatic humerus disease.[2]

Relatively poor cancer status (indicated by a low modified Bauer score) was the only independent predictor of developing systemic complications. Previous studies demonstrated that cancer status –as measured by the modified Bauer score– was associated with survival;[1,19] however, its association with complications –as far as we know– has not been shown before. This means that patients with a poor cancer status not only have a decreased life-expectancy, they also have a higher risk of postoperative systemic complications. Type of fixation seemed to be associated with complication risk in bivariate analysis; however, this association was confounded by a difference in Bauer score among surgical strategies as can be gleaned from the multivariable analysis. The Bauer score could be used for preoperative risk stratification to identify patients at higher risk for postoperative systemic complications.

In conclusion, we found a reoperation rate of 8.5% and a systemic complication rate of 5.8%. Poor cancer status was an independent predictor of postoperative systemic complications. This could help inform the patient and anticipate postoperative problems.

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Appendix 1: International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Codes Used to Flag Systemic Complications

Complication	Codes Flagged
Pulmonary embolism	451.11, 451.19, 451.2, 451.81, 451.9, 453.41, 453.42, 453.8, 453.9, 453, 453.4, 415.1, 415.11, 415.19, 453.9, 415.11, 415.12, 415.13, 415.19, 416.2, 444.1, 444.21, 444.22, 444.81, 444.89, 444.9, 445.01, 445.02, 445.81, 445.89, 453.2, 453.3, 453.40, 453.41, 453.42, 453.50, 453.51, 453.52, 453.6, 453.71, 453.72, 453.73, 453.74, 453.75, 453.76, 453.77, 453.79, 453.81, 453.82, 453.83, 453.84, 453.85, 453.86, 453.87, 453.89, 453.9
Pneumonia	481, 482.0, 482.1, 482.2, 482.30, 482.31, 482.32, 482.39, 482.40, 482.41, 482.49, 482.81, 482.82, 482.83, 482.84, 482.89, 482.9, 483.8, 485, 486, 495.7, 507
Sepsis	038.0, 038.10, 038.11, 038.19, 038.3, 038.40, 038.41, 038.42, 038.43, 038.44, 038.49, 038.8, 038.9, 790.7
Myocardial infarction	427.5, 410.00, 410.01, 410.10, 410.11, 410.20, 410.21, 410.30, 410.31, 410.40, 410.41, 410.50, 410.51, 410.60, 410.61, 410.70, 410.71, 410.80, 410.81, 410.90, 410.91

Appendix 2: Modified Charlson Comorbidity Index Algorithm Based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Codes

Comorbidity	Weight*	Codes
AIDS/HIV	4	042
Any malignancy, including leukemia and lymphoma*	2	150.0-159.0, 162-173.59, 173.70-175.9, 180.0-183.9, 185-186.9, 188.0-188.6, 188.8-189.4, 189.9, 191.0-192.3, 192.9-194.4, 200.2-202.38, 202.70-202.81, 203.0-204.22, 204.90-208.22, 208.90-209.36, 209.70, 209.72-209.79, 230.2-230.6, 230.8, 231.2, 231.9, 232.5-232.7, 233.0, 233.1, 233.31, 233.32, 233.4, 233.7, 235.2-235.4, 235.7, 235.8, 236.2, 236.4, 236.5, 236.7-236.91, 237.1-237.4, 237.6, 238.0-238.3, 238.79, 239.0-239.4, 239.6, 239.7, 239.89, 239.9
Chronic pulmonary disease	1	416.8, 416.9, 490-491.0, 491.2-495.2, 495.4-505, 506.4, 508.1, 508.8
Congestive heart failure	2	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428-428.43
Dementia	2	290, 290.0, 290.3, 290.8-290.43, 294.1, 294.11-294.21, 331.2
Diabetes with chronic complications	1	249.40-249.91, 250.40-250.90
Hemiplegia or paraplegia	2	342.00-342.92, 344.00-344.5, 344.89-344.9
Metastatic solid tumor*	6	197.0-198.7, 198.81-190.9, 192.0-196.9, 199.0
Mild liver disease*	2	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570, 570.1, 573.3, 573.4, 573.8, 753.9, V42.7
Moderate or severe liver disease*	4	456.0-456.2, 572.2-572.8
Renal disease	1	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582-583.7, 585-586, 588.0, V42.0, V45.1, V56-V56.8
Rheumatologic disease	1	466.5, 710.0-710.4, 714.0-714.2, 714.8, 725

*The following comorbidities were mutually exclusive: mild liver disease and moderate or severe liver disease, and any malignancy and metastatic solid tumor. For example, a patient with a metastatic solid tumor received 6 points total (not 6 points for metastatic solid tumor and 2 points for any malignancy).

Appendix 3: Bivariate analysis reoperations and 30 day systemic complications

	Reoperations		30-day Systemic complications	
	n = 295			
	Unadjusted hazard ratio (95% confidence interval)†	***p* value†**	**Unadjusted odds ratio (95% confidence interval)‡**	***p* value‡**
Age	0.99 (0.96 - 1.03)	*0.72*	0.99 (0.95 - 1.04)	*0.77*
Men	0.72 (0.32 - 1.60)	*0.42*	0.42 (0.15 - 1.23)	*0.12*
Body mass index*	1.06 (1.00 - 1.13)	*0.078*	0.97 (0.88 - 1.08)	*0.61*
Modified Charlson Comorbidity Index	0.94 (0.79 - 1.11)	*0.47*	0.99 (0.78 - 1.26)	*0.94*
Modified Bauer score	1.10 (0.74 - 1.62)	*0.63*	0.47 (0.29 - 0.75)	***< 0.001***
White blood cell count*	1.11 (1.02 - 1.20)	***0.01***	0.97 (0.88 - 1.08)	*0.63*
Estimated blood loss	1.00 (1.00 - 1.00)	*0.44*	1.00 (1.00 - 1.00)	*0.32*
Duration of hospital admission	1.02 (0.94 - 1.11)	*0.58*	1.08 (1.02 - 1.14)	***0.01***
Anesthesia time*	1.01 (1.00 - 1.01)	*0.057*	1.00 (0.99 - 1.01)	*0.85*
Tumor type				
Other tumor types	*reference value*	*reference value*	*reference value*	*reference value*
Thyroid	1.00 (1.00 - 1.00)	*0.99*	1.00 (1.00 - 1.00)	*0.99*
Renal cell	1.32 (0.50 - 3.52)	*0.58*	1.00 (1.00 - 1.00)	*0.99*
Pathological fracture	3.15 (0.74 - 13.42)	*0.12*	0.57 (0.19 - 1.67)	*0.30*
Anatomical location				
Proximal humerus	*reference value*	*reference value*	*reference value*	*reference value*
Diaphyseal humerus	0.58 (0.25 - 1.37)	*0.21*	1.16 (0.43 - 3.11)	*0.77*
Distal humerus	0.88 (0.20 - 3.90)	*0.87*	1.00 (1.00 - 1.00)	*0.99*
Preoperative local radiotherapy	1.28 (0.53 - 3.06)	*0.59*	1.03 (0.32 - 3.27)	*0.96*
Preoperative systemic therapy	0.58 (0.26 - 1.28)	*0.18*	0.94 (0.35 - 2.53)	*0.90*
Postoperative local radiotherapy	0.63 (0.29 - 1.40)	*0.26*	–	–
Postoperative systemic therapy	0.79 (0.33 - 1.90)	*0.60*	–	–
Operation				
Intramedullary nailing	*reference value*	*reference value*	*reference value*	*reference value*
Plate-screw fixation	1.32 (0.55 - 3.17)	*0.54*	0.22 (0.05 - 0.99)	***0.048***
Proximal endoprosthetic reconstruction	1.24 (0.42 - 3.67)	*0.69*	0.48 (0.10 - 2.19)	*0.34*
Intramedullary nailing + plate-screw fixation	1.00 (1.00 - 1.00)	*0.99*	1.00 (1.00 - 1.00)	*0.99*
Allograft	2.37 (0.80 - 6.98)	*0.12*	1.00 (1.00 - 1.00)	*0.99*
Reaming	1.13 (0.51 - 2.53)	*0.76*	1.29 (0.48 - 3.44)	*0.61*
Cement	1.07 (0.49 - 2.36)	*0.86*	0.30 (0.08 - 1.07)	*0.06*
Concomitant other surgery	1.42 (0.33 - 6.06)	*0.64*	2.92 (0.77 - 11.06)	*0.11*

bold font indicates a significant difference (two-tailed *p* value below 0.05).
* Body mass index was available in 241 (82%) cases, white blood cell count in 267 (91%), estimated blood loss in 264 (89%), duration of hospital admission in 293 (99%), and anesthesia time in 218 (74%).

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– Postoperative adjuvant treatment is not included in the analysis for systemic complications as it is frequently started after the 30 day period.
† Unadjusted hazard ratios with 95% confidence interval and *p* value were derived from univariate Cox regression analysis.
‡ Unadjusted odds ratios with 95% confidence interval and *p* value were derived from univariate logistic regression analysis.

Appendix 4: Systemic complications

						n = 17
Sex, age	**Fracture type**	**Humerus Location**	**Tumor type**	**Operation**	**Implant type**	**Complication within 30 days**
Female, 61	Pathological	Diaphysis	Lung	IMN	Interlocking nail	Pulmonary embolism
Male, 62	Pathological	Diaphysis	Lung	IMN	Interlocking nail	Pneumonia
Male, 68	Pathological	Diaphysis	Lymphoma	IMN	Interlocking nail	Pneumonia
Male, 58	Pathological	Proximal	Myeloma	IMN	Interlocking nail	Pneumonia
Female, 65	Pathological	Proximal	Lung	IMN	Interlocking nail	Pneumonia
Female, 39	Impending	Diaphysis	Breast	IMN	Interlocking nail	Pneumonia
Male, 66	Impending	Proximal	Prostate	IMN	Interlocking nail	Pneumonia
Male, 86	Pathological	Diaphysis	Lung	IMN	Interlocking nail	Pneumonia
Female, 62	Pathological	Proximal	Lung	IMN	Interlocking nail	Pneumonia
Female, 69	Pathological	Proximal	Lymphoma	IMN	Interlocking nail	Pneumonia
Female, 71	Pathological	Diaphysis	Lung	IMN	Interlocking nail	Sepsis
Female, 66	Pathological	Diaphysis	Pancreatic	IMN	Interlocking nail	Pulmonary embolism, sepsis
Female, 61	Impending	Diaphysis	Lung	IMN	Interlocking nail	Fat embolism
Female, 68	Impending	Proximal	Lung	Prox EPR	Humeral head	Pulmonary embolism
Female, 55	Pathological	Proximal	Lung	Prox EPR	Humeral head	Pulmonary embolism
Female, 51	Impending	Diaphysis	Lung	PSF	1 Plate	Pneumonia
Female, 44	Pathological	Proximal	Lung	PSF	1 Plate	Pneumonia

Prox EPR = proximal endoprosthetic reconstruction, IMN = intramedullary nailing, PSF = plate-screw fixation