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Surgical decision-making for long bone metastases

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CHAPTER 2

Complications After Surgery For Proximal Femoral Metastasis: A Retrospective Study Of 417 Patients

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ABSTRACT

Objectives

To compare outcomes among surgical strategies for proximal femoral metastases.

Design

Retrospective cohort study.

Setting

Two tertiary care referral centers for orthopaedic oncology.

Participants

417 consecutive patients with proximal femoral metastasis who underwent surgery between 1999 and 2014.

Interventions

Intramedullary nailing ($n = 302$), endoprosthetic reconstruction ($n = 70$), and open reduction and internal fixation ($n = 45$).

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

Reoperation rates did not differ among surgical strategies (5.3% after intramedullary nailing, 11% after endoprosthetic reconstruction, and 13% after open reduction and internal fixation; $p = 0.134$). When reasons for reoperation were assessed separately, fixation failure was most common after open reduction and internal fixation (13% versus 3.0% after intramedullary nailing and none after endoprosthetic reconstruction; $p < 0.001$), whereas deep infection was most common after endoprosthetic reconstruction (8.6% versus 2.0% after intramedullary nailing and none after open reduction and internal fixation; $p = 0.010$). Overall 30-day systemic complication rates did not differ among surgical strategies (8.3% after intramedullary nailing, 14% after endoprosthetic reconstruction, and 11% after open reduction and internal fixation; $p = 0.268$).

Conclusions

Implant-specific complications and their timing should be considered in the choice of surgical strategy. Analysis of secondary outcomes and risk factors for systemic complications could aid in surgical decision making.

INTRODUCTION

The proximal femur is the long bone most commonly affected by metastatic disease.^{1,2} Bone metastases weaken the bone and reduce load bearing capabilities. These changes can result in pain and eventually pathological fracture. Surgical treatment is often indicated in patients with pathological fracture, whereas indications are less clear in patients with non-fractured lesions.^{3,4} Factors considered in the decision to pursue surgical treatment and the selection of surgical technique include the location of the lesion, presence of a fracture, tumor type, cortical destruction, the patient's life expectancy, patient preferences, and the expected outcome.³⁻⁷

Only a few studies have rigorously compared outcomes among implant types.^{3,4} Although most studies are limited by retrospective design and inherent bias, they provide useful information about implant durability and complications.^{3-5,8} However, studies comparing surgical strategies need large numbers of patients because outcomes such as reoperation are relatively rare (6.4 to 10.3%).^{3,4} A survey study of 98 orthopaedic oncologists demonstrated large variation in the physicians' preferred surgical strategies, emphasizing the need for further study to improve understanding of surgical outcomes.⁹

The aim of this study was to assess reoperation rates and systemic complications after surgical treatment of patients with metastases and multiple myeloma of the proximal femur. Multiple myeloma was included because the surgical approach is comparable to metastatic lesions resulting from solid tumors.⁵ Specifically, we compared reoperation rate and 30-day systemic complication rate among surgical strategies. Secondly, we compared blood loss, anesthesia time, duration of hospital admission, and 30-day survival among surgical strategies. Additionally, we assessed risk factors for 30-day systemic complications.

METHODS

Study Design

This retrospective study was approved by our institutional review board. All electronic medical records of patients who had an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code for any pathological fracture (ICD-9-CM code 733.1) or a Current Procedural Terminology (CPT) code for prophylactic fixation of any bone (CPT codes 24498, 23491, 23490, 27495, 27187, 27745, 25490, 25492, 25491, or 24498) between January 1999 and January 2014 at two tertiary care referral centers for orthopaedic oncology were flagged. All flagged electronic medical records were manually reviewed to establish whether the patient fulfilled our predefined eligibility criteria. We included a consecutive series of 417 eligible patients who underwent

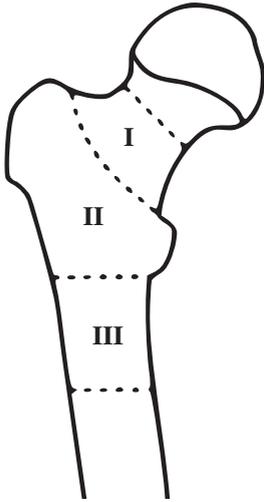


Figure 1: Illustration of the proximal femur demonstrating the anatomic areas included in the study. Area I consists of the isthmus to the base of the femoral neck, area II is the trochanteric region, and area III is the subtrochanteric region to 5 cm below the lesser trochanter. If the lesion spanned multiple areas, we included it in the area most affected by the lesion.

surgical treatment of a proximal femoral metastasis or myeloma. In the 21 patients who had bilateral lesions, we included only the first surgical procedure so as to not violate the assumption of independence.¹⁰ The proximal femur is defined as the region extending from the isthmus of the femoral neck to 5 cm below the lesser trochanter (Figure 1).¹¹ We excluded patients younger than 18 years, patients undergoing revision procedures, patients with substantial tumor involvement of the acetabulum, and patients with a lesion proximal to the isthmus of the femoral neck. The latter were excluded because these proximal lesions are almost exclusively managed with endoprostheses, hampering comparison of techniques. Patients were included regardless of followup duration because we considered both short-term and long-term outcomes to be relevant.

Surgical Strategies

Although preferences varied among surgeons, in general, a pathological fracture was treated surgically when the patient was expected to live longer than 30 days. An impending fracture was treated surgically when the patient was expected to live longer than 30 days and had substantial bone destruction or pain on load bearing. In terms of surgical strategy, proximal femur resection and endoprosthetic reconstruction was generally preferred in patients with extensive bone destruction (and therefore more often in patients with pathological fractures), in patients with tumors resistant to radiation therapy (e.g. renal cell carcinoma), and in patients with more proximal metastatic lesions. Intramedullary nailing was primarily used in patients with limited bone loss and trochanteric or subtrochanteric lesions. Open reduction and internal fixation (ORIF) was typically used in patients with small focal lesions around the trochanteric area.¹²

Ten orthopaedic oncologists performed 372 of 417 procedures (89%). These surgeons had a median of 10 years (range, 1 to 40 years) of experience at the time of the procedure. The remaining 45 procedures were performed by 34 trauma or arthroplasty surgeons who were not supervised by orthopaedic oncologists. No difference was found in reoperation rates between orthopaedic oncologists (7.3% [27 of 372]) and other surgeons (6.7% [3 of 45]) by the Fisher exact test ($p = 0.999$). The procedure was performed at hospital 1 for 237 patients (57%) and at hospital 2 for 180 patients (43%). No difference was found in the number of pathological fractures between institutions (40% [94 of 237] at hospital 1 and 44% [79 of 180] at hospital 2) by the Fisher exact test ($p = 0.422$).

Table 1: Surgical strategy by anatomic location

			n = 417
Anatomic location	Operation type	Implant type	n (%)
Neck area (I) (n = 59)	IMN (n = 28)	Intramedullary nailing	28 (47)
	EPR (n = 28)	Unipolar hemiarthroplasty	10 (17)
		Bipolar hemiarthroplasty	10 (17)
		Total Hip Arthroplasty	4 (7)
		Long-stem bipolar hemiarthroplasty	2 (3)
		MTP - Total Hip Arthroplasty	1 (2)
		MTP Bipolar hemiarthroplasty	1 (2)
	ORIF (n = 3)	Dynamic Hip Screw	3 (5)
	Trochanteric area (II) (n = 203)	IMN (n = 146)	Intramedullary nailing
EPR (n = 30)		MTP Bipolar hemiarthroplasty	15 (7)
		Long-stem bipolar hemiarthroplasty	6 (3)
		MTP - Total Hip Arthroplasty	3 (1)
		Total Hip Arthroplasty	2 (1)
		Bipolar hemiarthroplasty	2 (1)
		Long-stem Total Hip Arthroplasty	1 (0)
ORIF (n = 27)		Unipolar hemiarthroplasty	1 (0)
		1 Plate with screws in head/neck area	9 (4)
		Dynamic Hip Screw	18 (9)
Subtrochanteric area (III) (n = 155)	IMN (n = 128)	Intramedullary nailing	128 (83)
	EPR (n = 12)	MTP Bipolar hemiarthroplasty	11 (7)
		Long-stem bipolar hemiarthroplasty	1 (1)
	ORIF (n = 15)	1 Plate with screws in head/neck area	8 (5)
		2 Plates with screws in head/neck area	1 (1)
		1 Plate	1 (1)
		Long-plate with Dynamic Hip Screw	5 (3)

IMN = intramedullary nailing, EPR = endoprosthesis reconstruction, ORIF = Open Reduction and Internal Fixation, MTP = Modular Tumor Prosthesis

Most patients with femoral neck lesions (area I) were treated with endoprosthetic reconstruction (47% [28 of 59]) or non-cemented intramedullary nailing (47% [28 of 59]). The remaining three patients (5.1%) with femoral neck lesions were treated with ORIF, with cement packing after curettage of the lesion in two of those patients (Figure 1 and Table 1). Twenty-six of the 28 prostheses (93%) were cemented. Most patients with trochanteric lesions (area II) were treated with intramedullary nailing (72% [146 of 203]; 145 non-cemented, 1 cemented). The remaining patients with trochanteric lesions were treated with endoprosthetic reconstruction (15% [30 of 203], all cemented) or ORIF (13% [27 of 203]). In 16 of the 27 ORIF procedures (59%), cement was used after curettage of the lesion. Most patients with subtrochanteric lesions (area III) were treated with intramedullary nailing (83% [128 of 155]; 122 non-cemented, 6 cemented). The remaining patients with subtrochanteric lesions were treated with ORIF (10% [15 of 155]) or endoprosthetic reconstruction (8% [12 of 155], all cemented). In 9 of the 15 ORIF procedures (60%), cement was used after curettage of the lesion. Postoperative care and rehabilitation varied among patients depending on the severity of the underlying disease. However, immediate and unrestricted postoperative weight bearing was allowed in most patients.

Outcome Measures

The primary outcome measures were reoperation and 30-day systemic complications. We included any reoperation described in the medical record, but only the first reoperation was accounted for in the analyses. Two research fellows (S.J.J. and J.T.P.K.) independently reviewed all reports of subsequent surgeries to capture reoperations. We included the following systemic complications that occurred ≤ 30 days postoperatively: pneumonia, pulmonary embolism, fat/cement embolism, myocardial infarction, sepsis, and intraoperative death. All medical records of patients with an ICD-9-CM code for any of these complications (Appendix 1) were flagged and subsequently reviewed independently by two research fellows (S.J.J. and J.T.P.K.) to assess whether the infection fulfilled the predefined criteria: a diagnosis of pneumonia is based on symptoms consistent with pneumonia, chest radiographs, and a positive sputum culture or empiric start of antibiotics; a pulmonary embolism is based on a CT or ventilation/perfusion scan plus symptoms; a diagnosis of myocardial infarction is based on electrocardiography or echocardiography plus symptoms; and sepsis is defined as systemic inflammatory response syndrome requiring intensive care admission with a positive culture.

Secondary outcome measures were total estimated blood loss, anesthesia time, duration of hospital admission, and 30-day survival. These outcome measures were derived from medical records. In addition, we used the Social Security Death Index to establish date of death.¹³

Data on age, body mass index (BMI), comorbidity status, tumor type, preoperative white blood cell count and hematocrit level, sex, fracture type and area, visceral and bone

metastases, previous local radiation therapy, and previous systemic therapy were derived from medical records. We reviewed radiographs to assess the location of the lesion when surgical or radiologic reports were unclear or when the lesion was located in the femoral neck, subtrochanteric area, or proximal shaft. We used an algorithm based on the ICD-9-CM code to assess the modified Charlson Comorbidity Index, an index ranging from 0 to 24 based on 12 weighted comorbidities (Appendix 2).^{14,15} The modified Bauer score was used as a surrogate for cancer status.^{16,17} The Bauer score is commonly used to estimate life expectancy in patients with bone metastases and is a composite of four prognostic factors: (1) no visceral metastases, (2) no lung cancer, (3) the presence of breast cancer, kidney cancer, multiple myeloma, or lymphoma, and (4) the presence of one solitary bone metastasis. The score ranges from 0 to 4, with a higher score indicating relatively better prognosis.

Followup

Three hundred forty-seven (83%) patients were followed for 3 months or until death at ≤ 3 months. At 3 months, 241 patients (58%) were alive, 106 patients (25%) were deceased, and 70 patients (17%) were lost to followup. Three hundred forty-five patients (83%) were followed for 1 year or until death at ≤ 1 year. At 1 year postoperatively, 105 patients (25%) were alive, 240 patients (58%) were deceased, and 72 patients (17%) were lost to followup. The median followup was 4 months (range, 0 to 144 months), primarily because of the poor survival rate.

Statistical Analysis

Categorical variables are presented with frequencies and percentages. Continuous variables are presented as median with interquartile range because inspection of histograms suggested non-normality.

Baseline characteristics were compared among implants using the Fisher exact test for categorical variables and the Kruskal-Wallis test for continuous variables. The Levene test indicated homogeneity of variances. Patients with missing values for one of the variables (BMI, 21% [87 of 417]; white blood cell count, 5% [19 of 417]; hematocrit level, 3% [11 of 417]) were not included in the respective baseline analyses.

Log-rank analysis was used to compare the reoperation rate among surgical strategies. Reasons for reoperation were subdivided into fixation failure (i.e. nonunion, implant fracture, implant loosening, tumor progression), deep infection, and tumor progression, and log-rank analyses were used to compare these reasons among surgical strategies. Two patients died intraoperatively and were not included in the log-rank analyses. No left censoring occurred, and right censoring was assumed to be non-informative. Visual inspection of log-log plots suggested no serious violation of the proportional hazards assumption.¹⁸

The Fisher exact test was used to compare 30-day systemic complication rates among surgical strategies.

Secondary outcome measures were compared among surgical strategies with the Kruskal-Wallis test for estimated blood loss, anesthesia time, and duration of hospital stay and with the Fisher exact test for 30-day survival. Patients with missing values for estimated blood loss (8% [32 of 417]) and anesthesia time (16% [66 of 417]) were excluded from the analyses. The Levene test indicated a violation of the assumption of equality of variances for blood loss but not for anesthesia time or duration of hospital stay. We therefore reported the p value from a Kruskal-Wallis test on the log of blood loss, which resolved the inequality of variance.

Additionally, we assessed risk factors for systemic complications. Variables were selected on the basis of previous studies or theoretic association with systemic complications.¹⁹ Exploratory bivariate logistic regression analysis was used to test associations of the variables with systemic complications. Multivariable logistic regression analysis was used to further explore the cause-effect relationship and adjust for sex and age.

All statistical analyses were performed using Stata® 14.0 (StataCorp LP, College Station, TX, USA). A two-tailed p value less than 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

Among the 417 patients, 163 (39%) were men. The median age was 62 years (range, 23 to 94 years). There were 173 pathological fractures (41%) and 244 impending fractures (59%). Breast (30% [125 of 417]) and lung (23% [95 of 417]) tumors were most common (Appendix 3). The median survival was 8 months. In comparing baseline characteristics among surgical strategies, we found that pathological fractures were more common in the endoprosthetic reconstruction group (79%) than in the intramedullary nailing and ORIF groups (33% and 40% respectively; $p < 0.001$); the presence of multiple bone metastases was more common in the intramedullary nailing group (85%) than in the endoprosthetic reconstruction and ORIF groups (74% and 73% respectively; $p = 0.023$); and previous systemic therapy was more common in the intramedullary nailing group (73%) than in the endoprosthetic reconstruction and ORIF groups (51% and 47% respectively; $p < 0.001$; Table 2). Anatomic location ($p < 0.001$; Table 2) and tumor type ($p = 0.014$; Figure 2) also varied among surgical strategies. Age, sex, BMI, comorbidity and cancer status, white blood cell count, hematocrit level, presence of visceral metastases, and previous radiation therapy did not differ among surgical strategies (Table 2).

Table 2: Baseline characteristics of patients by surgical strategy

	n = 417			
	Intramedullary nailing (n = 302)	Endoprosthetic reconstruction (n = 70)	ORIF (n = 45)	
	Median (Interquartile range)	Median (Interquartile range)	Median (Interquartile range)	p value
Age in years	62 (52 - 70)	63 (55 - 72)	65 (54 - 75)	0.44
Body mass index*	26 (23 - 30)	24 (27 - 29)	25 (23 - 30)	0.90
Modified CCI	6 (6 - 8)	6 (6 - 8)	7 (6 - 8)	0.94
Modified Bauer score	2 (1 - 3)	2 (2 - 3)	2 (1 - 3)	0.17
WBC count (in K/uL)*	8.6 (5.6 - 12.3)	9.2 (6.5 - 12.5)	10.8 (7.7 - 13.1)	0.15
Hematocrit (in %)*	33 (30 - 36)	33 (30 - 34)	34 (31 - 37)	0.10
	n (%)	n (%)	n (%)	
Men	114 (38)	32 (46)	17 (38)	0.46
Pathological fracture	100 (33)	55 (79)	18 (40)	<0.001
Anatomical location				
Neck area (below isthmus)	28 (9)	28 (40)	3 (7)	
Trochanteric area	146 (48)	30 (43)	27 (60)	<0.001
Subtrochanteric area	128 (42)	12 (17)	15 (33)	
Visceral metastases	147 (49)	32 (46)	23 (51)	0.84
Multiple bone metastases	258 (85)	52 (74)	33 (73)	0.023
Previous local radiotherapy	63 (21)	15 (21)	7 (16)	0.72
Previous systemic therapy	220 (73)	36 (51)	21 (47)	<0.001

ORIF = Open Reduction and Internal Fixation, CCI = Charlson Comorbidity Index, WBC = White blood cell. **bold font** indicates a significant difference (two-tailed p value below 0.05)

*Body mass index was available in 330 (79%) of the patients: 259 (86%) in the intramedullary nailing group, 45 (64%) in the endoprosthetic reconstruction group, and 26 (58%) in the ORIF group. White blood cell count was available in 398 (95%) of the patients: 286 (95%) in the intramedullary nailing group, 69 (99%) in the endoprosthetic reconstruction group, 43 (96%) in the ORIF group. Hematocrit was available in 406 (97%) of the patients: 294 (97%) in the intramedullary nailing group, 69 (99%) in the endoprosthetic reconstruction group, 43 (96%) in the ORIF group.

Reoperations

The overall reoperation rate was 7.2% (30 of 417 patients) and did not differ among surgical strategies (5.3% [16 of 302] after intramedullary nailing, 11% [8 of 70] after endoprosthetic reconstruction, and 13% [6 of 45] after ORIF; $p = 0.134$; Figure 3). Reoperation for failure of fixation was highest after ORIF (13% [6 of 45] versus 3.0% [9 of 302] after intramedullary nailing and zero [0 of 70] after endoprosthetic reconstruction; $p < 0.001$; Figure 4). The rate of reoperation for deep infection was highest after endoprosthetic reconstruction (8.6% [6 of 70] versus 2.0% [6 of 302] after intramedullary nailing and zero [0 of 45] after ORIF;

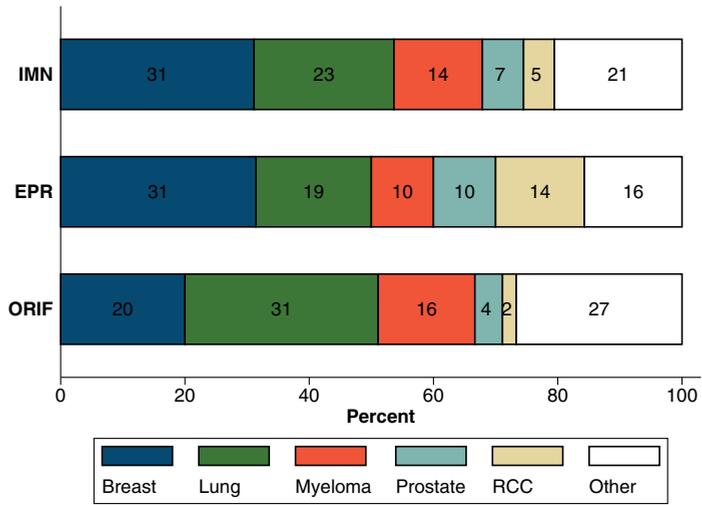


Figure 2: Bar graph depicting tumor distribution among surgical strategies ($p = 0.014$, by chi-square test).

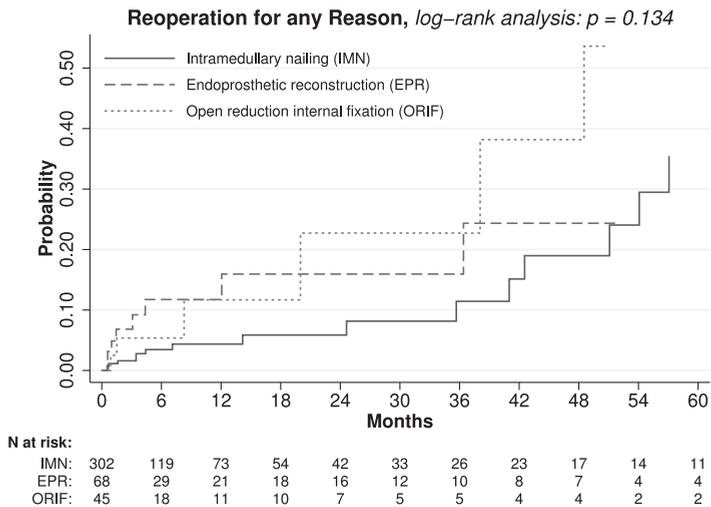


Figure 3: Kaplan-Meier failure plot demonstrating the probability of reoperation for any reason among surgical strategies (log-rank analysis, $p = 0.134$). The probability of reoperation was 1.6% at 3 months (95% confidence interval [CI], 0.60% to 4.2%) and 4.4% at 12 months (95% CI, 2.1% to 8.9%) for intramedullary nailing; 6.8% at 3 months (95% CI, 2.6% to 17%) and 12% at 12 months (95% CI, 5.4% to 25%) for endoprosthetic reconstruction; and 5.4% at 3 months (95% CI, 1.4% to 20%) and 12% at 12 months (95% CI, 3.5% to 35%) for open reduction and internal fixation.

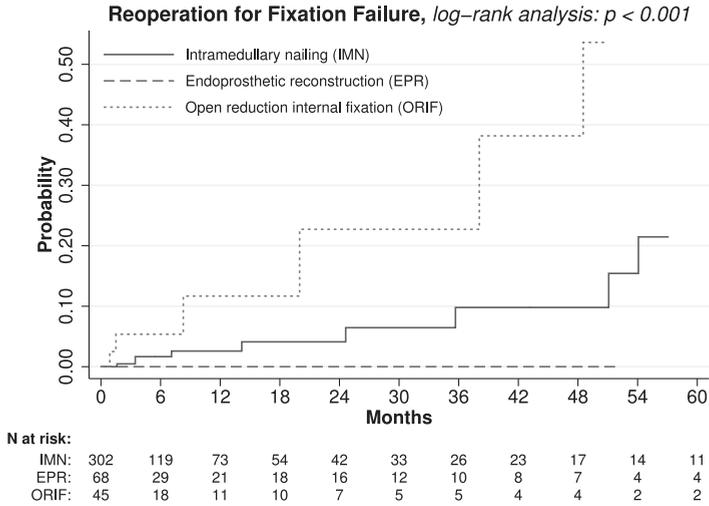


Figure 4: Kaplan-Meier failure plot demonstrating the probability of reoperation for failure of fixation (nonunion, implant fracture, implant loosening, and tumor progression) among surgical strategies (log-rank analysis, $p < 0.001$). The probability of reoperation for failure of fixation was 0.47% at 3 months (95% confidence interval [CI], 0.07% to 3.3%) and 2.6% at 12 months (95% CI, 0.95% to 7.0%) for intramedullary nailing; 0% at 3 and 12 months for endoprosthetic reconstruction; and 5.4% at 3 months (95% CI, 1.4% to 20%) and 12% at 12 months (95% CI, 3.5% to 35%) for open reduction and internal fixation.

$p = 0.010$; Figure 5). The rate of reoperation for tumor progression did not differ among surgical strategies (0.66% [2 of 302] after intramedullary nailing, 2.2% [1 of 45] after ORIF, and zero [0 of 70] after endoprosthetic reconstruction; $p = 0.366$; Figure 6).

The number of patients who underwent reoperation increased steadily over time, with the exception of reoperations for deep infections in the endoprosthetic reconstruction group, all of which occurred ≤ 4 months postoperatively (Appendix 4).

30-Day Systemic Complications

The study identified 40 patients (9.6%) with 46 instances of complications: pneumonia (5.3% [22 of 417]), pulmonary embolism (2.2% [9 of 417]), sepsis (1.7% [7 of 417]), myocardial infarction (1.2% [5 of 417]), fat embolism (0.24% [1 of 417] during cementation of a modular prosthesis), and intraoperative death (0.48% [2 of 417]). Both intraoperative deaths occurred during endoprosthetic reconstructions with cemented femoral implants (a unipolar hemiarthroplasty and a modular bipolar tumor hemiarthroplasty) and were attributed to pulmonary fat/cement embolisms, although the cause of death was not confirmed.

Overall 30-day systemic complication rates did not differ among surgical strategies (8.3% [25 of 302] after intramedullary nailing, 14% [10 of 70] after endoprosthetic reconstruction, and 11% [5 of 45] after ORIF; $p = 0.268$). Looking specifically at all pulmonary

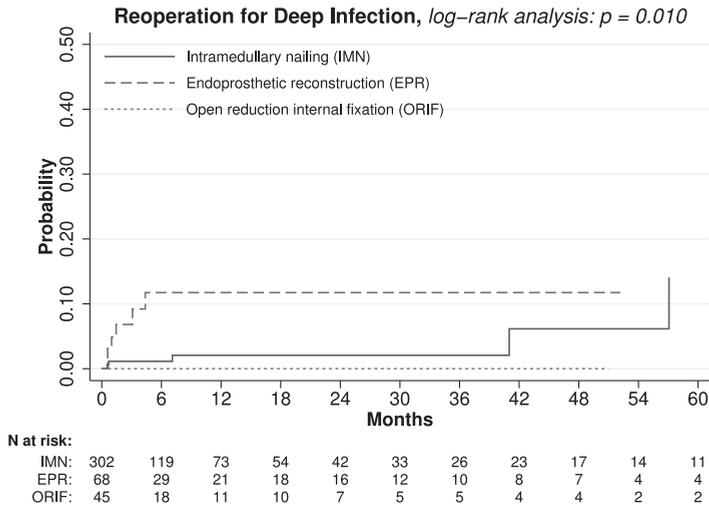


Figure 5: Kaplan-Meier failure plot demonstrating the probability of reoperation for deep infection among surgical strategies (log-rank analysis, $p = 0.010$). The probability of reoperation for deep infection was 1.1% at 3 months (95% confidence interval [CI], 0.37% to 3.5%) and 2.1% at 12 months (95% CI, 0.71% to 6.0%) for intramedullary nailing; 6.8% at 3 months (95% CI, 2.6% to 17%) and 12% at 12 months (95% CI, 5.4% to 25%) for endoprosthetic reconstruction; and 0% at 3 and 12 months for open reduction and internal fixation.

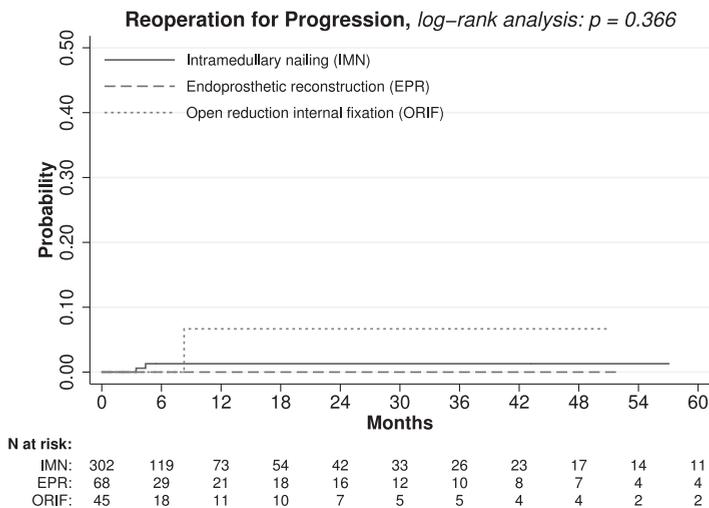


Figure 6: Kaplan-Meier failure plot demonstrating the probability of reoperation for tumor progression among surgical strategies (log-rank analysis, $p = 0.366$). The probability of reoperation for tumor progression was 0% at 3 months and 1.3% at 12 months (95% confidence interval [CI], 0.32% to 5.1%) for intramedullary nailing; 0% at 3 and 12 months for endoprosthetic reconstruction; and 0% at 3 months and 6.7% at 12 months (95% CI, 0.97% to 39%) for open reduction and internal fixation.

embolic events, we did not find a difference among surgical strategies (2.3% [7 of 302] after intramedullary nailing, 5.7% [4 of 70] after endoprosthetic reconstruction, and 2.2% [1 of 45] after ORIF; $p = 0.296$).

Secondary Outcome Measures

Blood loss ($p < 0.001$) and anesthesia time ($p = 0.003$) were both highest for endoprosthetic reconstruction rather than for intramedullary nailing or ORIF, whereas duration of hospital admission ($p = 0.017$) was longest for ORIF (Table 3). No difference was found in 30-day survival among the three surgical strategies ($p = 0.99$). Median 30-day survival for each treatment strategy was 93%.

Table 3: Secondary outcome measures by surgical strategy

	n = 417			
	Intramedullary nailing (n = 302)	Endoprosthetic reconstruction (n = 70)	ORIF (n = 45)	p value
	Median (Interquartile range)	Median (Interquartile range)	Median (Interquartile range)	
Estimated blood loss* (in mL)	200 (150 - 400)	400 (250 - 800)	275 (200 - 500)	<0.001
Anesthesia time* (in minutes)	181 (151 - 216)	222 (192 - 274)	178 (149 - 204)	<0.001
Duration of hospital admission (in days)	6 (4 - 10)	7 (5 - 10)	8 (5 - 11)	0.017

ORIF = Open Reduction Internal Fixation, **bold font** indicates a significant difference (two-tailed p value below 0.05)

*Estimated blood loss was available in 385 (92%) of the patients: 290 (96%) in the intramedullary nailing group, 57 (81%) in the endoprosthetic reconstruction group, and 38 (84%) in the ORIF group. Anesthesia time was available in 351 (84%) of the patients: 258 (85%) in the intramedullary nailing group, 60 (86%) in the endoprosthetic reconstruction group, 33 (73%) in the ORIF group.

Risk Factors For Systemic Complications

Exploratory bivariate analysis revealed an association of age, modified Charlson Comorbidity Index, and modified Bauer score with systemic complications (Table 4). We included only the modified Bauer score in the multivariable model— accounting for age and sex— because we considered the comorbidity index to be an intermediary variable rather than a true confounder. This model, which accounted for male sex (odds ratio [OR], 1.36; 95% CI, 0.69 to 2.68; $p = 0.372$) and age (OR, 1.03; 95% CI, 0.99 to 1.05; $p = 0.067$), demonstrated an effect of the modified Bauer score on postoperative systemic complications (OR, 0.67; 95% CI, 0.49 to 0.92; $p = 0.014$; Hosmer-Lemeshow goodness-of-fit test, $p = 0.56$; c-statistic, 0.67). This finding suggests that an increase in modified Bauer score—indicating better prognosis— is associated with a decreased chance of systemic complication.

Table 4: Bivariate analysis of factors associated with 30-day systemic complications

	Unadjusted Odds Ratio (95% confidence interval)	p value
Age	1.03 (1.00 - 1.06)	0.046
Men	1.64 (0.85 - 3.15)	0.140
Body mass index*	0.97 (0.90 - 1.05)	0.472
Modified CCI	1.22 (1.02 - 1.47)	0.028
Modified Bauer score	0.68 (0.50 - 0.92)	0.014
WBC count (in K/uL)*	1.04 (0.98 - 1.10)	0.244
Hematocrit (in %)*	1.03 (0.96 - 1.11)	0.461
Pathological fracture	1.18 (0.61 - 2.26)	0.636
Previous systemic therapy	0.83 (0.42 - 1.62)	0.581

CCI = Charlson Comorbidity Index, WBC = White blood cell. **bold font** indicates a significant difference (two-tailed *p* value below 0.05).

*Body mass index was available in 330 (79%) patients, white blood cell count in 398 (95%), and hematocrit in 406 (97%).

DISCUSSION

In the surgical management of metastatic femoral lesions, the goal is a single procedure that allows for immediate weight bearing and remains stable throughout the patient's lifetime while minimizing complications.¹² We assessed differences in reoperation rate, 30-day systemic complication rate, blood loss, anesthesia time, duration of hospital admission, and 30-day survival among surgical strategies in the largest (to the best of our knowledge) cohort of patients surgically treated for proximal femoral metastases. The relatively large sample size also allowed us to compare reasons for reoperation among surgical strategies. We found that the overall reoperation rate did not differ among intramedullary nailing, endoprosthetic reconstruction, and ORIF. However, when patients were subdivided by reasons for reoperation, endoprosthetic reconstruction was found to be the most durable over time (no failures) but most likely to require (early) reoperation for infection. This finding emphasizes the importance of estimating life expectancy when weighing treatment strategies in these terminally ill patients.^{16,20,21} No difference was found in 30-day systemic complication rates among surgical strategies, but cancer status was identified as a risk factor for development of a systemic complication.

This study has several limitations. First, no uniform criteria were used in the decision to perform surgical treatment, and many surgeons were involved. However, most of the procedures (89%) were performed by 10 orthopaedic oncologists, and we found no difference in reoperation rate between orthopaedic oncologists and other subspecialty surgeons. Selection bias could not have been eliminated from the study and is an important

limitation. We explored differences in baseline characteristics among surgical strategies to understand possible confounding and found that, in patients with pathological fractures and more proximal lesions, endoprosthetic reconstruction was used more often than intramedullary nailing or ORIF. These factors could have compromised the comparison of surgical strategies. Unfortunately, the low number of reoperations and complications did not allow correction for potential confounders in our analyses.²² Second, although we found no difference in overall reoperation rate or 30-day complication rate among implant types, a larger sample size might have revealed a significant difference. A post-hoc power analysis for reoperation rate comparing intramedullary nailing with ORIF (chosen because the effect size [i.e. difference] between these groups was largest) demonstrated that, to achieve a power of 0.80, we would have needed slightly more patients (i.e. 334 in the intramedullary nailing group and 50 in the ORIF group) to demonstrate a significantly higher overall reoperation rate in the ORIF group. The current sample size achieved a power of 0.76. A post-hoc power analysis for the 30-day systemic complication rate comparing intramedullary nailing with endoprosthetic reconstruction (chosen because the effect size [i.e. difference in proportion: 6.0%] between these groups was largest) demonstrated that, to achieve a power of 0.80, we would have needed substantially more patients (i.e. 1,166 in the intramedullary nailing group and 271 in the endoprosthetic reconstruction group) to demonstrate a significantly higher complication rate in the endoprosthetic reconstruction group. The current sample size achieved a power of 0.29. Third, we did not account for postoperative radiation therapy because it was not always provided at the included institutions, nor did we account for preoperative ambulatory status because the Eastern Cooperative Oncology Group performance status was available for only a limited number of patients. Fourth, diagnostic and billing codes were used to flag potentially eligible patients, flag systemic complications, and determine comorbidity status. Because inaccuracies in coding could have occurred, we reviewed all electronic medical records to assess whether the flagged patients fulfilled eligibility criteria and whether the flagged systemic complications met definitions. This methodology resolved the issue of overcoding but did not address the possibility of undercoding. However, we think that undercoding is relatively uncommon and is independent of the surgical strategy and, therefore, that it did not influence the results. Fifth, poor patient survival affected followup duration in our study, as in other studies of patients with bone metastases. Our median followup was short (4 months), but 83% of the patients were available for followup or were deceased at 3 and 12 months postoperatively. Implant survival in this patient population should be considered relative to the patients' short life expectancy. We accounted for variation in followup duration among surgical strategies by using log-rank analysis for reoperations and using a relatively short time frame for systemic complications. Sixth, we assessed nine risk factors for systemic complications in an exploratory fashion, which increases the chance of a type I error. Future research should assess how the identified risk factor –modified

Bauer score— relates to systemic complications before it is used for risk stratification. Seventh, we were unable to account for the possible scenario in which a patient's illness precluded a necessary reoperation, nor were we able to account for treatment performed at a different institution.

The overall reoperation rate in our study (7.2%) is consistent with that reported in previous studies (6.4 to 10.3%).^{3,4} Our results are also consistent with those of previous studies that demonstrated that endoprosthetic reconstruction is more durable (i.e. resulted in fewer failures) than intramedullary nailing or ORIF. Steensma et al³ found that 0.5% of endoprosthetic reconstructions (1 of 197) required implant exchange after failure compared with 6.1% of intramedullary nailing procedures (5 of 82) and 42% of ORIF procedures (8 of 19) ($p < 0.01$). Wedin and Bauer⁴ demonstrated an 8.3% rate of failure requiring reoperation after endoprosthetic reconstruction (9 of 109) compared with 13% (3 of 24) after intramedullary nailing and 25% (3 of 12) after the use of a dynamic hip screw. However, no formal statistical analyses were performed in the latter study.

Prostheses are associated with additional complications, such as higher rates of infection (8.6% in our study) and dislocation. Wedin and Bauer⁴ reported deep infections after endoprosthetic reconstruction (3.7% [4 of 109]) but none after intramedullary nailing or ORIF; however, no statistical analysis was conducted. No infections requiring reoperation were reported by Steensma et al.³ We found one instance of dislocation after endoprosthetic reconstruction that required open reduction (1.4%). Steensma et al reported open reduction for dislocation in 5 of 197 endoprosthetic reconstructions (2.5%), and Wedin and Bauer⁴ reported that 3 of 109 endoprosthetic reconstructions (2.8%) required reoperation for dislocation. Our results and these studies demonstrate that infection is more common after endoprosthetic reconstruction than after other treatment strategies.

The overall systemic complication rate in our study (9.6%) is in line with that reported in previous studies (1.4% to 12.5%), and we found no difference among surgical strategies.^{4,5,23} We demonstrated that poor cancer status— independent of age and sex— is a risk factor for the development of systemic complications. A study of 5,716 patients undergoing musculoskeletal tumor surgery demonstrated that older age, male sex, blood transfusion, longer duration of anesthesia, and higher Charlson Comorbidity Index score were associated with postoperative complications.¹⁹ The modified Bauer score is commonly used to estimate life expectancy in patients with bone metastases, but its association with systemic complications has not been shown.^{16,17} This risk factor could be used to anticipate postoperative complications, stratify patients by risk, and, if possible, optimize a patient's health before surgical treatment. Postoperative complications, such as infection, can hamper a patient's ability to resume or begin medical treatment (e.g. chemotherapy) for the underlying malignancy, potentially affecting the patient's survival.

We found that blood loss was almost twice as high and anesthesia time was approximately 40 minutes longer in patients treated with endoprosthetic reconstruction than in

patients treated with intramedullary nailing or ORIF. These findings are comparable to those of previous studies demonstrating longer duration of surgery and increased blood loss after hip arthroplasty than after internal fixation for non-pathological femoral neck fractures.^{24,25} However, the difference in blood loss in our study might be explained in part by the difference in vascularity of the tumors or by the proportion of fractures because prostheses were more commonly used in patients with renal cell carcinoma and pathological fractures than in patients with other conditions.²⁶ These factors should be considered when planning surgical treatment because patients might be too ill to withstand lengthy procedures or substantial blood loss.

Acknowledging the limitations of this retrospective study, we found that ORIF and intramedullary nail fixation fail more often than does endoprosthetic reconstruction, whereas deep infections are most common following endoprosthetic reconstruction and often occur within the first months after surgical treatment. These implant-specific complications and their timing should be considered in the choice of surgical strategy. The findings also emphasize the importance of incorporating estimated life expectancy into surgical decision making. The risk factor of poor cancer status could be used to predict systemic complications.

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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: Tumor Distribution

Tumor Type	n (%)
Bone metastasis	
Breast	125 (30)
Lung	95 (23)
Prostate	29 (7)
Kidney	26 (6)
Melanoma	13 (3)
Unknown	13 (3)
Esophageal	12 (3)
Adenocarcinoma of unknown origin	10 (2)
Thyroid	9 (2)
Other*	28 (7)
Primary bone tumor (myeloma)	57 (14)

*Other primary tumor types were colorectal (n = 7), bladder (n = 4), hepatocellular (n = 5), vulvar (n = 3), neuroendocrine (n = 3), cutaneous squamous cell carcinoma (n = 2), uterus (n = 2), pancreas (n = 1), and ovarian (n = 1).

Appendix 4: Reasons for Reoperation and Surgical Strategy

Patient Sex (Age in Yr)	Fracture Type	Location	Primary Tumor	Surgical Strategy	Reason for Reoperation	Months to Reoperation (Procedure)
F (62)	Impending	Subtrochanteric	Breast	IMN	Deep infection	1 (I & D)
F (61)	Pathological	Trochanteric	Breast	IMN	Deep infection	1 (I & D)
F (56)	Impending	Neck	Breast	IMN	Deep infection	1 (I & D)
M (63)	Impending	Trochanteric	RCC	IMN	Peri-implant fracture after a minor fall	2 (distal screw replacement)
M (68)	Impending	Trochanteric	Bladder	IMN	Painful recurrence	4 (MTP THA)
F (65)	Pathological	Trochanteric	Myeloma	IMN	Nonunion, bone collapse, blade prominence	4 (long-stem THA)
M (61)	Impending	Neck	Lung	IMN	Soft-tissue painful recurrence	4 (resection of recurrence)
F (76)	Pathological	Subtrochanteric	Breast	IMN	Deep infection and helical blade prominence	7 (I & D and screw and blade replacement)
F (30)	Impending	Subtrochanteric	Breast	IMN	Implant fracture (distal screw), nonunion	14 (new IMN)

Appendix 4: Reasons for Reoperation and Surgical Strategy (*continued*)

Patient Sex (Age in Yr)	Fracture Type	Location	Primary Tumor	Surgical Strategy	Reason for Reoperation	Months to Reoperation (Procedure)
F (58)	Pathological	Subtrochanteric	Breast	IMN	Implant fracture, nonunion	25 (blade plate with intramedullary plate)
M (58)	Pathological	Subtrochanteric	Myeloma	IMN	Implant fracture (distal screw), nonunion	36 (New IMN and bone graft)
M (79)	Pathological	Trochanteric	Myeloma	IMN	Deep infection	42 (I & D)
F (44)	Pathological	Subtrochanteric	Breast	IMN	Painful bursitis	43 (trimming of intramedullary nail)
M (78)	Pathological	Neck	Prostate	IMN	Nonunion, bone collapse, blade prominence	52 (THA)
F (37)	Impending	Subtrochanteric	Breast	IMN	Implant fracture, nonunion	55 (new IMN)
F (52)	Impending	Trochanteric	Breast	IMN	Deep infection, secondary to arm cellulitis	58 (removal of intramedullary nail)
F (69)	Pathological	Subtrochanteric	Breast	EPR (MTP bipolar hemiarthroplasty)	Hematoma, deep infection, nerve compression	1 (I & D)
F (57)	Impending	Neck	Adenocarcinoma of unknown origin	EPR (long-stem bipolar hemiarthroplasty)	Deep infection	1 (I & D)
M (70)	Pathological	Trochanteric	RCC	EPR (MTP bipolar hemiarthroplasty)	Deep infection	1 (I & D)
F (53)	Pathological	Trochanteric	Breast	EPR (MTP bipolar hemiarthroplasty)	Hematoma, deep infection	1 (I & D)
M (56)	Pathological	Neck	RCC	EPR (unipolar hemiarthroplasty)	Deep infection	3 (I & D and bipolar head exchange)
M (58)	Pathological	Neck	Lung	EPR (MTP bipolar hemiarthroplasty)	Deep infection	4 (I & D and bipolar head exchange)
F (74)	Impending	Trochanteric	Thyroid	EPR (MTP bipolar hemiarthroplasty)	Dislocation	12 (open reduction)
F (48)	Impending	Trochanteric	Breast	EPR (MTP bipolar hemiarthroplasty)	Bursitis and painful exostoses	37 (trimming of exostoses)

Appendix 4: Reasons for Reoperation and Surgical Strategy (*continued*)

Patient Sex (Age in Yr)	Fracture Type	Location	Primary Tumor	Surgical Strategy	Reason for Reoperation	Months to Reoperation (Procedure)
F (76)	Pathological	Subtrochanteric	Thyroid	ORIF (1 plate)	Peri-implant fracture	1 (MTP bipolar hemiarthroplasty)
M (75)	Pathological	Subtrochanteric	Lung	ORIF (1 plate)	Implant fracture	2 (MTP bipolar hemiarthroplasty)
M (64)	Impending	Trochanteric	Esophageal	ORIF (DHS)	Local recurrence	8 (MTP bipolar hemiarthroplasty)
M (46)	Pathological	Subtrochanteric	Myeloma	ORIF (DHS)	Implant fracture (screws), nonunion	20 (new intramedullary nail)
F (52)	Impending	Trochanteric	Breast	ORIF (DHS)	Fixation failure (loosening)	39 (MTP bipolar hemiarthroplasty)
F (56)	Impending	Subtrochanteric	Thyroid	ORIF (1 plate)	Implant fracture, nonunion	49 (MTP bipolar hemiarthroplasty)

F = female, DHS = dynamic hip screw, EPR = endoprosthetic reconstruction, I & D = irrigation and débridement, IMN = intramedullary nailing, M = male, MTP = modular tumor prosthesis, ORIF = open reduction and internal fixation, RCC = renal cell carcinoma, THA = total hip arthroplasty