Optimising the treatment of patients with long bone metastases

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Chapter 6

What factors are associated with implant breakage and revision after intramedullary nailing for femoral metastases?

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Abstract

Background

Actual and impending pathologic fractures of the femur are commonly treated with intramedullary nails because they provide immediate stabilization with a minimally invasive procedure and enable direct weight bearing. However, complications and revision surgery are prevalent, and despite common use, there is limited evidence identifying those factors that are associated with complications.

Questions/purposes

Among patients treated with intramedullary nailing for femoral metastases, we asked the following questions:

(1) What is the cumulative incidence of revision surgery and what factors are associated with revision surgery?
(2) What is the cumulative incidence of implant breakage and what factors are associated with implant breakage?
(3) What is the cumulative incidence of revision surgery and what factors are associated with revision surgery?

Methods

Between January 2000 and December 2015, 245 patients in five centers were treated with intramedullary nails for actual and impending pathologic fractures of the femur caused by bone metastases. During that period, the general indications for intramedullary nailing of femoral metastases were impending fractures of the trochanter region and shaft and actual fractures of the trochanter region if sufficient bone stock remained; nails were used for lesions of the femoral shaft if they were large or if multiple lesions were present. Of those treated with intramedullary nails, 51% (117) were actual fractures and 49% (111) were impending fractures. A total of 60% (128) of this group were women; the mean age was 65 years (range, 29-93 years). After radiologic followup (at 4-8 weeks) with the orthopaedic surgeon, because of the palliative nature of these treatments, subsequent in-person followup was performed by the primary care provider on an as-needed basis (that is, as desired by the patient, without any scheduled visits with the orthopaedic surgeon) throughout each patient's remaining lifetime. However, there was close collaboration between the primary care providers and the orthopaedic team such that orthopaedic complications would be reported. A total of 67% (142 of 212) of the patients died before 1 year, and followup ranged from 0.1 to 175 months (mean, 14.4 months). Competing risk models were used to estimate the cumulative incidence of local complications (including persisting pain, tumor progression, and implant breakage), implant breakage separately, and revision surgery (defined as any reoperation involving the implant other than débridement with implant retention for infection). A cause-specific multivariate Cox regression model was used to estimate the association of factors (fracture type / preoperative radiotherapy and fracture type / use of cement) with implant breakage and revision, respectively.

Results

Local complications occurred in 12% (28 of 228) of the patients and 6-month cumulative incidence was 8% (95% confidence interval [CI], 4.7-11.9). Implant breakage occurred in 8% (18 of 228) of the patients and 6-month cumulative incidence was 4% (95% CI, 1.4-6.5). Independent factors associated with increased risk of implant breakage were an actual (as opposed to impending) fracture (cause-specific hazard ratio [HR_cs], 3.61; 95% CI, 1.23-10.53, p = 0.019) and previous radiotherapy (HR_cs, 2.97; 95% CI, 1.13-7.82, p = 0.027). Revisions occurred in 5% (12 of 228) of the patients and 6-month cumulative incidence was 2.2% (95% CI, 0.3-4.1). The presence of an actual fracture was independently associated with a higher risk of revision (HR_cs, 4.17; 95% CI, 0.08-0.82, p = 0.022), and use of cement was independently associated with a lower risk of revision (HR_cs, 0.25; 95% CI, 1.20-14.53, p = 0.025).

Conclusion

The cumulative incidence of local complications, implant breakage, and revisions is low, mostly as a result of the short survival of patients. Based on these results, surgeons should consider use of cement in patients with intramedullary nails with actual fractures and closer followup of patients after actual fractures and preoperative radiotherapy. Future, prospective studies should further analyze the effects of adjuvant therapies and surgery-related factors on the risk of implant breakage and revisions.

Introduction

The femur is the most common long bone affected by bone metastases.[1] Treatment modalities of actual and impending pathologic fractures should provide direct and robust (prophylactic) stabilization to enable immediate weight bearing without pain and to regain quality of life. Intramedullary (IM) nails are commonly used to treat actual and impending pathologic fractures of the femur because of the smaller surgical exposure, which may result in less blood loss and surgical time, perhaps enabling more rapid postoperative rehabilitation. In general, no extensive muscle releases are used and immediate weight bearing is possible.[2] Furthermore, the construct provides prophylactic protection of the long bone against future fractures in other regions as a result of its mechanical support over the entire length. The downside of IM nails is that they are designed as load-sharing devices, but they function as load-bearing devices in actual pathologic fractures that generally show only minimal healing tendencies, unlike traumatic fractures.[3] Should a non-union ensue, hardware breakage (either of the distal interlocking screws or of the nail itself) will occur over time because of the loads involved.[4-6] Although an IM nail suffices as palliative treatment for many patients because their survival will not exceed the fatigue life of the implant,[7] the occurrence of complications and need for revision surgery are not compatible with the palliative intent of the treatment, which aims to meet the patient's need for the balance of his or her lifetime and to require minimal surveillance.[8]

Long survival is recognized as one of the most important risk factors for failure and stresses the importance of adequate survival estimation.[9-12] Previous studies on the use of IM nails have limitations because they are heterogenic and describe small cohorts with short-term followup.[2,5,7,9,11,13,14] Few have looked at treatment-related risk factors for failure or revision. If such factors, however, are prognostic, surgeons can further improve treatment.

Therefore, this multicenter study aims to answer the following questions among patients treated with IM nailing for femoral metastases: (1) What is the cumulative incidence of local complications? (2) What is the cumulative incidence of implant breakage and what factors are associated with implant breakage? (3) What is the cumulative incidence of revision surgery and what factors are associated with revision surgery?

Patients and methods

Between January 2000 and December 2015, 245 patients in five centers were treated with IM nails for actual and impending pathologic fractures of the femur caused by bone metastases. Two hundred twelve patients with 245 actual or impending femoral pathologic fractures were evaluated in this retrospective study after local institutional review board approval. Patients with flexible nails (such as Nancy nails), angle blade plates, dynamic hip screws, retrograde nails (13 patients, 15 nails), IM nails with a bicortical proximal fixation, or in whom the nail was a revision (n = 2) were excluded (total n = 18). During the study period, the general indications for IM nails were impending fractures of the trochanter region and shaft and actual fractures of the trochanter region if sufficient bone stock remained; nails were used for lesions of the femoral shaft if they were large or if multiple lesions were present. Throughout the study period, these indications were generally adhered to. Nails were placed percutaneously except when a large cortical defect called for extensive curettage and cementation. Reaming was performed according to the manufacturers' guidelines. Indications for the type of nail and the use of cement were set by the treating surgeon as was the indication for postoperative radiotherapy. In general, cement was used for additional fixation of the collum screw (the lag screw in the femoral head) or filling of the metastatic lesion. As a result of the multicenter aspect of the study and developments over time, several different IM nails were used (table 6.1). Prophylactic antibiotics were administered to all patients according to each centers' own protocol (most commonly cefazolin). Adjuvant cement was administered to 50 femurs (22%; table 6.1). In general, cement was used if bone stock was regarded insufficient for adequate screw fixation or if the lesion was very large. Thirty-nine patients (17%) had received radiotherapy on the lesion before surgery (table 6.1), of whom the majority (n = 25 [64%]) had received one fraction of 8 Gy. The median time between radiotherapy and surgery was 8 weeks (range, 0.4–134 weeks). Preoperative radiotherapy was most commonly administered for pain. Twenty-seven patients (69%) sustained a pathologic fracture after radiation after a median of 3.5 weeks (range, 0.4-134 weeks), whereas 12 patients (31%) were treated for an impending fracture after a median of 13 weeks (range, 0.9-59 weeks). Postoperative radiotherapy was administered after 124 stabilizations (54%; table 6.1) after a mean of 4 weeks (SD 2.0). No protocol existed for administration of postoperative radiotherapy; whether it was used depended on local practice. The most common regimens were one or two fractions of 8 Gy (n = 29 [23%] and n = 33 [27%], respectively) and five or six fractions of 4 Gy (n = 26 [21%] and n = 27 [22%], respectively). Irradiation schemes were determined by the local protocols of each centers' radiotherapy department. Radiotherapy was given more often to patients after prophylactic stabilization than to those treated for actual fractures (65% versus 44%; p = 0.015) after correction for prior radiotherapy.

Demographic data, fracture and treatment details, and followup data including complications, revisions, and survival were collected from medical files. Fracture details included location, date of diagnosis, type (actual or impending), primary tumor, and previous radiotherapy. Treatment details included type of IM nail, locking mechanism, use and location of adjuvant cement, curettage, and postoperative radiotherapy. Radiotherapy was regarded as postoperative if given within 12 weeks of surgery. Dates of death were obtained from medical records or the municipal personal records database. If patients were alive, the last known dates were collected from the medical records.

After radiologic followup (at 4-8 weeks) with the orthopaedic surgeon, because of the palliative nature of these treatments, subsequent in-person followup was performed by the primary care provider on an as-needed basis (that is, as desired by the patient, without any scheduled visits with the orthopaedic surgeon) throughout each patient's remaining lifetime. However, there was close collaboration between the primary care providers and the orthopaedic team such that orthopaedic complications would be reported. A total of 67% (142 of 212) of the patients died before 1 year and 17% (36 of 212) were alive after 2 years. Followup ranged from 0.1 to 175 months (mean, 14.4 months).

Local complications included persisting pain (that is, lasting pain despite surgery and adequate analgesics), tumor progression, and implant breakage. Persisting pain and tumor progression were scored as such if these were stated as the reason for adjuvant treatment (such as radiotherapy or surgery). The subgroup of implant breakage was further analyzed separately. Implant breakage included all nail and screw fractures, migrations, deformations or malplacements, and peri-implant fractures. Infections and systemic complications (deep venous thrombosis, pulmonary embolism, fat or cement embolism, pneumonia, urinary tract infection, cardiac events, sepsis, intraoperative death, and postoperative death [within 3 weeks of surgery]) were recorded. Revision was defined as any reoperation that was performed as a result of local complications, but reoperations for infection in which the implant was retained were not counted.

Two hundred twelve patients with 228 actual and impending fractures were included in this study with a median age of 65 years (range, 29-93 years) and prominently women (60% [n = 128]). Metastases originated most commonly from breast cancer (36% [n = 76]) followed by lung (24% [n = 51]), kidney (11% [n = 24]), and prostate (11% [n = 23]) cancer. The remaining 18% (n = 38) included primary tumors of the thyroid, colorectum, head and neck, and bladder, among others. Actual fractures (117 [51%]) were most commonly located in the subtrochanteric region (50 [43%]; table 6.2), whereas impending fractures (111 [49%]) were primarily in the shaft (53 [48%]; table 6.2).

Median overall survival (OS) was 6 months (95% confidence interval [CI], 4.4-7.3). Overall 6-month, 1-year, and 2-year survival for the entire cohort was 49%, 33%, and 19%, respectively. Median OS was longer for impending fractures (median, 8 months; 95% CI, 3.1-12.7) than for impending fractures (median, 5 months; 95% CI, 3.5-5.8) (figure 6.1). There were differences in median OS between primary tumor types: 11 months (95% CI, 4.9-17.1) for breast cancer, 7 months (95% CI, 2.4-11.6) for prostate cancer, 6 months (95% CI, 1.5-11.2) for kidney cancer, 3 months (95% CI, 1.0-4.2) for lung cancer, and 6 months (95% CI, 3.8-7.4) for other primary tumors (figure 6.2).

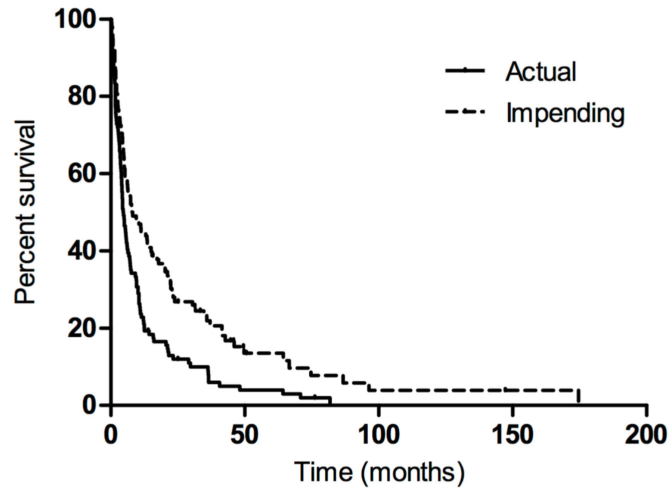

Figure 6.1 The Kaplan-Meier curve for OS is stratified for fracture type.

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Statistical Analysis

Time to local complication, implant breakage, revision, and survival time were calculated from the date of surgery. For survival analysis, only the first treatment was included for patients with bilateral treatments. A competing risk model was used to estimate the cumulative incidence of local complication, implant breakage, and revision with death as a competing event.[15] The cumulative incidence was defined as the probability of failing from a specific cause before time (t). Factors (fracture type; fixation type; pre- and postoperative radiotherapy; cement) were explored for the association with implant breakage or revision with a univariate cause-specific Cox regression. Subsequently multivariate cause-specific Cox regression analyses were performed, evaluating the following factors for the endpoints implant breakage and revision, respectively: type of fracture and postoperative radiotherapy and type of fracture and use of cement. As a result of the limited number of events for both endpoints, we were not able to include a third factor in the multivariate analyses. A p value < 0.05 was considered significant. Competing risk analysis was performed by using the mstate library in R.[16,17]

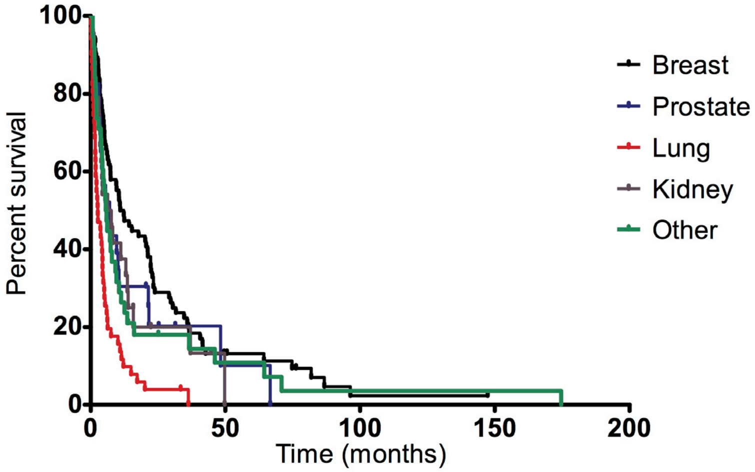

Figure 6.2 The Kaplan-Meier curve for OS is stratified for primary tumor type.

Table 6.1 Treatment characteristics of 228 intramedullary nails

Characteristic		*All*	*Actual fracture*	*Impending fracture*
Total		228	117	111
Nail type				
	Gamma nail[†]	164 (72)	79 (68)	85 (77)
	PFN/PFNa[‡]	21 (9)	16 (14)	5 (5)
	IMHS[§]	24 (11)	8 (7)	16 (14)
	TFN[||]	9 (4)	5 (4)	4 (4)
	T2–Recon[¶]	6 (3)	6 (5)	0 (0)
	UFN[**]/CFN[††]	4 (2)	3 (3)	1 (1)
Adjuvant cement				
	Yes, mechanical support[*]	22 (10)	12 (10)	10 (9)
	Yes, at location of tumor	16 (7)	9 (8)	7 (6)
	Yes, mechanical support[*] and tumor location	12 (5)	2 (2)	10 (9)
	No	178 (78)	94 (80)	84 (76)
Radiotherapy				
	Previous only	32 (14)	23 (20)	9 (8)
	Previous and postoperative	7 (3)	4 (3)	3 (3)
	Postoperative only	117 (51)	48 (41)	69 (62)
	None	72 (32)	42 (36)	30 (27)
Reaming				
	Yes	213 (93)	109 (93)	105 (95)
	No	7 (3)	5 (4)	2 (2)
	Unknown	7 (3)	3 (3)	4 (4)
Fixation				
	Static	166 (73)	85 (73)	81 (73)
	Dynamic	52 (23)	22 (19)	30 (27)
	Unknown	10 (4)	10 (9)	0 (0)
Proximal locking				
	Femoral head fixation (single)	211 (93)	103 (88)	108 (97)
	Femoral head fixation with second screw	17 (8)	14 (12)	3 (3)
Distal locking				
	None	3 (1)	0 (0)	3 (3)
	1 locking screw	48 (21)	23 (20)	25 (23)
	2 locking screws	176 (77)	93 (80)	83 (75)
	3 locking screws	1 (0)	1 (1)	0 (0)

Values are numbers with percentages in parentheses; [*]mechanical support of collum screw in the femur neck; [†]gamma nail (Stryker Trauma GmbH, Schonkirchen, Germany); [‡]proximal femoral nail (antirotation) (Synthes GmbH, Oberdorf, Germany); [§]intramedullary hip screw (Smith & Nephew, Inc, Cordova, TN, USA); [||]titanium trochanteric fixation nail (Synthes GmbH); [¶]T2–Recon (Stryker Trauma GmbH); [**]unreamed femoral nail, [††]distal femoral nail (Synthes GmbH).

Table 6.2 Locations of actual and impending pathologic fractures of the femur

Femurs (n = 228)	*Actual fracture, number (%)*	*Impending fracture, number (%)*
Total	117	111
Head and neck	10 (9)	14 (13)
Pertrochanteric	23 (20)	31 (28)
Subtrochanteric	50 (43)	13 (12)
Shaft	34 (29)	53 (48)

Results

Three-month, 6-month, and 9-month cumulative incidences of local complications were 4% (95% CI, 1.7-7.1), 8% (95% CI, 4.7-11.9), and 9% (95% CI, 5.1-12.5), respectively (figure 6.3). Overall, 28 IM nails (12%) were involved with 35 local complications (table 6.3), including tumor progression in nine patients (4%) and persisting pain in five patients (2%). Four of the nine patients with tumor progression and three of the five patients with persisting pain had not received postoperative radiotherapy. Tumor progression was treated with (re)irradiation (n = 6) or revision surgery (n = 3). Persisting pain was treated with adjuvant radiotherapy (n = 5) after a mean of 4 months (range, 3-6 months).

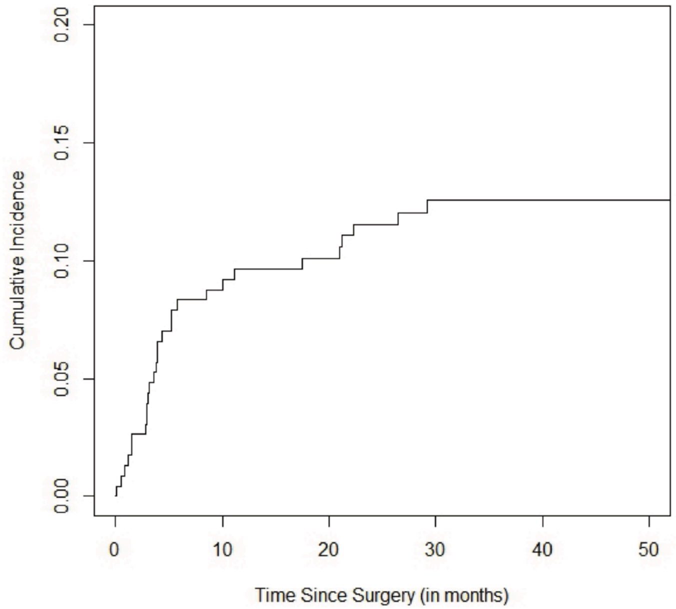

Figure 6.3 Cumulative incidence functions are shown for local complication.

Overall, the 3-month, 6-month, and 9-month cumulative incidences of implant breakage were 3% (95% CI, 0.8-5.3), 4% (95% CI, 1.4-6.5), and 4% (95% CI, 1.7-7.1), respectively (figure 6.4). Overall, 21 implant breakages occurred in 18 IM nails (8%; table 6.3). In three patients one of the distal screws broke before the nail fractured; both complications were registered. Seven nails fractured at the site of the collum screw junction, leading to a nail fracture percentage of 3%. The majority of the structural failures occurred after fixation of actual pathologic fractures (n = 13 of 18 [72%]).

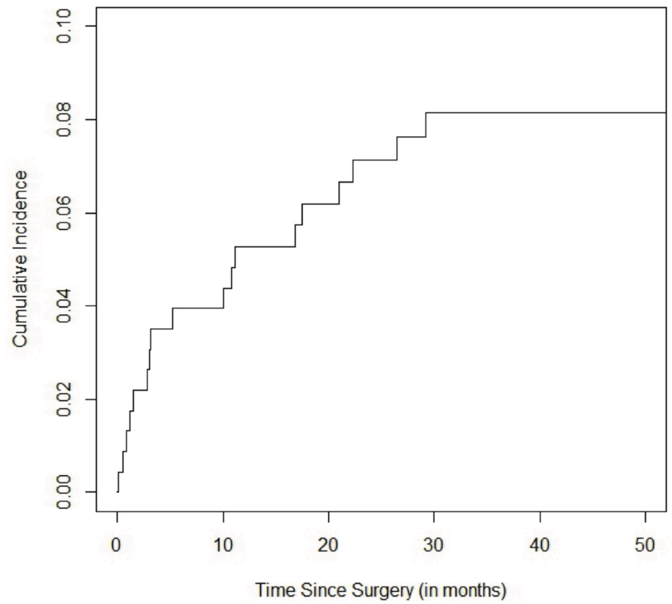

Figure 6.4 Cumulative incidence functions are shown for structural failure.

Table 6.3 Local complications per fracture location

Complication	*All locations A/I*	*Head and neck A/I*	*Pertrochanteric A/I*	*Subtrochanteric A/I*	*Shaft A/I*	*Total*
Implant breakage	16/5	1/0	2/2	7/0	6/3	21
Fracture of nail	6/1	1/0	1/0	3/0	1/1	7
Fracture or migration of distal screw	10/2	-	1/0	4/0	5/2	12
Deformation of nail	0/1	-	0/1	-	-	1
Malplacement	0/1	-	0/1	-	-	1
Persisting pain	5/0	-	1/0	2/0	2/0	5
Tumor progression	4/5	0/1	1/1	1/0	2/3	9
Total	25/10	1/1	4/3	10/0	10/6	35

A = actual fracture; I = impending fracture.

After controlling for confounding between fracture type and radiotherapy, both factors were independently associated with an increased risk of implant breakage: actual (as opposed to impending pathologic) fractures had a cause-specific hazard risk of 3.61 (95% CI, 1.23-10.53, p = 0.019) and radiotherapy before surgery of 2.97 (95% CI, 1.13-7.82, p = 0.027) (table 6.4). Revision surgery resulting from structural failure was performed for the seven fractured nails, the displaced nail, and the initially malplaced collum screw (nine of 18 [50%]).

The 3-month, 6-month, and 11-month cumulative incidences of revision were 0.4% (95% CI, 0.0-1.3), 2% (95% CI, 0.3-4.1), and 3% (95% CI, 0.5-4.7), respectively (figure 6.5). Twelve patients (5%) underwent revision (table 6.5). The majority of the lesions were located per-/subtrochanteric or in the shaft (nine of 12). The presence of an actual fracture was independently associated with a higher risk of revision (cause-specific hazard ratio, 4.17; 95% CI, 0.08-0.82, p = 0.022), and use of cement was independently associated with a lower risk of revision (cause-specific hazard ratio, 0.25; 95% CI, 1.20-14.53, p = 0.025) (table 6.4). Five of the 12 revisions caused further complications that resulted in further interventions. Infection (n = 2), protrusion of the collum screw (n = 1), and loosening or fracture of the collum screw (n = 2) were reasons for rereoperation. In addition to surgery, both patients with infections were treated with lifelong antibiotics. The three patients with implant breakage developed further complications, which all resulted in further surgery.

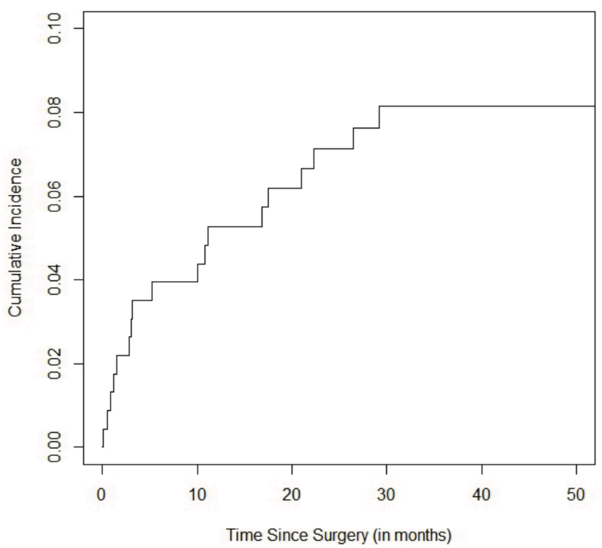

Figure 6.5 Cumulative incidence functions are shown for revision.

Table 6.4 Factors associated with implant breakage (n=18) and revision (n=12)

	Implant breakage						Revision					
	Univariate			Multivariate			Univariate			Multivariate		
Variables	*HR*	*95% CI*	*p value*	*HR*	*95% CI*	*p value*	*HR*	*95% CI*	*p value*	*HR*	*95% CI*	*p value*
Location												
Shaft	-	-	0.451				-	-	0.881			
Head and neck	0.27	0.03-2.16	0.216				0.42	0.05-3.60	0.427			
Pertrochanteric	0.57	0.15-2.16	0.408				0.94	0.23-4.00	0.937			
Subtrochanteric	1.20	0.41-3.46	0.741				0.98	0.23-4.11	0.978			
Fracture type*	4.31	1.50-12.37	0.007	3.61	1.24–10.53	0.019	3.55	1.05-12.04	0.042	4.17	0.08-0.82	0.022
Static fixation†	0.52	0.15-1.79	0.517				0.51	0.11-2.35	0.389			
Reamed nail‡	1.33	0.18-10.04	0.781				2.04	0.26-15.93	0.495			
Use of cement‡	0.61	0.22-1.71	0.344				0.31	0.10-1.00	0.044	0.25	1.20-14.53	0.025
Previous RT§	3.84	1.49-9.94	0.006	2.97	1.13–7.82	0.027	0.25	0.08-0.78	0.017			
Postoperative RT‡,‖	0.24	0.08-0.70	0.009				0.10	0.02-0.47	0.003			
Primary tumor												
Other	-		0.676				-		0.459			
Breast	0.70	0.21-2.30	0.556				0.29	0.08-1.12	0.073			
Prostate	0.37	0.04-3.30	0.371				0.32	0.04-2.89	0.309			
Lung	0.29	0.03-2.64	0.274				0.00	0.00-3.76	0.962			
Kidney	1.16	0.26-5.20	0.845				0.72	0.13-3.96	0.709			

*Actual versus impending (as reference); †dynamic versus static (as reference); ‡no versus yes (as reference); §yes versus no (as reference); ‖as a time-dependent variable; HR = hazard ratio; CI = confidence interval; RT = radiotherapy. *O = original cohort, and E = external cohort. †Data concerning 1 of the 3 variables were missing for 126 and 41 patients for the original and external cohort, respectively. Mo: months.

Table 6.5 Characteristics of fractures undergoing revision surgery

Characteristics	*Revisions, number (%)*
Total (nails)	12
Primary tumor	
Breast	5 (42)
Kidney	2 (17)
Prostate	1 (8)
Other	4 (33)
Fracture type	
Actual	8 (67)
Impending	4 (33)
Location	
Collum	1 (8)
Pertrochanteric	3 (25)
Subtrochanteric	3 (25)
Proximal shaft	3 (25)
Midshaft	1 (8)
Distal shaft	1 (8)
Radiotherapy	
Previous only: 1*8 Gy	2 (17)
Previous only: 2*8 Gy	3 (25)
Postoperative only: 2*8 Gy	1 (8)
Postoperative only: 6*4 Gy	2 (17)
Previous and postoperative	0 (0)
None	4 (33)
Cement	
Yes	5 (42)
No	7 (58)
Locking	
Static	10 (83)
Dynamic	2 (17)
Local complication	
Structural failure: nail fracture	7 (58)
Structural failure: displaced nail	1 (8)
Structural failure: malplacement	1 (6)
Tumor progression	3 (25)

Discussion

The aim of the IM fixation of actual and impending pathologic fractures is to minimize pain and stabilize the limb for the patient's remaining lifetime. Long survival has been associated with complications of IM nails,[9,18] but only one study has looked into factors associated with these complications.[11] Our study presents a larger cohort and aims to identify treatment-specific factors as opposed to patient-specific factors. In this study, after controlling for confounding variables, we found that actual fractures (as opposed to impending fractures) and previous radiotherapy were independently associated with an increased risk of implant breakage, actual fractures (again, as opposed to impending fractures) were associated with an increased risk of revision, whereas use of cement was associated with a lower likelihood of a patient undergoing revision during his or her remaining lifetime. Although the cumulative incidences of implant breakage and revision were low in this series, we note that this likely was because of the very short survival of most of these patients (median survival was 6 months after surgery). Finally, we identified an alarmingly high frequency of re-revision once a revision was performed.

This study has several limitations. First, underestimation of all endpoints might be possible because followup was not standardized. However, patients were seen throughout their remaining lifetimes by primary care providers on an as-needed basis and had clinically meaningful problems arisen; it seems likely that these would have been reported, which may mitigate the problem of underestimation. In addition, the methods here probably are fairly reflective of real-world palliative practice. Also, based on the medical system in The Netherlands and Austria and the small sizes of both countries, we can assume that loss of patients to other hospitals is limited. Second, the retrospective design may have introduced selection bias. This bias may involve details of the surgical strategies such as nail type, adjuvant cement, and postoperative radiotherapy, but it probably does not influence the choice of the IM nail itself, because general indications are recognized for the main implant choice and we are not comparing IM nails with other treatment modalities in this study. The decisions for the details of treatment were made by the surgeons as opposed to according to a pre-set, shared algorithm.

The study also is limited by the small number of events of interest. This is predominantly caused by the short survival of patients with metastatic cancer, which is inevitable with the study population, but nonetheless limits the analytic possibilities, especially with regard to the multivariate analysis. As a result of the few implant breakages (n = 21) and revisions (n = 12), only two factors could be included in the multivariate analyses for each event. For both multivariate analyses, confounding by adjuvant radiotherapy could therefore not be excluded; however, this was regarded as less relevant for our specific (implant-related) research questions. The results imply that further research should focus on the role and effect of adjuvant treatments (cement and radiotherapy). Finally, patients might have received systemic treatments, which we did not include in the analysis. This could be regarded as a limitation, because it might have affected the course of disease of patients. However, the focus of our study was on a detailed analysis of local treatment and the complexity of systemic treatments would intervene too much with obtaining these local results. Given the personalization of systemic therapies, there is such a variety of systemic treatments given at different time points that the factor cannot be regarded as one. Including this variable would complicate the analysis to such level that the results would stray from our initial research questions.

The frequency of complications we observed (12% [28 of 228]) is comparable to some studies,[6] whereas others report fewer complications.[9,13] The differing results can be attributed to the definitions for complication. The current study regarded all causes of secondary treatment for mechanical stabilization (surgery and/or radiotherapy) and all structural problems of the implant as complications because the surgical treatment of an actual or impending fracture is meant to meet the patient's needs for his or her remaining lifetime. The cumulative incidence of complications (figure 6.3) shows that although the assumption might be that all complications occur in the short term, this is not the case.

Implant breakage caused most of the observed local complications (60% [21 of 35]). As a result of the nature of pathologic fractures and their general lack of bone healing, IM nails and locking screws carry more pressure and during a longer period than in general trauma care. The common persisting non-union often leads to implant fractures (that is, breakage of screws and nails) over time.[19] In the current cohort, 3% (seven of 228) of the nails fractured, all at the junction with the collum screw. The design of modern IM nails, with the collum screw locked into the proximal nail, prevents protrusion of the collum screw through the femur head, but inevitably causes a weak point of the nail by reducing the diameter (1.5-3 mm) of the nail adjacent to the hole.[20] Although the power of this study was insufficient to perform any further analyses into specific causes of the nail breakage (e.g., nail diameter, collum screw length, type of screws for distal locking), the frequent fractures at the junction with the collum screw suggest that a larger proximal diameter of the nail is mandatory, especially in patients with an expected survival of > 6 months. Two independent factors associated with implant breakage were identified: both actual fracture

and previous radiotherapy increase the risk of implant breakage threefold. This emphasizes the importance of accurate fracture prediction. If a lesion erroneously gets classified as low risk for fracture, it is possible that the patient will get referred for radiotherapy, subsequently develops a pathologic fracture, and then has to undergo surgery burdened with both risk factors for complications. Unfortunately, up to date there is still no accurate and quick method for determining the risk of fracture. The well-known Mirels classification is still commonly used[21] despite studies showing its poor predictive value resulting in an overestimation of the fracture risk.[22] We would therefore advise to refrain from using the Mirels classification any longer. Van der Linden et al. advise to use 3-cm cortical involvement as a cut-off point.[23,24] The most promising are CT-based algorithms that are currently being developed.[25] Once such models will be able to provide quick predictions in the clinical setting, hopefully the everlasting question of how to determine the fracture risk will belong to the past. Actual fracture as a risk factor has been recognized previously[26] and the clinical and economic benefits of prophylactic stabilization are well known.[27] The association of radiotherapy before surgery with an increased risk of implant revision has been reported;[11] we were able to analyze the topic further with respect to additional risk factors in the present study. When a patient presents after radiotherapy and with an actual fracture, the prognosis of the implant is already influenced, even before any incision has been made. If these patients are expected to survive for a reasonably long period of time, a prosthesis could be considered. However, in patients with only short- or medium-term expected survival, an IM nail remains an adequate choice because the risk of complications and revision seems low. Use of adjuvant cement and stricter followup with regular radiographs to recognize failure in an early stage could be considered for patients with risk factors.

Others have reported the risk of revision to range between 0% and 14%, which is comparable to the revision percentage in this cohort (5% [12 of 228]).[5,6,9,11,13,14,28-30] It was striking to observe that the early revisions (within 6 months) were predominantly the result of tumor progression (of kidney, thyroid, and breast cancer), whereas implant breakage generally did not occur until later. This observation has not, to our knowledge, been described previously and could be an expression of the aggressiveness of certain tumors. The primary reason for the low frequency of complications and revisions is the short overall survival of this patient population (median, 6 months). Most patients die of metastatic disease before complications have had time to develop. The association between failure and revision and survival is well known,[5,9,11,13,31-33] but to our knowledge, this is the first study that shows this result in such a large cohort. The low percentages of complications and revisions also show that the implant selection of this cohort was well chosen to the needs of the patient and his or her disease, including survival estimation. The latter is an important step to identify the adequate surgical modality. Only a precise survival estimation will enable a "once and for all" treatment, which should be aimed for in the palliative setting, and prevent over- and undertreatment. Several models have been developed to aid surgeons in estimating survival.[34-36] One of these models has been transformed into a dynamic application (OPTIModel; www.optimal-study.nl/tool), which is available in app stores free of charge. Survival is estimated with a prognostic model including three variables (tumor profile, presence of visceral and/or brain metastases, Karnofsky performance score). The prognostic model was based on a large retrospective study and validated by an external data set. [37]

We found that the cumulative incidences of local complications, implant breakage, and revisions after IM nails for femoral pathologic fractures are low, but that the success rate of revision surgery is poor. Actual (as opposed to impending) fractures and preoperative radiotherapy were independently associated with a higher risk of implant breakage, and actual fractures and lack of the use of cement were independently associated with a higher risk of revision. Surgeons might consider treating patients with these risk factors and a long expected survival with prosthetic reconstructions. If expected survival is short or medium term, IM nailing remains a suitable option; however, adjuvant cement and closer followup should be considered. Future studies should focus on the role of adjuvants (cement and radiotherapy) and their effect on implant survival. To prevent the limitations faced by the current study, these studies should be large, prospective, and, ideally, randomized. In light of the palliative intent of the treatment, not only complications and functional outcomes should be registered, but also the effect of treatment (and possible complications) on the quality of life.

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