# Optimising the treatment of patients with long bone metastases

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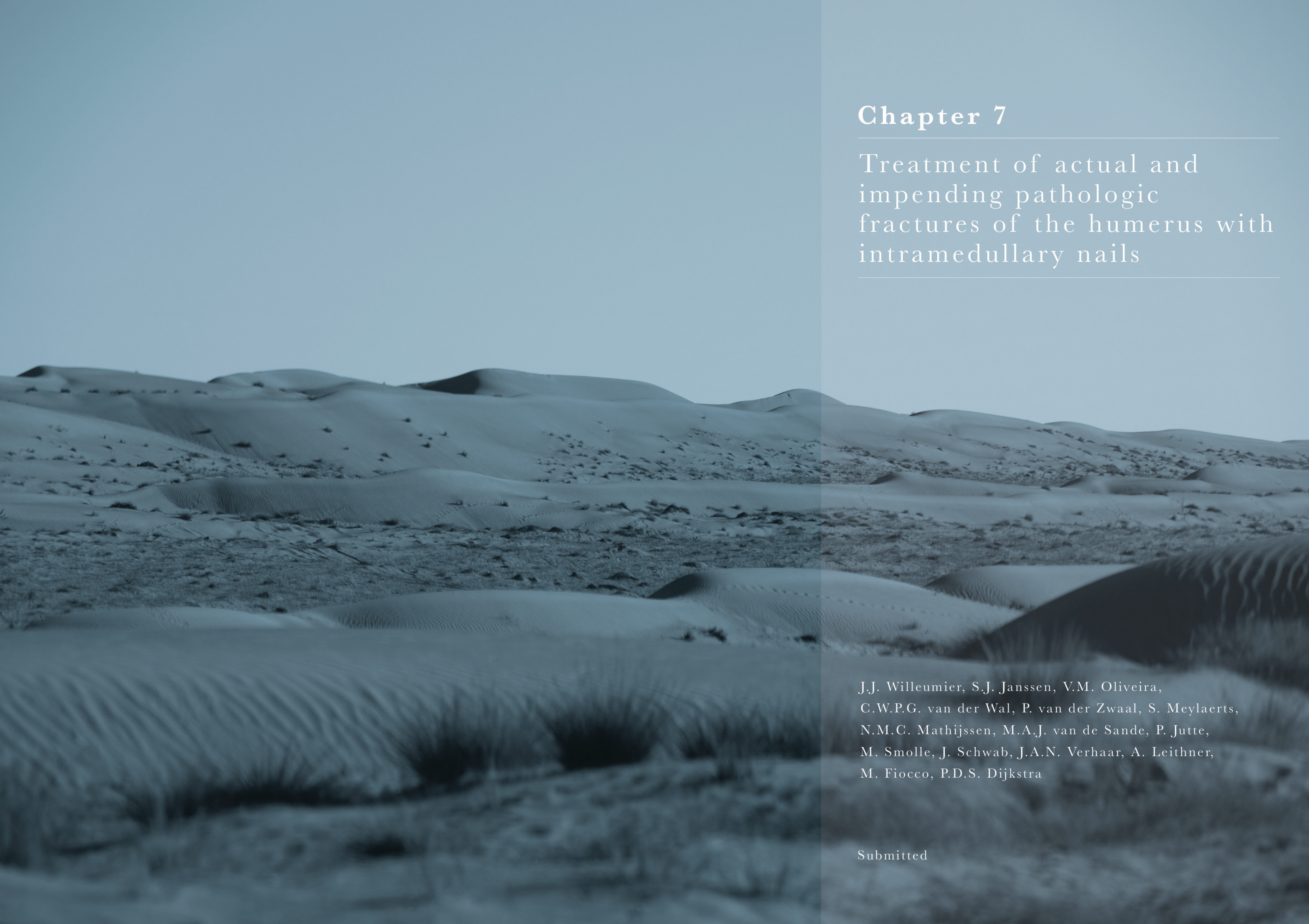
**Title**: Optimising the treatment of patients with long bone metastases
**Issue Date**: 2018-11-06



# Chapter 7

## Treatment of actual and impending pathologic fractures of the humerus with intramedullary nails

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Submitted

## Abstract

### Background

Actual and impending pathologic fractures of the humerus can be challenging to treat. The (prophylactic) fixation of a pathologic fracture due to bone metastases is a palliative treatment and should aim at direct rotation-stabilization, enabling immediate use while corresponding with the expected survival. Up to date, no risk factors for failure of intramedullary nails in humeral pathologic fractures have been identified.

### Purposes

Among patients treated with intramedullary nails for actual or impending pathologic fractures caused by bone metastases of the humerus:

(1) What is the cumulative incidence of failure?
(2) What are risk factors for failure?
(3) What per-operative and postoperative (neurological) complications occur?

### Methods

Between 2000 and 2015, 178 patients in eight centers were treated with IM nails for 182 actual (n=143, [79%]) or impending (n=39, [21%]) pathologic fractures of the humerus caused by bone metastases, of which 62% were located in the diaphysis. Throughout the study period general indications for an intramedullary nail were an impending fracture, a fracture of the diaphysis, or a proximal fracture with sufficient bone stock in the humeral head. The cohort consisted predominantly of women (61% [n=108]) and the median age was 62.7 years (range 33.5–88.9).

### Results

Twenty-three failures were registered, leading to an overall failure rate of 12.6% (23/182). Cumulative incidence of failure was 1.1% at 1 month (95%CI 0–2.6), 3.3% at three months (95%CI 0.7–5.9), 3.8% at six months (95%CI 1.0–6.6), 8.2% at 1 year (95%CI 4.2–12.3), and 10.0% at two years (95%CI 5.6–14.5). Univariate Cox regression analysis did not show any significant association between risk factors and failures. Intraoperative complications were reported in six patients (3.3%), all concerning fractures caused by introducing the nail. Seven patients (3.8%) had neurological complications of the radial nerve.







### Conclusion

Although overall results are good, surgeons should be aware of the fact that intramedullary treatment of pathologic humeral fractures may not prove as simple as one may expect. Most important is to pursue a non-rotating and durable fixation that corresponds with the estimated survival to prevent complications that occur mainly with prolonged survival.

## Introduction

After the femur, the humerus is the second most common location for long bone metastases, causing actual and impending pathologic fractures in 16-27% of patients with metastatic bone disease.[1,2] The (prophylactic) fixation of an actual or impending pathologic fracture caused by bone metastasis is a palliative treatment and fixation should be "once and for all" to limit the burden for the patient and to regain quality of life as soon as possible. The treatment of such fractures of the humerus however can be challenging. Like all pathologic fractures caused by bone metastases, fracture healing cannot be expected.[3] Most pathologic fractures in the humerus and femur are due to rotational movements, but reconstruction of the humerus may prove more difficult than of the femur, as the predominant force on the femur is an axial compression, while the humerus is subject to a combination of axial compression (especially if a patient uses crutches or a walking aid), distraction (inherent in lifting and pulling), and rotational forces.[4,5] The rotator cuff, deltoid, pectoralis major and latissimus dorsi muscles can inflict great torsional movement on destructed bone or the fracture parts. Also the movement of the lower arm greatly affects the stability of a fractured humerus. The most important aspect of the fixation is therefore a non-rotating fixation that can withstand the rotational forces as well as control impaction and distraction and therefore enables maximal functioning.

An adequate fixation can be realized with an intramedullary (IM) nail, plate fixation, or prosthetic reconstruction.[4] Cement can be used to provide adjuvant stability.[6] An IM nail is ideally suited for impending fractures and for actual fractures in the area between 2-3 cm distal to the greater tuberosity and 5-6 cm proximal to the olecranon fossa provided that the bone stock on both ends of the humerus is sufficient.[7,8] For such actual fractures a plate fixation can also be regarded a suitable option.[9] Nailing may have several advantages over plate fixation, including; a minimal invasive approach and minimal soft tissue dissection, short operative time, protection of a long segment of bone, rigid fixation possibilities, and early rehabilitation.[8]

Important factors to take into account when deciding on the type of stabilization are the type and location of the fracture, the expected survival, and the amount of bone stock. The choice for a certain modality is currently based primarily on experience and preference of the surgeon.[10] As with the surgical treatment of many other pathologic fractures, insufficient research has been published to adequately determine which modality would fit a patient best. No randomized studies have been performed, and most retrospective studies report only small cohorts. Only two large cohorts of more than 100 patients have been published that have tried to identify risk factors for poor outcomes related to specific patient characteristics or stabilization modalities.[2,11] Such retrospective studies, trying to make comparisons between treatment modalities, are however strongly affected by indication bias and comparisons should not be made. To derive the most relevant conclusions from retrospective data, we believe focus should be on a single treatment modality in a large dataset. That does not fully eliminate indication bias, but can inform surgeons more specifically about the pearls and pitfalls of the modality once it is selected.

This multicenter study aims to determine the cumulative incidence of and risk factors for failure of intramedullary nailing for actual or impending pathologic fractures caused by bone metastases of the humerus.

## Methods

Between 2000 and 2015, 185 patients in eight centers were treated with IM nails for actual or impending pathologic fractures of the humerus caused by bone metastases. One hundred and seventy-eight patients, with 182 actual or impending humeral fractures were evaluated in this retrospective study, after local institutional review board approval. Patients with primary bone tumors (including multiple myeloma, solitary plasmacytoma, or malignant lymphoma of bone), pathologic fractures from other causes than metastases, unavailable medical records (2 patients), or receiving revision surgery after failed stabilization elsewhere (5 patients) were excluded. The study includes 72 patients that were reported in a previous cohort of humerus pathologic fractures.[11]



### Surgical treatment

Stabilization was prophylactic for an impending fracture in 21% of the cases (n=39). The most common location for both actual and impending fractures was the diaphysis (62% each; n=89 and n=24, respectively) (table 7.1). The type of operative procedure, including the type of nail, the method of fixation, and the use of adjuvant cement, was determined by the surgeon, taking the location, type of fracture, primary tumor, expected survival and patients' expectations into account. Throughout the study period, indications for an intramedullary nail were generally an impending fracture, a fracture of the diaphysis, or a proximal fracture providing sufficient bone stock in the humeral head. As multiple hospitals participated in this study, a range of intramedullary nails was used. Reaming was performed according to the manufacturers' guidelines. Most commonly, a nail of 250 mm long and 7.5 mm wide was used for stabilization (table 7.1). The proximal fixation method differed between a single spiral blade

(20%; n=36), a spiral blade in combination with a bicortical screw (10%; n=19), or one (24%; n=44), two (34%; n=61) or three (10%; n=18) locking screws (table 7.1). Almost all nails (98%) were fixated distally with one (48%; n=88), two (45%; n=82) or three (3%; n=5) bicortical screws. All patients received pre-operative prophylactic antibiotics according to each centers' protocol (most commonly cefazolin). Adjuvant cement was applied in 10% of the nails (n=19) for reinforcement of the humeral head (11%; n=2) or shaft (11%; n=2), filling of the metastatic lesion (47%; n=9), or a combination (32%; n=6). In general, cement was used if bone stock was regarded insufficient for adequate screw fixation or if the lesion was very large. Mode of cement application was open in 15 cases (79%) and percutaneous in 4 cases (21%). In 21% of the fractures (n=38; 30 actual and 8 impending fractures), radiotherapy had previously been applied, most commonly for pain. Post-operative radiotherapy was given in 58% following surgical stabilizations (n=105) after a mean of 5.1 weeks (SD 6.1). The choice of administering postoperative radiotherapy was not protocol-bound, but subject to local practice.

### Primary outcome

The aim of palliative stabilization of actual and impending pathologic fractures of the humerus is to maintain or regain function and control pain with a single intervention. The primary outcome of this study therefore was any failure of achieving this goal. This included all implant failures, and persisting pain or tumor progression requiring local treatment. Medical and radiological records were screened to collect demographic data and details on the fracture (location, type, primary tumor), the treatment (type of nail, number of screws, curettage, use and location of adjuvant cement, post-operative radiotherapy), and follow-up (complications, revisions, and last known date). Intraoperative complications, neurological complications, and infections were recorded separately.

Due to the palliative nature of the treatment and the poor health of many patients in this population, follow-up is not standardized. After radiological follow-up (at 4–8 weeks) at the orthopedic surgeon, subsequent in-person follow-up was generally performed by the primary care giver (for example, general practitioner, referring medical doctor). Follow-up visits to the orthopedic surgeon were made on an as-needed basis, thus when required by the patient. However, close collaboration between the primary care giver and the orthopedic surgeon ensured reporting of orthopedic complications. Among patients who were alive at final analysis, a follow-up moment (either in-person, by telephone or by the primary care giver) at one year was available. A total of 69% (123 of 178) of the patients died within one year, and 17% (30 of 178) were alive at 2 years. Follow-up ranged from 0.03 to 167 months. Median follow-up as calculated by reversed Kaplan Meier was 60.4 months (95%CI 15.0–105.7).

### Patients

One-hundred and seventy-eight patients with 182 actual and impending fractures were included in this study with a median age of 62.7 years (range 33.5–88.9) and prominently women (61% [n=108]). Breast (29%), lung (25%), and kidney (16%) cancer were the most common primary tumors (table 7.2). Visceral and/or brain metastases were present in 107 patients (60%).

### Survival

Median overall survival (OS) was 5.7 months (95%CI 4.8–6.7). The median OS of patients treated for an impending fracture (8.6 months [95%CI 5.5–11.7]) did not significantly differ from patients treated for actual fractures (5.3 months [95%CI 4.2–6.4]). Between primary tumors there was a large difference in median OS: 2.7 months (95%CI 0.2–5.2) for lung cancer, 6.9 months (95%CI 5.4–8.4) for breast cancer, and 21.6 months (95%CI 0.0–48.2) for kidney cancer.



### Statistical analysis

Time to failure and survival time were calculated from the date of surgery. For survival analysis, only the first treatment was included for patients with bilateral nails. A competing risk model was used to estimate the cumulative incidence of failure with death as competing event.[12] The cumulative incidence was defined as the probability of failing from a specific cause before time (t). Univariate cause-specific Cox regression analyses were performed to determine whether factors such as location, fracture type, proximal and distal fixation, cement, and pre- and postoperative radiotherapy were associated with failure. Survival curves were estimated by using the Kaplan-Meier method and compared with log-rank analysis. Median follow-up was estimated with the reversed Kaplan-Meier.[13] A p-value <0.05 was considered significant. SPSS (version 23.0, SPSS Inc., Armonk, NY) was used to perform statistical analysis. The cumulative incidence was estimated with the mstate library in R environment.[14,15]

## Results

Twenty-three failures were registered, leading to an overall failure rate of 12.6% (23/182). Cumulative incidence of failure was 1.1% at 1 month (95%CI 0–2.6), 3.3% at three months (95%CI 0.7–5.9), 3.8% at six months (95%CI 1.0–6.6), 8.2% at 1 year (95%CI 4.2–12.3), and 10.0% at two years (95%CI 5.6–14.5) (figure 7.1). Thirteen failures had a predominant mechanical component (including (peri-)

implant fracture, non-union, migration of nail or screw) whereas nine failures had a predominantly oncological cause (ranging from painful moderate tumor progression to massive recurrence) (table 7.3).

One patient developed acute compartment syndrome directly postoperatively, requiring immediate fasciotomy followed by revision surgery several weeks later. All other complications occurred after 0.4 to 57.2 months. The majority of complications with an oncological cause occurred after 12 months, while mechanical complications occurred predominantly between 6 to 12 months after surgery (table 7.4). Seventeen of the 23 failures (74%) underwent revision surgery. Two failed implants were not revised because of the patients' condition. Four patients with progressive disease received radiotherapy or a brace as opposed to revision surgery.

**Table 7.1** Fracture and treatment characteristics

| | *All* *N (%)* | *Actual fracture* *N (%)* | *Impending fracture* *N (%)* |
|---|---|---|---|
| Humeri total | 182 | 143 | 39 |
| Side: right | 102 (56) | 83 (58) | 19 (49) |
| Location | | | |
| Proximal | 61 (34) | 50 (35) | 11 (28) |
| Diaphyseal | 113 (62) | 89 (62) | 24 (62) |
| Distal | 8 (4) | 4 (3) | 4 (10) |
| Median length of nail (SD)* | 250 (22) | 250 (22) | 260 (22) |
| Median diameter of nail (SD)* | 7.5 (1.1) | 7.5 (1.0) | 7.5 (1.4) |
| Proximal fixation | | | |
| Spiral blade only | 36 (20) | 30 (21) | 6 (15) |
| Spiral blade + 1 screw | 19 (10) | 14 (10) | 5 (13) |
| 1 screw | 44 (24) | 31 (22) | 13 (33) |
| 2 screws | 61 (34) | 49 (34) | 12 (31) |
| 3 screws | 18 (10) | 16 (11) | 2 (5) |
| Not reported | 4 (2) | 3 (2) | 1 (3) |
| Distal fixation | | | |
| None | 4 (2) | 4 (3) | 0 |
| 1 screw | 88 (48) | 66 (46) | 22 (56) |
| 2 screws | 82 (45) | 66 (46) | 16 (41) |
| 3 screws | 5 (3) | 5 (3) | 0 |
| Not reported | 3 (2) | 2 (1) | 1 (3) |
| Reamed | | | |
| Yes | 138 (76) | 109 (76) | 29 (74) |
| No | 44 (24) | 34 (24) | 10 (26) |
| *(Table 7.1 continued)* | | | |
| Adjuvant cement | | | |
| Yes | 19 (10) | 15 (10) | 4 (10) |
| No | 163 (90) | 128 (90) | 35 (90) |
| Location of cement‡ | | | |
| Humeral head | 2 (11) | 2 (13) | 0 |
| Fracture / lesion | 9 (47) | 7 (47) | 2 (50) |
| Humeral head & lesion | 6 (32) | 4 (27) | 2 (50) |
| Entire shaft | 2 (11) | 2 (13) | 0 |
| Preoperative radiotherapy | | | |
| Yes | 38 (21) | 30 (21) | 8 (21) |
| No | 144 (79) | 133 (79) | 31 (79) |
| Postoperative radiotherapy | | | |
| Yes | 105 (58) | 79 (55) | 26 (67) |
| No | 77 (42) | 64 (45) | 13 (33) |

*in mm; data of 65 nails missing. ‡percentage of nails with cement. SD: standard deviation.

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**Table 7.2** Primary tumour types

| *Primary tumour* | *N (%)* |
|---|---|
| Breast | 51 (29) |
| Lung | 45 (25) |
| Kidney | 28 (16) |
| Thyroid | 9 (5) |
| Prostate | 8 (5) |
| Oesophagus | 7 (4) |
| Unknown primary | 7 (4) |
| Melanoma | 5 (3) |
| Colorectal | 4 (2) |
| Liver/pancreas | 3 (2) |
| Bladder | 2 (1) |
| Other | 9 (5) |

Univariate Cox regression analyses did not show any significant association between factors such as fracture type, fracture location, fixation technique, adjuvant cement, or pre- or postoperative radiotherapy and the risk of failure (table 7.5).

Intraoperative complications were reported in six patients (3.3%), all concerning fractures caused by introducing the nail. Seven patients (3.8%) had neurological complications: one patient had post-operative paresis of the radial nerve for which neurolysis was performed; six patients had post-operative neurapraxia of the radial nerve, which recovered spontaneously between one week and six months. No local infections were reported.

**Table 7.3** Characteristics of patients and treatments with failed intramedullary nails

| *Characteristic* | *Failures no. (%)* |
|---|---|
| Total (nails) | 23 |
| Primary tumour | |
| Breast | 6 (26) |
| Kidney | 6 (26) |
| Lung | 4 (17) |
| Thyroid | 2 (9) |
| Prostate | 2 (9) |
| Unknown primary | 2 (9) |
| Colorectal | 1 (4) |
| Fracture type | |
| Actual | 20 (87) |
| Impending | 3 (13) |
| Location | |
| Proximal | 8 (34) |
| Diaphyseal | 14 (61) |
| Distal | 1 (4) |
| Proximal fixation | |
| Spiral blade | 8 (34) |
| 1 screw | 4 (17) |
| 2 screws | 6 (26) |
| 3 screws | 4 (17) |
| Not reported | 1 (4) |
| Distal fixation | |
| None | 0 |
| 1 screw | 9 (39) |
| 2 screws | 13 (57) |
| Not reported | 1 (4) |
| Cement | |
| No | 21 (91) |
| Yes | 2 (9) |
| Radiotherapy | |
| Previous only | 3 (13) |
| Postoperative only | 14 (61) |
| Previous and postoperative | 2 (9) |
| None | 4 (17) |





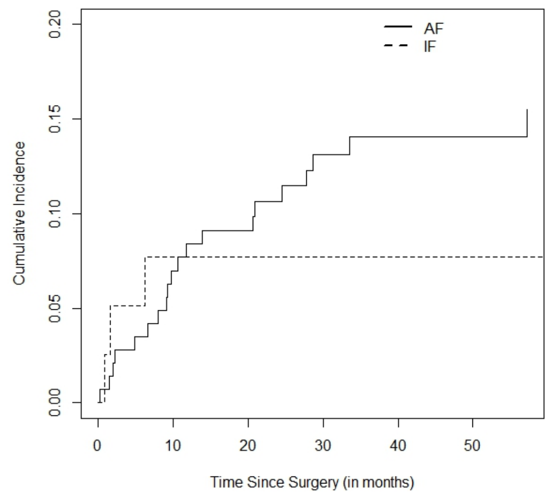


**Figure 7.1** Cumulative incidence of failure for actual (AF) and impending fractures (IF).

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**Table 7.4** Distribution of timing of complications according to origin (mechanical or oncological)

| *Months after surgery* | *Mechanical* | *Oncological* |
|---|---|---|
| 0 to less than 3 | 2 | 3 |
| 3 to less than 6 | 1 | 0 |
| 6 to less than 12 | 6 | 1 |
| 12 to less than 18 | 2 | 0 |
| 18 to less than 24 | 1 | 1 |
| More than 24 | 1 | 4 |
| Total | 13 | 9 |

**Table 7.5** Cause specific hazard ratio (HR) along with 95% confidence interval (CI) from a univariate Cox-regression model for failure

| *Variables* | *HR* | *95% CI* | *P value* |
|---|---|---|---|
| Location | | | |
| Proximal | - | | 0.932 |
| Shaft | 1.13 | 0.47 - 2.72 | 0.787 |
| Distal | 0.82 | 0.10 - 6.70 | 0.855 |
| Fracture: actual vs. impending | 2.91 | 0.82 - 10.35 | 0.098 |
| Proximal spiral blade[a] | 0.88 | 0.37 – 2.10 | 0.769 |
| Number of distal screws[b] | 0.74 | 0.31 – 1.74 | 0.486 |
| Use of cement[c] | 0.80 | 0.19 – 3.42 | 0.761 |
| Previous RT[c] | 0.92 | 0.34 – 2.50 | 0.868 |
| Post-op RT[a] | 1.70 | 0.71 – 4.60 | 0.235 |

[a]no vs. yes; [b]one vs. two; [c]yes vs. no.

## Discussion

Pathologic fractures of the humerus account for 15-31% of all pathologic fractures[16-20] and their optimal treatment is unclear. Choices for the optimal surgical modality depend partly on risk factors for failure, but these are unknown for intramedullary (IM) nails of the humerus. This retrospective cohort of 182 IM nails, the largest cohort regarding humeral IM nails for actual and impending pathologic fractures to date, shows an overall good result, but a failure percentage of 12.6% with the cumulative incidence increasing with a longer survival. None of the included variables were identified as risk factors for failure.

This study is limited by several factors. First, it is plausible that the actual incidence of complications is higher and the cumulative incidence is an underestimation because follow-up was not standardized. Nearly all studies on the treatment of bone metastases are limited by this aspect, because these patients, whose treatment is palliative and who are commonly in the last phase of life, are seen on indication as opposed to a pre-determined follow-up scheme. Second, the retrospective design of the study inherently introduces selection bias. Although this study does not compare treatment modalities, indication bias might have affected the Cox regression analyses for factors associated with failure. Furthermore, the retrospective design also limits the extent of available data for analysis. Detailed information on function and pain relief would have provided valuable information for this study, however documentation of these outcome measures has been insufficient in past medical records.

The number of failures (23; 12.6%) reported in this cohort is higher than reported in two other large studies; both Wedin et al. and Janssen et al. report 7% failures. [2,11] All reported failure percentages, including this study, are most likely an underestimation, predominantly due to lack of standardized follow-up. Furthermore, the short survival of this patient population limits the number of registered events and possibly gives a distorted perception of the performance of IM nails. The increasing cumulative incidence over time as shown in this study supports this assumption. To provide the most genuine number of failures, we scored all events that did not meet the primary goal of treatment (i.e. regain function and provide pain control with a single stabilization) as failure. If only revisions are scored, as in the studies by Janssen et al. and Wedin et al., this gives an even greater underestimation, because in the palliative setting it is not uncommon that patients with an indication for revision surgery are treated conservatively because their medical condition is too poor to undergo surgery.

The failures can be roughly categorized by their origin, mechanical or oncological, although a combination of both elements might be present in some cases. The timing of the occurrence of these complications (table 7.4) provides further information of what can be expected during follow-up. Also, based on these results, other surgical modalities could be considered in cases with a long expected survival. Oncological complications predominantly arise very shortly postoperatively or after one year. For patients with large and quick growing tumor masses, an open approach could thus be considered as opposed to a minimally invasive IM nail. In patients with an expected long survival, surgeons should be aware of the risk of failure and perhaps consider more extensive resection and reconstruction. The latter stresses the importance of survival estimation when determining the most appropriate surgical modality for each individual patient.[21] Mechanical complications arise largely between 6 and 12 months postoperatively. All healthcare providers should be aware of this, to provide timely referral and thus keep quality of life as optimal as possible.



In this large cohort, no factors (such as location, fracture type and fixation, use of cement, and preoperative and postoperative radiotherapy) were identified as significantly associated with an increased risk of failure. No previous studies have tried to identify factors related with failures of specifically intramedullary nails in the humerus for pathologic fractures. Studies by Janssen et al. and Wedin et al. only analyzed factors associated with failure of all modalities (i.e. prostheses, nails, and plates).[2,11] Unfortunately, regarding prognostic factors, the current study has brought us no further yet, for it remains questionable whether it is now correct to conclude that these factors play no role in the risk of failure. Based on experience with femoral stabilizations, an association would be expected at least with fracture type (actual or impending).[22] The lack of this association can be due to (a combination of) two factors: first, the number of impending fractures included in the cohort is small. Second, the short survival could eliminate an actual association. The lack of a significant difference in median overall survival between patients with actual or impending fractures corresponds with the results of Wedin et al.,[2] but is in contrast to IM nails in the femur.[22] This is most likely due to the difference in biomechanical loading which causes humeral impending fractures to be diagnosed later than femoral fractures thereby masquerading the difference in remaining survival between impending and actual fractures. Regarding the use of cement and preoperative radiotherapy, the lack of an association is possibly due to small number of patients (10% and 20%, respectively) who had received these adjuvant treatments.

The use of cement is supported by several authors, especially in more dated studies.[6,23] Laitinen et al. showed that the number of complications did not differ between patients treated with and without cement, but that those treated with cement experienced faster pain relief.[24] Choi et al. used cement in all intramedullary fixations, including proximal femoral lesions. They advocate the use of cement, especially in lesions affecting the humeral head; in those cases, a stable fixation could be achieved despite extensive osteolysis and thin cortex due to the use of cement.[25] In other recent studies however, the effect of cement is not evaluated because the outcomes are subject to selection bias, for cement is generally used in larger and more extensive lesions, which are a priori at a higher risk of failure. No biomechanical studies have evaluated the effect of cement in pathologic fractures of the humerus, as opposed to proven effects in the femur.[26] One of the difficulties to take into account when using cement in (extensive) humeral fractures is the risk of cement leakage and, depending on the location, associated damage of the radial nerve or joint space. Based on experience, we would advise to use cement only in situations where an IM nail is indicated but the bone-stock is insufficient to ensure firm stabilization proximal and distal to the fracture.

This study intentionally did not evaluate the indication for an IM nail. The results can however help when choosing between different surgical modalities. When choosing between a prosthesis and an IM nail, the 0% infection in this cohort of IM nails is a factor to take into account. Also, the relatively high percentages of peri-operative complications (3.3%) and postoperative complications affecting the radial nerve (3.8%) show that we should not only associate these complications with plate fixations. Particular focus should be on the radial nerve during reduction of a dislocated fracture and distal fixation.

In conclusion, this large retrospective cohort shows that intramedullary nails should be regarded as a safe and effective treatment for actual and impending pathological humeral fractures. If mechanical failure develops, this occurs mainly 6 to 12 months postoperatively. Although overall results are good, surgeons should be aware of the fact that intramedullary treatment of pathologic humeral fractures may not prove as simple as one may expect. Most important is to pursue a rotation-stable and durable fixation that corresponds with the estimated survival to prevent complications that occur mainly with prolonged survival.





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