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Optimising the treatment of patients with long bone metastases

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Chapter 8

Pathologic fractures of the distal femur: current concepts and treatment options

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Abstract

Pathologic fractures of the distal femur caused by bone metastases are not as common as those in the proximal femur but provide great difficulty to adequately treat. This systematic review shows that insufficient literature exists to draw clinically relevant conclusions for essential questions, such as 'what factors indicate an endoprosthetic reconstruction for distal femur pathologic fractures?' Due to paucity of literature in the systematic review, a current concepts review (including treatment flowchart), based on instructional reviews and experience, was also performed.

Introduction

Patients with actual or impending pathologic fractures caused by bone metastases require surgical stabilisation to regain function and quality of life. Pathologic fractures show none or only minimal healing tendencies so they cannot be treated with the same principles as traumatic fractures. The palliative intent of the treatment adds further difficulty, because the scope of the treatment should correlate with the expected survival. Stabilisation must enable immediate full weight-bearing, be sufficient for the remaining lifetime while avoiding the need for extensive rehabilitation.

The femur is the most common long bone affected by bone metastases and subsequent pathologic fractures.[1] One third of the femur metastases is located in the inter- and subtrochanteric regions, followed by the neck and diaphysis.[2,3] The distal femur is the least affected region of the femur; in our large retrospective database approximately 10% of all femoral metastases were located distally.[4] However, the distal femur is one of the most difficult areas to treat.

Treatment options include endoprosthetic reconstruction (EPR; total knee or modular tumour prostheses), single or double plate fixation, intramedullary (IM) nail fixation, and cement arthroplasty.[5] Due to the magnitude of prosthetic knee reconstructions, internal fixation is generally preferred, but due to the location sufficient screw fixation on both sides of the lesion is often not possible. Additionally, adequate fixation of screws in the condyls is often difficult due to poor bone stock. Adjuvant cement can provide more grip for the screws, but is challenging to apply to the desired location. Cement alone can also be used to fill the lesions, but is only a short-term solution when a short survival is expected.

A brief glimpse on current literature shows little mentioning of how to treat pathologic fractures of the distal femur, while all orthopaedic and trauma surgeons come across these fractures and need to decide on the most optimal treatment. With the lack of evidence, treatment is based on clinical experience, but only few surgeons have sufficient experience to depend on. The treatment of these difficult fractures is therefore a common subject of discussion and consultation among colleagues. As survival of patients with metastatic disease prolongs [6,7] and the incidence of pathologic fractures grows,[8] including those of the distal femur, the need to identify the optimal treatment of pathologic fractures of the distal femur increases. The optimal treatment however differs for each individual patient. Factors that identify the most suitable treatment would therefore be helpful for clinicians. If possible, this should be based on

peer-reviewed publications. To that end, this study aims to perform a systematic review to identify factors that indicate the need of an endoprosthetic reconstruction for a distal femur pathologic fracture. Additionally, a current concepts review was performed.

Methods

This systematic review is reported according to the MOOSE guidelines for reporting observational studies.[9]

Literature search

The search strategy was developed by an experienced medical librarian (JWS), and applied in the following databases: PubMed, Embase (OVID-version), Web of Science, COCHRANE Library, CENTRAL, CINAHL/Emcare (OVID-version), and ScienceDirect. The following keywords were used and combined with the Boolean operators 'OR' and 'AND': distal femur, metastasis, pathologic fracture, fracture, neoplasm AND surgery, treatment, endoprosthesis, intramedullary nail, plate, implant. For the different concepts, all relevant keyword variations were used (i.e. keyword variations in the controlled vocabularies as well as free text word variations). The search strategy was optimized for all consulted databases. The final search was performed on 15-12-2017. Reference lists of retrieved papers, review articles, and clinical practice guidelines were checked for relevant publications. Inclusion was limited to results in English or Dutch and publications between 1990 and 2017. Meeting abstracts, case reports, and review articles were excluded. Articles reporting on functional outcomes, complications, revisions or survival after treatment with prostheses, plate-screw fixations, IM nails, or cementplasty for an actual or impending pathologic fracture of the distal femur due to bone metastases were defined as eligible.

Articles were selected in two steps, both performed by two authors (JJW, CWPGvdW) independently. First, all titles and abstracts were screened according to the predefined criteria. Subsequently, all potentially eligible studies and all studies that could not be scored based on title and abstract were retrieved in full-text and screened based on the same criteria. Disagreements were dissolved by consensus after both steps.

Data extraction and analysis

The same two authors independently extracted data using an electronic data collection form. Available data concerning study characteristics, patient demographics, and outcome measures was collected. Outcome measures included functional outcomes as measured by an internationally accepted

standardized instrument and local complications (infections, structural failures (including implant loosening or breakage, dislocation, peri-prosthetic fracture), and tumour progression).

Statistical analysis

All data were summarized descriptively. Complications were reported as frequencies with percentages for each surgical modality. No pooled effects were estimated because the studies included did not report complication rates (including 95% confidence intervals), but only frequencies.

Quality assessment

The methodological quality of all included studies was assessed using the Methodological Index for non-Randomized Studies (MINORS) scale.[10] MINORS is a validated score for non-randomised studies based on eight items with a maximum score of 16 for non-comparative studies. A score of 12 or higher was considered as 'high' methodological quality, 9-11 was considered 'moderate', and 8 points or less was considered 'low' quality.[11] All included studies were assessed independently by two authors (JJW, CWPGvdW). Any discrepancies were resolved by consensus.

Results

Literature search

The literature search identified 469 unique titles. Figure 8.1 shows the flowchart of in- and exclusion resulting in two articles to be included in this review.[12,13] In total, 441 articles were excluded because the study population did not include distal femoral metastases, and 21 articles were excluded because although the study included distal femoral metastases, the results were not reported specifically for this group. Another 20 articles were excluded because they were reviews or case reports, 11 articles were excluded because they were not in English or Dutch, and one article was excluded because the full-text was not available. The two included studies reported on outcomes after surgery of metastases in the long bones or femur in general, but provided (some of) their results specified per location and were thus eligible for inclusion.

Study characteristics

Mavrogenis et al. report on 29 distal femur fractures in 29 patients, 16 of which treated with femoral reconstruction nails (Grosse & Kempf Locking Nail System and T2 Recon Nailing System, Stryker, Italy) and 13 were treated with fixed hinge

knee distal femoral prostheses (HMRS, Howmedica Modular Reconstruction System, Stryker, UK). Wedin et al. describe the results of 16 distal femoral fractures in 16 patients, one of which treated with a prosthesis, ten treated with plate fixation (eight with gliding screws, two with regular screws), and five with other treatment modalities (e.g. curettage). Unfortunately, no further treatment details are presented. In total, the two studies reported on 45 distal femora: 14 treated with EPR, 16 with IM nails, 10 with plates, and five with other modalities. Baseline patient characteristics were not reported specifically for the distal femur and can therefore not be presented in the current review.

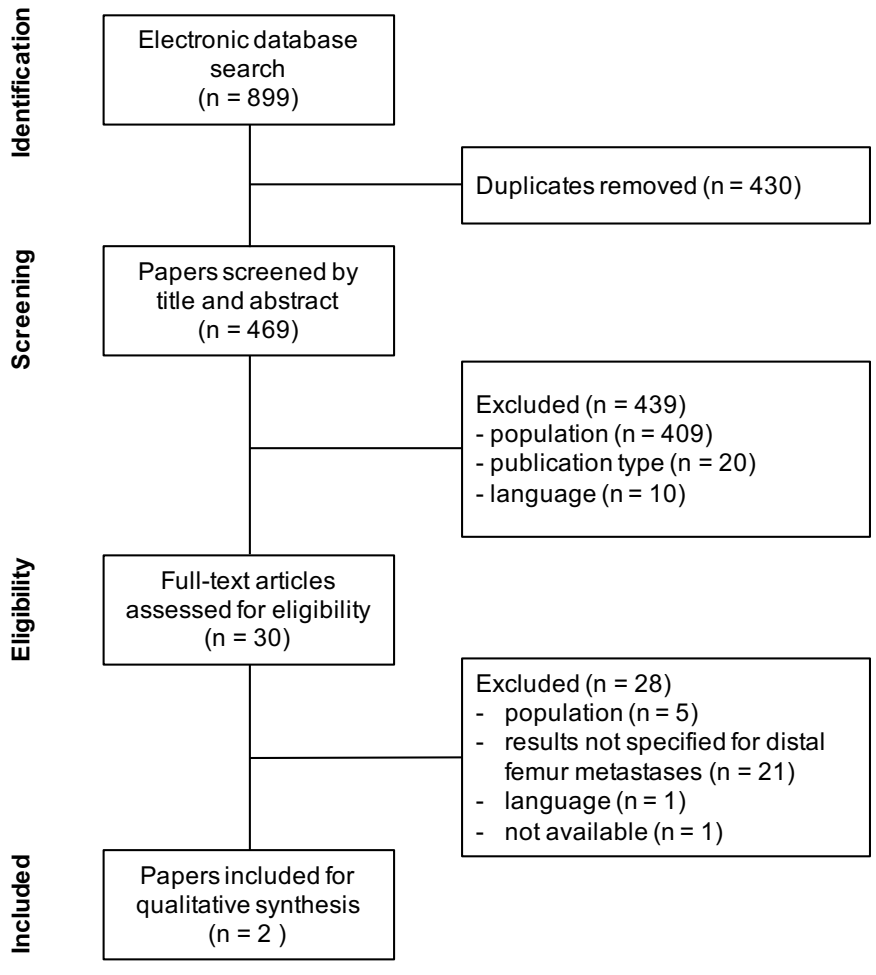

Figure 8.1 Flow chart of in- and exclusion.

Table 8.1 MINORS scale for methodological quality. Items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). Total score of 16 points is possible.

Author	*Aim*[1]	*Inclusion*[2]	*Data*[3]	*End-points*[4]	*Assess-ment*[5]	*Follow-up*[6]	*Loss to FU*[7]	*Study size*[8]	*Total*
Mavrogenis et al.	1	2	0	1	0	2	2	0	8
Wedin et al.	2	2	0	2	0	0	0	0	6

1: A clearly stated aim: the question addressed should be precise and relevant in the light of available literature.
2: Inclusion of consecutive patients: all patients potentially fit for inclusion (satisfying the criteria for inclusion) have been included in the study during the study period (no exclusion or details about the reasons for exclusion).
3: Prospective collection of data: data were collected according to a protocol established before the beginning of the study.
4: Endpoints appropriate to the aim of the study: unambiguous explanation of the criteria used to evaluate the main outcome which should be in accordance with the question addressed by the study. Also, the endpoints should be assessed on an intention-to-treat basis.
5: Unbiased assessment of the study endpoint: blind evaluation of objective endpoints and double-blind evaluation of subjective endpoints. Otherwise the reasons for not blinding should be stated.
6: Follow-up period appropriate to the aim of the study: the follow-up should be sufficiently long to allow the assessment of the main endpoint and possible adverse events.
7: Loss to follow up less than 5%: all patients should be included in the follow up. Otherwise, the proportion lost to follow up should not exceed the proportion experiencing the major endpoint.
8: Prospective calculation of the study size: information of the size of detectable difference of interest with a calculation of 95% confidence interval, according to the expected incidence of the outcome event, and information about the level for statistical significance and estimates of power when comparing the outcomes.

Quality assessment

The mean MINOR quality assessment score was 7 (table 8.1), which was considered low methodological quality. There were no items of major discrepancy between the reviewers.

Functional outcomes

Neither study reported on functional outcomes.

Complications

In the study by Mavrogenis et al. four complications were reported among 13 EPR (31%). The complications included three infections and one aseptic loosening (table 8.2). One of the IM nails failed (1/16; 6%). The complications of

the distal femur made up 83% of all complications reported (5 of 6); only one of 81 (1.2%) treated proximal and diaphyseal fractures failed, while five of the 29 (17.2%) treated distal femurs failed.

Wedin et al. reported two complications in the patients treated with plates (20%), and two in those who received curettage and augmentation (40%). Causes of the latter four failures were stress fractures in two patients and tumour progression in two cases after 7 and 13 months. The distal femur complications were 21% of all femoral complications reported in the study (15 complications in 143 proximal and diaphyseal fractures).

Overall, four of 14 EPR (29%; 9% of all distal femora), one of 16 IM nails (6%; 2% of all distal femora), two of ten plate fixations (20%; 4% of all distal femora), and two of five variety of treatments (40%; 4% of all distal femora) led to complications.

Table 8.2 Complications

Author, year	*Implant*	*Femurs (N)*	*Local complications N (%)*	*Complication*	*Treatment*
Mavrogenis et al. 2012	EPR	13	4 (31)	Deep infection Deep infection Deep infection Aseptic loosening	DAIR DAIR DAIR No treatment
Wedin et al. 1999	EPR	1	0 (0)		
Mavrogenis et al. 2012	IMN	16	1 (6)	Tumour progression	Above-knee amputation
Wedin et al. 1999	Plate	10	2 (20)	Tumour progression Stress fracture	Revision of plate with cement Revision of plate with cement
Wedin et al. 1999	Other‡	5	2 (40)	Tumour progression Stress fracture	Plate with cement Screw with cement

*Time between surgery and complications. ‡ Patients with complications had received curettage and cement; EPR: endoprothetic reconstruction; IMN: intramedullary nail; DAIR: debridement, antibiotics, irrigation, retention.

Discussion

This study aimed to systematically review the literature on treatment of distal femoral pathologic fractures and identify factors that indicate the need for endoprosthetic reconstruction. The predominant conclusion is that there are hardly any studies reporting on pathologic fractures of the distal femur. Despite broad inclusion criteria, this systematic review identified only two studies that reported outcomes regarding this subgroup of fractures; 21 studies were excluded because, despite describing the relevant study population, they did not report the outcomes specifically for the distal femur (figure 8.1). Moreover, there are no studies focussing solely on the treatment of distal femoral pathologic fractures. The paucity of studies on the distal femur as opposed to the elaborate number of studies on the proximal femur is not in proportion with the difference in incidence. A reason for the lack of publications is not apparent and cannot be clearly explained. Rarity cannot be the only reason, for studies have been published on the most uncommon diseases. Perhaps these fractures have up to now simply been overshadowed by those of the proximal femur.

The second conclusion is that based on the included studies no factors can be identified that indicate the need for an EPR. Overall, the revision rates of plates and variety of treatments (e.g. curettage and cement) are higher than of EPRs and IM nails.[13] However, taking the limitations of the studies into account, firm conclusions are not possible. The interpretation of the results of the two included studies is difficult because no baseline data is presented of the patients treated for distal femur fractures. Thus although information on the primary tumour and fracture type is reported in those cases that failed, these factors cannot be placed into perspective of the entire cohort and no risk factors can be deduced. Additionally, only one of the studies reported exactly what implants were placed and neither studies gave details on the extent of the metastatic lesion.

Several limitations are present in this study. An important limitation is the lack of baseline characteristics because it impairs detailed comparison of the cohorts. Follow-up was neither adequately reported in the included studies. Short follow-up or loss to follow-up can lead to underreporting of complications. Although an elaborate literature search was performed in six databases and bibliographies were checked for missed publications, it is possible that relevant publications were not found. Also, restricting the language to English and Dutch possibly excluded relevant studies. Further, despite the aim to focus on only distant femoral metastases, heterogeneity regarding prostheses and implants, surgical techniques and surgeons, and adjuvant treatments could not be prevented. Selection bias undeniably plays a role in the included studies.

Although this is a limitation for this study, it is also a representation of clinical practise and therefore acceptable.

In the light of the conclusions and limitations of this study, advice regarding the use of EPR for distal femoral fractures can solely be expert based. Several instructional reviews make recommendations. Quinn et al. advise to treat smaller lesions in the distal femoral area with plate osteosynthesis and polymethylmethacrylate (PMMA), while larger destructive lesions should be treated with plate fixation when the articular surface can be maintained and the joint is otherwise normal. If the latter is not the case, a total knee replacement is indicated. Quinn et al. do not further elaborate whether plate fixation should be with locking plates or classical plates.[14] Scolaro et al. note that lateral locking plate osteosynthesis (LPO) with lesion curettage and PMMA provide reliable fixation for extra-articular and well-contained lesions, but IM nailing with PMMA or EPR are also options. For intra-articular or uncontained lesions an EPR should be used.[5] A similar conclusion is presented by Bryson et al., noting that if bone stock is adequate conventional fixation with locking plates of retrograde nailing with PMMA is usually sufficient.[15] Anract et al. report that LPO (with cement to strengthen the construct) should be used in patients whose life expectancy is short or when union of the fracture can be expected after adjuvant therapy. In other situations, resection and reconstruction with a tumor prosthesis is advised.[16] Concerning the use of LPO as described by Anract et al. we do not completely agree, for union should rarely be expected. Therefore, in our own instructional review, we recommend locking plate fixation with adjuvant PMMA if the bone stock is sufficient for adequate grip of the screws, irrespective of any expected union. If the condyles are largely affected or a long survival is expected a prosthesis should be considered. If the lesion is more metaphyseal and impending with sufficient bone stock in the condyls, an IM nail should be considered.[17] Whether IM nails should be placed ante- or retrograde is debatable and is not discussed in the cited instructional reviews. In trauma surgery, (reamed) antegrade and retrograde placed nails for distal femur fractures have shown comparable results regarding union and complications.[18,19] These results are however difficult to translate to the (impending) pathologic fracture population. For the fixation of pathologic fractures, all nails should be locked and sufficiently bridge the lesion, which for antegrade nails often means they should extend to the subchondral level. The risk of intra-articular metastatic spread is a proclaimed downside of retrograde nailing. Opening of the joint can lead to other complaints such as knee pain or osteoarthritis. Nail protrusion caused by insufficient distal fixation in poor bone stock can require revision surgery, although adequate use of PMMA can decrease this risk. Also, the alignment of the knee in the frontal plane can be a

problem with retrograde placing of nails. Finally, it should be noted that the use of retrograde nails has its limitations as it leaves the femoral neck unprotected and thus at risk for fracture after stabilisation. The incidence of these complications in pathologic fracture treatment is however not known. One small study reports of one nail protrusion into the knee after retrograde fixation in 12 distal femur fractures.[20]

As mentioned in previous instructional reviews, plate osteosynthesis plays a large role for distal femoral fixations; much larger than for other femoral locations. Osteosynthesis with locking compression (LC) plates is the current standard, as opposed to reduction with dynamic compression (DC) plates. LC plates function as internal fixators with multiple fixation points, creating a stable construct [21] and therefore double plating (two DC plates in 90-degree angle) is redundant. In fractures where both LPO and IM nail fixation would be suitable options, it is not evident which of the two should be preferred. However, PMMA commonly plays a role in the stabilisation – requiring clear access of the fracture – and this is easily combined with open reduction and plate fixation. Adequate cementation with IM nailing is difficult and often insufficient. Some authors prefer IM nails over LPO because less soft tissue dissection is required which is preferable as to prevent local soft tissue complications from post-operative radiotherapy.[20] The necessity of post-operative radiotherapy however, not only after ORIF but also after EPR, should be reconsidered. The use of post-operative radiotherapy has become common practise, but the evidence upon which it is based is limited to one 20-year-old retrospective study with few patients.[22]

Based on the instructional reviews, EPRs are indicated when the articular surface is affected, the condyles are largely affected or a long survival is expected. The latter is the case when it concerns a solitary metastasis, especially from renal cell cancer [23] or a favourable presentation of breast or thyroid cancer. This is illustrated by the case presented in figures 8.2a - d. The depicted case is an example in which a primary en-bloc resection and prosthetic reconstruction should have been considered. The location of the fracture and the expected long-term survival of the patient were signs that a plate fixation could be insufficient. Keeping in mind that a stabilisation of a pathologic fracture should be “once in a lifetime” and that the aim of the surgery is to maintain quality of life (i.e. full weight-bearing), a more durable option as primary stabilisation would have been preferable. Generally, such en-bloc resections and reconstructions are performed in tertiary orthopaedic-oncology centres, so patients should be referred if a more straightforward stabilisation is expected to be insufficient. Once again, the importance of adequate survival estimation is stressed. Multiple tools have been developed to aid surgeons in survival

estimation and these should be used before resection and reconstruction with endoprostheses.[4,24-26] One of the most important aspects to take into account when estimating survival is the primary tumour, for the prognosis can differ widely depending on tumour biology and available systemic options.[4] The primary tumour type and its sensitivity to radiotherapy also influences the local treatment options for impending and actual pathologic fractures. To provide an overview of the current treatment concepts a detailed treatment flowchart was developed (figure 8.3). As shown in this flowchart, the amount of bone stock (i.e. the size of a lesion and amount of cortical destruction) and whether the condyls are affected, are important aspects to take into account, in addition to the fracture type and expected survival.

Despite not answering our research question, the included studies show that the overall revision rate for the distal femur is high compared to other femoral locations. Mavrogenis et al. report a 14% revision rate in the distal femur and only 1% in the proximal femur (1 dislocation in 78 treated proximal femora).[12] Wedin et al. report 25% revision rate in the distal femur and 9% in the proximal femur (10 of 108 treated proximal femora).

The overall failure rate of EPRs in this systematic review (31%) is comparable to the overall failure rate in a study evaluating modular knee prostheses for primary tumours (29%).[27] It is however higher than the 18% complication rate of prosthetic reconstructions of proximal femur metastases as reported by Harvey et al. Moreover, in the latter study infections accounted for only half of the complications, while dislocations caused the other half. For the distal femur, as evident in the current study, infections are the most common cause of complications. This is a well-known problem with endoprostheses,[28] but should be regarded with even more caution in the metastatic population because these patients often are elderly and have further decreased immunity due to the extensive disease. Pre-operative radiotherapy has been reported as risk factor for infection in this patient population, but further analyses are required to determine whether this should affect the choice of a prosthetic reconstruction.[29]

Pathologic fractures of the distal femur are one of the most difficult pathologic fractures to stabilise, but current literature is insufficient to provide evidence based recommendations on when to use an EPR. It is easy to conclude that randomised controlled trials and subsequent meta-analyses based on such randomised studies are required to find answers. However, the heterogeneity of patients with bone metastases and the relatively low incidence of pathologic fractures, especially of the distal femur, challenge performing a valuable randomised study. A second best option would be a prospective, multicentre cohort to record all treatments and complications. Such a cohort will still face

indication bias, but with a sufficient number of patients, some robustness will be granted. A current study (Clinicaltrials.gov NCT02705157) will hopefully provide much needed data.

To conclude, based on this systematic review no evidence based recommendation can be given for the use of EPR in the treatment of distal femur pathologic fractures. The paucity of results in this literature search and poor quality of the few included studies illustrate the issues that surgeons treating pathologic fractures are constantly confronted with: there is insufficient adequate research on the treatment of pathologic fractures to answer relevant questions. International, prospective collaborations are needed to fill this void. Based on literature and expert opinion, indications for EPR in distal femur fractures are solitary metastases in patients with a long survival, a major affected joint surface, and insufficient bone stock for internal fixation.

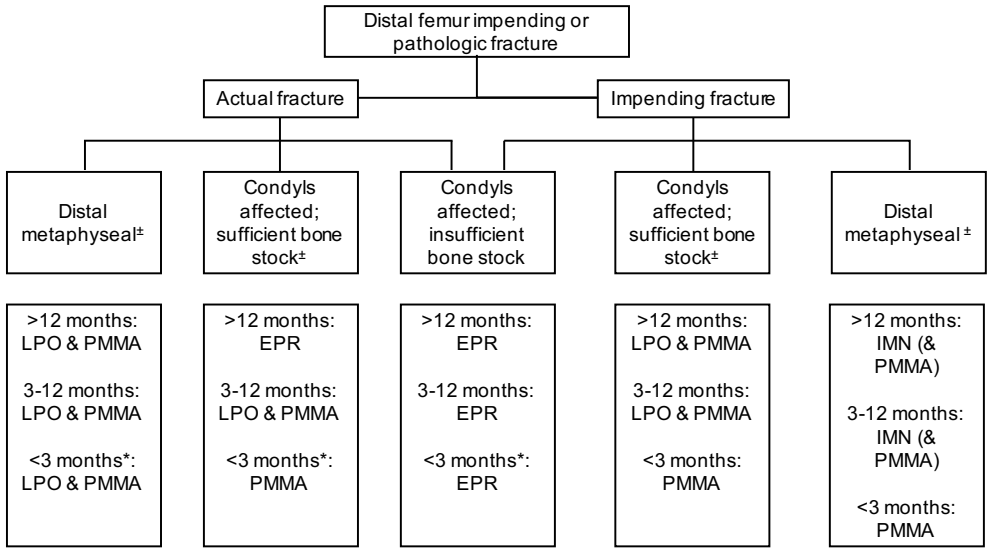

Figure 8.3 Overview of treatment options for pathologic fractures of the distal femur taking estimated survival into account.
±If the lesion concerns a distal metastasis of kidney of thyroid carcinoma an en-bloc resection and reconstruction with EPR should be considered to improve survival. *Taking expected benefit on quality of life into account. If no improvement of quality of life is to be expected, comfort care should be the preferred treatment. LPO: lateral plate osteosynthesis. PMMA: polymethylmetacrylate. EPR: endoprosthetic reconstruction.

Figure 8.2 Distal femur fracture in a 45-year-old woman caused by a solitary metastasis of renal cell carcinoma (figure a). Stabilisation of the distal femur fracture was performed with a plate osteosynthesis without cement (figure b) and post-operative radiotherapy (5 x 4Gy) was administered. A maximum load of 25 kg was set for the left leg, so the patient could only mobilise with crutches. Over the next months the knee remained painful despite optimal pain medication. Further imaging of the knee (figure c) showed that there was no consolidation of the transverse fracture, that there were also vertical fractures, and that the plate was not completely adjacent to

the bone. To improve the quality of life of the patient (i.e. pain reduction and possibility for better mobilisation) the insufficient plate osteosynthesis was revised and a distal femur resection was performed and a modular tumour knee prosthesis was implanted (figure d).
This case is an example in which a primary en-bloc resection and prosthetic reconstruction should have been considered. The location of the fracture and the expected long-term survival of the patient were signs that a plate fixation could be insufficient. Keeping in mind that a stabilisation of a pathologic fracture should be “once in a lifetime” and that the aim of the surgery is to maintain quality of life (i.e. full weight-bearing), a more durable option as primary stabilisation would have been preferable. Generally, such en-bloc resections and reconstructions are performed in tertiary orthopaedic-oncology centres, so patients should be referred if a more straightforward stabilisation is expected to be insufficient.

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