Surgical decision-making for long bone metastases

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CHAPTER 6

Outcome Of Operative Treatment Of Metastatic Fractures Of The Humerus: A Systematic Review Of 23 Clinical Studies

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ABSTRACT

Objectives

To assess: (1) functional outcome, (2) local complication rate, and (3) systemic complication rate after surgery for humeral metastases. These outcomes were narratively reported for intramedullary nailing, open reduction and internal fixation with plate and screws, endoprosthetic reconstruction, and diaphysis prosthesis.

Design

Systematic review.

Data Sources

On September 5th, 2013, we searched the Pubmed, Embase and Cochrane database for studies (published after 1980) using the keywords: pathologic and fracture and surgery, including synonyms, in title and abstract, without any limits, yielding 6,276 publications.

Eligibility Criteria For Selecting Studies

Studies reporting on functional outcome or complications after surgery for impending or actual pathological humerus fractures caused by metastatic disease. Exclusion criteria were: case-reports, studies with less than 10 patients within a treatment arm, reviews, letters to the editor, meeting abstracts, technique papers, revision procedures, and indiscernible treatment arms for humeral metastasis.

Results

Average Musculoskeletal Tumor Society score ranged from 64 to 79 (3 studies, 100 patients) after intramedullary nailing, was 90 (1 study, 24 patients) after plate-screw fixation, and 73 (1 study, 30 patients) after endoprosthetic reconstruction. Reoperation rate varied from 0 to 10% after intramedullary nailing (overall 4.4%), 5 to 14% after plate-screw fixation (overall 9.3%), 14 to 16% after diaphysis prosthesis (overall 14.6%), and 0 to 6% after endoprosthetic reconstruction (overall 2.5%). Systemic complication rate varied between 0 and 26% after intramedullary nailing (overall 2.2%), between 0 and 6% after plate-screw fixation (overall 4.8%), was 0% after endoprosthetic reconstruction, and varied between 0 and 16% after diaphysis prosthesis (overall 9.7%).

Conclusions

Reported complication rates help surgeons inform their patients and could aid in surgical decision making. Functional outcome, pain, and quality of life were poorly reported. Patient reported outcomes are therefore an important direction for future research.

INTRODUCTION

After the spine and femur, the humerus is the third most commonly affected bone by metastatic cancer.[1,2] As metastases weaken the bone, pathological fractures can occur, resulting in pain and disability. In the final stages of life, quick recovery with preservation of function is most important and can be facilitated by surgery.[1,3] In the palliative setting, the decision to undergo surgery and the surgical strategy is made by patients, their families and their doctor together. This decision depends on many factors, including: estimated survival, tumor type, extent of visceral and osseous metastasis, and the expected complications, functional outcome, reduction in pain, and quality of life.[4,5] As far as we know, no systematic review exists and small numbers of patients limit most studies focusing on impending and pathological humerus fractures resulting from bone metastases.

We aimed to provide an overview of the functional outcome and local and systemic complication rate after (1) intramedullary nailing, (2) open reduction and internal fixation with plate and screws, (3) endoprosthetic reconstruction and (4) diaphysis prosthesis, to aid patients and their doctors in their decision to undergo surgery. Secondarily, we assessed pain reduction and quality of life.

METHODS

Article Selection

We report our results according to the PRISMA Statement for reporting systematic reviews.[6] Our protocol was registered on PROSPERO prior to study selection (registration number: 2013:CRD42013006564).

We searched the Pubmed, Embase, and the Cochrane database on September 5th, 2013 using the keywords: ("pathologic*" OR "impending") AND ("fracture*") AND ("surgery" OR "surgeries" OR "operation" OR "operations" OR "operativ*" OR "surgical*" OR "intramedull*" OR "fixation*" OR "resection*" OR "osteosynth*" OR "endoprosth*" OR "prosth*" OR "arthroplas*") in title and abstract, without limits, yielding 6,276 publications.

Two reviewers (SJ, TT) independently screened the titles and abstracts and subsequently the full texts using predefined eligibility criteria. The bibliographies of included studies were checked for additional publications. Discordant judgments were resolved by consensus discussion. We included studies reporting on functional outcome, complications, pain reduction, or quality of life after surgery for humeral metastasis (including lymphoma and myeloma).

We excluded meeting abstracts, reviews, indiscernible cohorts (e.g. studies mixing primary bone tumors, revision procedures or multiple treatment modalities), studies with less than ten patients within a treatment arm, revision procedures, and studies published

before 1980. In case of overlapping cohorts (eight studies),[7-14] we included the largest cohort per treatment arm.[7,8,11,13]

Two reviewers (S.J., T.T.) independently appraised the quality of studies using predetermined criteria and extracted data using standardized sheets.

Authors were contacted if studies published after the year 2000 insufficiently reported outcomes. Of the eleven authors;[1,5,13,15-22] five responded and three provided additional data on complications[5,16] and number of patients with functional outcome[17].

Outcome Measures

Four studies reported on functional outcome by standardized measure, all used the Musculoskeletal Tumor Society score (MSTS).[17,20,23,24] The MSTS score ranges from 0 to 100 with a higher score indicating better function.[25] Functional outcome scores from studies utilizing a non-standardized score were not included (12 studies).[5,7,8,13,16,18,26-31] None of the studies reported preoperative function.

We evaluated the following complications: reoperation, deep infection, transient or permanent nerve palsy, failure or loss of fixation, peri-implant fracture, tumor progression, systemic complication, and intraoperative mortality.

Only one study reported pain reduction assessed by a standardized outcome score.[32] Fourteen studies used a non-standardized or non-numerical measure, these scores were not included.[5,7,8,11,13,16-18,23,26-31] No study reported on quality of life.

Statistical Analysis

Because of heterogeneity of the studies, no meta-analysis was performed and we narratively report results. Cumulative numbers of complications are mentioned per treatment and presented as percentage. Some studies do not report on every complication, cases in these studies were not included in the calculation.

RESULTS

Study Characteristics

Twenty-three studies were included (Figure 1); 6 studies were level III, 17 were level IV evidence (Figure 2, Appendix 1). Sixty-one percent adequately reported eligibility criteria and methods of patient selection, leaving the remainder subject to selection bias. Only 13% state which complications are to be reported, leading to possible outcome bias in the other studies. Loss to followup was high or unclear in 52% of the studies, resulting in attrition bias (Figure 2, Appendix 1).

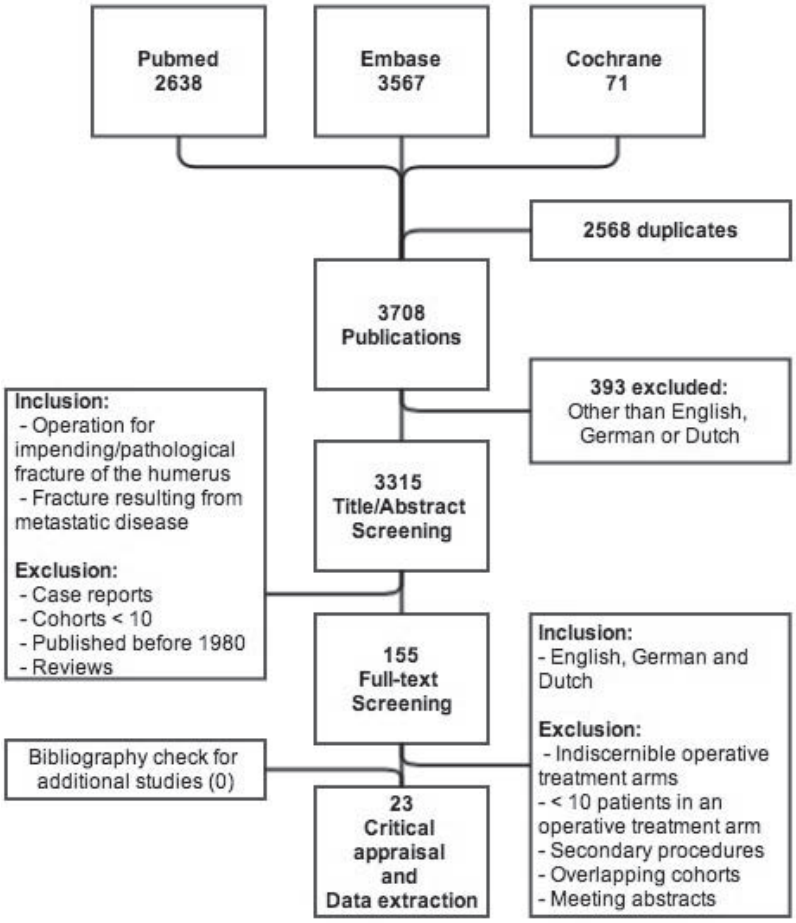

Figure 1: Flowchart demonstrating the literature search and the selection of publications including eligibility criteria.

Patient Characteristics

We included 23 studies reporting on 29 treatment arms totaling 909 fractures: 414 pathological fractures, 56 impending fractures, and in 439 cases the type of fracture was unclear. Average age varied from 58 to 78 years and the percentage men ranged between 29 and 79% (Table 1). The most common tumor types were: breast (30%), myeloma (15%), lung (15%) and kidney (13%) (Figure 3). Average survival ranged from 4 to 23 months (Table 1). The definition of an impending fracture was often unclear.

Intramedullary Nailing

Nineteen studies reported on intramedullary nailing in 596 fractures.[7,8,11,13,16,17,23,24,26-29,31-37] There were 265 pathological and 18 impending fractures. In 313 cases the type of fracture

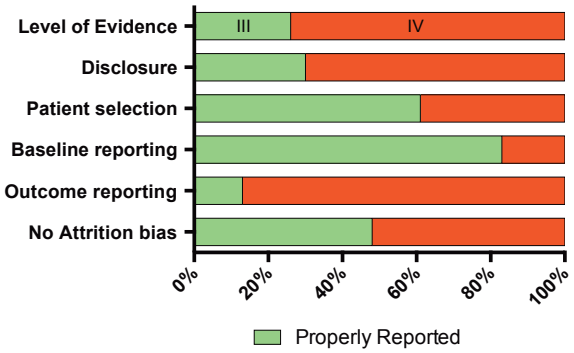

Figure 2: Overall quality of the included studies.

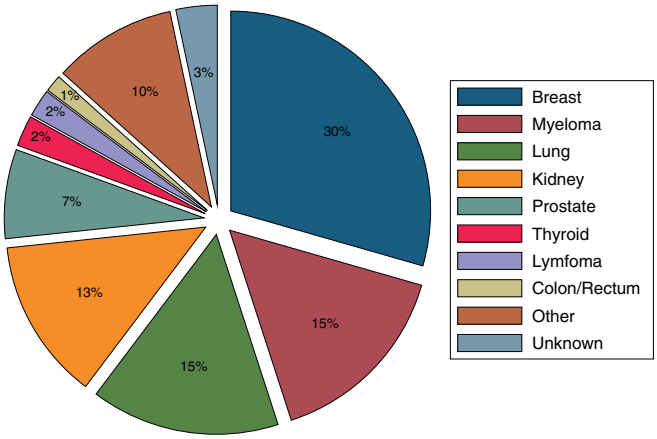

Figure 3: Distribution of primary tumors among the included studies. Tumors of the Breast, Myeloma, Prostate and Kidney were the most common. Appendix 2 demonstrates the distribution of tumors per study.

was not specified. The use of cement varied substantially from 0 to 100%. Five hundred sixty-five (95%) fractures treated with intramedullary nails were located in the diaphysis (Appendix 3).

Three studies reported on functional outcome measured by the MSTS score.[17,23,24] Mean MSTS scores reported were 64% in 20 patients after 2 months;[24] 69% in 25 patients after 6 months;[23] and 79% in 55 patients after 8 months (Table 2).[17]

One study reported on pain reduction assessed using the Visual Analog Scale (VAS) for pain. The mean score improved from 90 preoperative (range 80 to 100) to 15 postoperative (range 0 to 40) in 22 patients.[32]

Overall, 4.4% (26/585) of the intramedullary nails required reoperation, ranging from 0 to 10% among studies (Table 3). Overall, deep infection rate was 0.68% (4/585), nerve palsy rate 1.4% (8/585), failure of fixation rate 6.0% (36/596), and peri-implant fracture

rate 1.0% (5/585). Eleven studies reported on 11 cases of local tumor progression in 382 cases (2.9%); originating from lung (4 cases), kidney (3 cases), myeloma, prostate, head and neck, and in one case the tumor type was not mentioned (Appendix 4). Systemic complication rate varied between 0 and 26% (overall 2.2%, [9/406]).

Table 1: Study and patient characteristics of the included studies on humeral metastasis

Author, year	Study design	Surgical treatment modalities	Number of patients	Number of pathological or impending fractures	Mean age in years (range)	Male (%)	Minimum followup (months)	Mean survival (months)
Alvi et al., 2013	Retrospective	IMN	--	--	--	--	0	--
Wedin et al., 2012	Retrospective	IMN, PSF, EPR	208	214	67 (29 - 87)*	86 (40) †	--	9†
Laitinen et al., 2011	Retrospective	IMN	40	40	65 (38 - 95)	18 (45)	12	15
Weiss et al., 2011	Retrospective	PSF	63	63	63 (39 - 87)	43 (68)	1	--
Siegel et al., 2010	Retrospective	PSF	24	24	--	--	8	--
Piccioli et al., 2010	Retrospective	IMN, EPR	91	93	--	--	3	--
Pretell et al., 2010	Retrospective	IMN	22	23	63	13 (59)	3	23
Ofluogle et al., 2009	--	IMN	23	24	63 (43 - 81)*	19 (79) †	6	--
Sarahrudi et al., 2009	Retrospective	IMN, PSF	39	41	68 (37 - 89)*	15 (37) †	2	4†
Atesok et al., 2007	Retrospective	IMN	21	24	64 (40 - 86)	6 (29)	2	--
Hunt et al., 2006	Retrospective	IMN	14	15	62 (38 - 82)*	7 (50)	6	--
Bauze et al., 2003	Retrospective	IMN	29	31	67 (39 - 84)	14 (45) †	6	9
Piatek et al., 2003	Prospective	IMN	--	--	--	--	--	--
Franck et al., 2002	--	IMN	22	23	67 (45 - 86)*	--	--	--
Kumta et al., 2002	--	IMN	19	21	58 (39 - 88)	8 (42)	12	11†
Gebhart et al., 2001	Retrospective	IMN, EPR	53	56	62 (41 - 83)	23 (41) †	--	9†
Schurman et al., 2000	Retrospective	DP	50	50	63 (39 - 85)	--	--	12†
Flinkkila et al., 1998	Retrospective	IMN	16	18	64 (34 - 80)	4 (25)	6	5†
Muller-Farber et al., 1997	Retrospective	DP	32	32	66	16 (50)	4	15
Dijkstra et al., 1996	Retrospective	IMN, PSF	37	38	65 (43 - 89)	11 (30)	6	5
Redmond et al., 1996	Retrospective	IMN	13	16	63	7 (54)	7	4†
Ingman et al., 1994	Retrospective	IMN	15	15	78 (60 - 90)*	6 (40)	3	3†
Lancaster et al., 1988	Retrospective	IMN	52	57	62 (34 - 84)	17 (33)	1	--

IMN = intramedullary nailing; PSF = plate-screw open reduction and internal fixation; EPR = endoprosthetic reconstruction; DP = diaphysis prosthesis. -- = Not reported, * = Median, † = Per number of fractures

Open Reduction And Internal Fixation With Plate And Screws

Five studies reported on plate-screw fixation in 150 fractures.[5,8,13,20,37] There were 86 pathological and 19 impending fractures, in 45 cases the type of fracture was not specified. Cement was used in the majority of cases, between 86 and 100%. Most cases (93%, 140 of 150 cases) treated with plate-screw fixation were located in the diaphysis (Appendix 3).

One study reported a median MSTS score of 90 in 24 patients after 6 months and 90 in 12 patients after 12 months (Table 2).[20]

Overall, 9.3% (14/150) of the plate-screw fixations required reoperation; ranging from 5 to 14% among studies (Table 3). Overall, deep infection rate was 0.79% (1/126), nerve palsy rate 5.6% (7/126), failure of fixation rate 3.3% (5/150), and peri-implant fracture rate 2.4% (3/126). Local tumor progression rate varied between 0 and 13% (overall 6.0% [9/150]); and originated from: kidney (four cases), myeloma, lymphoma, colon, unknown and in one case the tumor type was not mentioned (Appendix 4). Systemic complication rate varied between 0 and 6% (overall 4.8% [5/105]).

Table 2: Functional outcome per surgical treatment modality for humeral metastasis

Author, year	Surgical treatment modality	Followup period	Patients	Mean MSTS-score (%)
Laitinen et al., 2011	IMN	6 months	25	69
Piccioli et al., 2010	IMN	8 months	55	79
Ofluogle et al., 2009	IMN	2 months	20	64
Siegel et al., 2010	PSF	6 months	24	90*
	PSF	12 months	12	90*
Piccioli et al., 2010	EPR	8 months	30	73

IMN = intramedullary nailing; PSF = plate-screw open reduction and internal fixation; EPR = endoprosthetic reconstruction; MSTS = Musculoskeletal Tumor Society Score. * = Median

Endoprosthetic Reconstruction

Three studies reporting on endoprosthetic reconstruction in 81 proximal humerus fractures.[7,17,37] Type of fracture was not specified. Several techniques for reconstruction were used: total joint arthroplasty, hemi-arthroplasty and modular prosthesis (Appendix 3).

One study reported a median MSTS score of 73 in 30 patients treated with a modular prosthesis after eight months (Table 2).[17]

Overall, 2.5% (2/81) of the reconstructions required reoperation, ranging from 0 to 6% (Table 3). Overall, deep infection rate was 1.2% (1/81), nerve palsy rate 1.2% (1/81), failure of fixation rate 2.5% (2/81), and peri-implant fracture rate 1.2% (1/81). Three cases (4.6% [3/65]) with local tumor progression were reported: originating from breast (2 cases) and kidney. No case of systemic complication was described.

Diaphysis Prosthesis

Two studies reporting on diaphysis prosthesis in 82 fractures.[18,30] There were 63 pathological fractures and 19 impending fractures.

Overall, 15% (12/82) of the diaphysis prostheses required reoperation, ranging from 14 to 16% (Table 3). Deep infection rate was 2%, nerve palsy occurred in 4% of the cases, overall failure of fixation rate was 11% (9/82), peri-implant fracture 4.8% (4/82) (Table 3). One case with local tumor progression was reported, origin of the tumor was not mentioned. Systemic complication rate ranged from 0 to 16% (overall 9.7%, [8/82]).

DISCUSSION

Pathological fractures of the humerus resulting from bone metastases lead to impaired function and pain, surgery is often indicated.[3,5,37] The reported complication rates help surgeons inform their patients and might aid surgical decision making. We encountered a paucity of reported functional outcome, pain, and quality of life data. Patient reported outcomes are therefore an important direction for future research.

There were several limitations. First, many included studies are subject to bias. This could skew our results and overestimate the benefits of treatment. Second, functional outcome was only reported by the widely used MSTS score. The MSTS score has not been vetted for floor and ceiling effects nor has it been validated. Furthermore it is commonly administered by the treating clinician rather than directly reported by the patient.[38] Third, due to lack of uniformity in reporting of treatment characteristics we were unable to account for all confounders (e.g. adjuvant treatment). Fourth, we included unpublished data that were not validated by peer review.[5,16,17]

Intramedullary nailing results in reasonable function (MSTS score 64% to 79%) and significantly reduces pain (90 preoperative to 15 postoperative). However, functional outcome is based on 100 patients with mixed followup (2-8 months), and pain reduction was measured in only 22 patients. Plate-screw fixation resulted in a MSTS score of 90 in a total of 24 patients after 6 months, and remained stable (MSTS score 90) in the 12 surviving patients.

Intramedullary nailing, plate-screw fixation, and diaphysis prosthesis were most commonly used for fractures of the diaphysis. Reoperation rate was lowest after intramedullary nailing (4.4%), followed by plate-screw fixation (9.3%), and highest after diaphysis prostheses (14.6%). The systemic complication rate was also highest for patients treated with diaphysis prostheses (9.7%), followed by those treated with plate-screw fixation (4.8%), and intramedullary nailing (2.2%). However, variation in reoperation and complication rate might be explained by other factors, such as cancer status, survival, and adjuvant treatment.

Table 3: Complication and reoperation rate per included surgical treatment modality for humeral metastasis

Author, year	Surgical treatment modality	Total Number fractures	Number of pathological fractures (%)	Number of impending fractures (%)	Reoperation (%)	Deep infection (%)	Transient or permanent nerve palsy (%)	Failure of fixation/loss of fixation (%)	Peri-implant fracture (%)	Local tumor progression (%)	Systemic complications (%)
Alvi et al., 2013	IMN	14	--	--	0	0	--	0	0	1 (7)	0
Wedin et al., 2012	IMN	148	--	--	9 (6)	3 (2)	3 (2)	2 (1)	1 (1)	0	--
Laitinen et al., 2011	IMN	40	40 (100)	0	2 (5)	1 (3)	0	2 (5)	0	--	0
Piccioli et al., 2010	IMN	57	--	--	0	0	1 (2)	6 (11)	0	0	0
Pretell et al., 2010	IMN	23	23 (100)	0	0	0	0	0	0	--	6 (26)
Ofluogle et al., 2009	IMN	24	24 (100)	0	2 (8)	0	0	6 (25)	0	2 (8)	0
Sarahrudi et al., 2009	IMN	19	19 (100)	0	1 (5)	0	0	2 (11)	0	1 (5)	0
Atesok et al., 2007	IMN	24	20 (83)	4 (17)	2 (8)	0	0	1 (4)	0	1 (4)	0
Hunt et al., 2006	IMN	11	11 (100)	0	--	--	--	2 (18)	--	--	--
Bauze et al., 2003	IMN	31	25 (81)	6 (19)	2 (6)	0	1 (3)	6 (19)	3 (10)	3 (10)	--
Piatek et al., 2003	IMN	10	--	--	1 (10)	0	1 (10)	1 (10)	0	1 (10)	0
Franck et al., 2002	IMN	23	23 (100)	0	0	0	0	0	0	--	0
Kumta et al., 2002	IMN	21	21 (100)	0	0	0	0	0	0	1 (5)	0
Gebhart et al., 2001	IMN	38	--	--	1 (3)	0	0	1 (3)	0	--	0
Flinkkila et al., 1998	IMN	18	18 (100)	0	0	0	0	0	0	--	1 (6)
Dijkstra et al., 1996	IMN	18	11 (65)	7 (5)	1 (6)	0	0	3 (17)	1 (6)	0	1 (6)
Redmond et al., 1996	IMN	16	15 (94)	1 (6)	1 (6)	0	0	0	0	1 (6)	0
Ingman et al., 1994	IMN	15	15 (100)	0	0	0	0	0	0	--	1 (7)
Lancaster et al., 1988	IMN	46	--	--	4 (9)	0	2 (4)	4 (9)	1 (2)	--	0
Wedin et al., 2012	PSF	21	--	--	3 (14)	0	0	2 (10)	2 (10)	0	--
Weiss et al., 2011	PSF	63	48 (76)	15 (24)	7 (11)	1 (2)	2 (3)	1 (2)	0	5 (8)	4 (6)
Siegel et al., 2010	PSF	24	--	--	2 (8)	--	--	0	--	3 (13)	--

Table 3: Complication and reoperation rate per included surgical treatment modality for humeral metastasis (*continued*)

Author, year	Surgical treatment modality	Total Number fractures	Number of pathological fractures (%)	Number of impending fractures (%)	Reoperation (%)	Deep infection (%)	Transient or permanent nerve palsy (%)	Failure of fixation/loss of fixation (%)	Peri-implant fracture (%)	Local tumor progression (%)	Systemic complications (%)
Sarahrudi et al., 2009	PSF	22	22 (100)	0	1 (5)	0	4 (18)	1 (5)	1 (5)	0	0
Dijkstra et al., 1996	PSF	20	16 (80)	4 (20)	1 (5)	0	1 (5)	1 (5)	0	1 (5)	1 (5)
Wedin et al., 2012	EPR	35	--	--	2 (6)	1 (3)	0	2 (6)	1 (3)	0	--
Piccioli et al., 2010	EPR	30	--	--	0	0	1 (3)	0	0	3 (10)	0
Gebhart et al., 2001	EPR	16	--	--	0	0	0	0	0	--	0
Schurman et al., 2000	DP	50	40 (80)	10 (20)	7 (14)	1 (2)	2 (4)	6 (12)	1 (2)	1 (2)	8 (16)
Muller-Farber et al., 1997	DP	32	23 (72)	9 (28)	5 (16)	--	--	3 (9)	3 (9)	--	0

IMN = intramedullary nailing; PSF = plate-screw open reduction and internal fixation; EPR = endoprosthetic reconstruction. -- = Not reported

Interestingly, although fat embolism is reported as severe complications in treatment of femoral metastasis,[39-41] no cases have been reported in one of the included studies.

Kidney tumors, being the fourth most common tumor (13%), were the most common tumor resulting in local tumor progression (30%, 8 of 27 cases). Renal cell bone metastasis are minimally radiosensitive and can be very aggressive; this probably explains the high recurrence rate.

Future studies should focus on function, pain, and quality of life using validated patient reported outcome measures.[4] Validated questionnaires to assess function are the QuickDASH (Disabilities of Arm, Shoulder, and Hand),[42,43] the PROMIS upper extremity questionnaire (Patient-Reported Outcomes Measurement Information System), and the Toronto Extremity Salvage Score.[44,45] The latter one is the only questionnaire tested in patients with upper extremity tumors. Measuring function pre- and postoperatively would allow assessment of the influence of treatment on function. Complication reporting should be standardized to allow for comparison across studies. Several guidelines, such as the Clavien-Dindo classification, are developed to standardize reporting.[46,47] Commonly used instruments to measure pain are the visual analog scale (marking the pain level on a scale from 0 to 100) and numeric rating scale (scoring pain on an ordinal scale from 0 to 10). Both are easy to apply and provide valid outcome measures.[48] Quality of life can be measured using the EuroQol – 5 dimensions (EQ-5D) questionnaire, a 5-item questionnaire validated and translated in many languages to assess quality of life.[49] Finally, providing criteria for patient selection, describing baseline characteristics and adjuvant treatment, and specifying the duration of followup and survival will further enhance quality of reporting.

Again, selection bias might impact the outcomes in each of these studies and our discussion here is meant to be a starting point for further study rather than a definitive treatise comparing these methods. Conscious of these limitations, it can be concluded that several treatment options are commonly employed, depending on tumor location. Complications rates vary from study to study but intraoperative death and fat-embolism were not reported. The knowledge on complication rates helps surgeons inform their patients and guides the decision for care. Future studies should focus on functional outcome, pain reduction, and quality of life and compare treatment modalities in prospective studies. Reporting of complications should be standardized and patient selection criteria specified to allow for future comparison of treatments across studies.

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Appendix 1: Critical appraisal

Author, year	Level of evidence	Disclosure	Patient selection	Baseline reporting	Outcome reporting	No attrition bias
Alvi et al., 2013	4	+	+	-	+	-
Wedin et al., 2012	3	-	+	+	+	+
Laitinen et al., 2011	3	-	+	+	-	+
Weiss et al., 2011	4	+	+	+	-	-
Siegel et al., 2010	4	-	+	+	-	+
Piccioli et al., 2010	3	+	-	-	-	-
Pretell et al., 2010	4	+	+	+	-	-
Ofluogle et al., 2009	4	-	-	+	-	-
Sarahrudi et al., 2009	3	-	+	+	-	+
Atesok et al., 2007	4	-	+	+	-	+
Hunt et al., 2006	3	-	+	+	+	-
Bauze et al., 2003	4	-	+	+	-	+
Piatek et al., 2003	4	-	+	-	-	-
Franck et al., 2002	4	-	-	-	-	-
Kumta et al., 2002	4	+	-	+	-	-
Gebhart et al., 2001	4	-	+	+	-	+
Schurman et al., 2000	4	-	-	+	-	-
Flinkkila et al., 1998	4	-	-	+	-	+
Muller-Farber et al., 1997	4	-	-	+	-	-
Dijkstra et al., 1996	3	-	-	+	-	+
Redmond et al., 1996	4	+	+	+	-	+
Ingman et al., 1994	4	+	-	+	-	+
Lancaster et al., 1988	4	-	+	+	-	-

Level of evidence
Disclosure
+ Reported
- Not reported
Patient selection
+ Eligibility criteria, sources and methods of selection of patients described
- Potential selection bias/not described
Baseline reporting
+ Detailed baseline characteristics per surgical treatment modality (age, gender, anatomical site and primary tumor type).
- Mixed or unspecified baseline characteristics
Outcome reporting
+ Clear definition of which complications are to be reported
- Complications to be reported not specified
No attrition bias (Completeness of outcome data)
+ <20% lost to follow up, and appropriate patient selection
- >20% Patients were lost to follow-up, withdrawn or missing for outcome assessment or not mentioned

Appendix 2: Distribution of primary tumors per study

Author, year	Number of patients	Number of patho-logical or impending fractures	Breast (%)	Myeloma (%)	Lung (%)	Kidney (%)	Prostate (%)	Thyroid (%)	Lymphoma (%)	Colon/ Rectum (%)	Other (%)	Unknown (%)
Wedin et al., 2012	208	214	64 (31)	24 (12)	26 (13)	30 (14)	21 (10)	0 (0)	0 (0)	0 (0)	43 (21)	0 (0)
Laitinen et al., 2011	40	40	17 (43)	4 (10)	4 (10)	4 (10)	7 (18)	0 (0)	2 (5)	0 (0)	1 (3)	1 (3)
Weiss et al., 2011	63	63	2 (3)	14 (22)	13 (21)	13 (21)	1 (2)	4 (6)	1 (2)	1 (2)	6 (10)	8 (13)
Siegel et al., 2010	24	24	5 (21)	4 (17)	7 (29)	4 (17)	0 (0)	2 (8)	2 (8)	0 (0)	0 (0)	0 (0)
Piccioli et al., 2010	91	93	24 (26)	8 (9)	17 (19)	13 (14)	5 (5)	7 (8)	5 (5)	1 (1)	8 (9)	3 (3)
Pretell et al., 2010	22	23	2 (9)†	9 (39)†	0 (0)†	1 (4)†	2 (9)†	0 (0)†	0 (0)†	3 (13)†	6 (26)†	0 (0)†
Ofluogle et al., 2009	23	24	5 (22)	2 (9)	12 (52)	3 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)
Sarahrudi et al., 2009	39	41	17 (44)	3 (8)	4 (10)	4 (10)	4 (10)	0 (0)	0 (0)	0 (0)	7 (18)	0 (0)
Atesok et al., 2007	21	24	11 (52)	2 (10)	0 (0)	2 (10)	1 (5)	1 (5)	1 (5)	2 (10)	0 (0)	1 (5)
Hunt et al., 2006	14	15	4 (29)	3 (21)	0 (0)	5 (36)	0 (0)	0 (0)	0 (0)	1 (7)	1 (7)	0 (0)
Bauze et al., 2003	29	31	8 (26)†	9 (29)†	1 (3)†	4 (13)†	0 (0)†	0 (0)†	2 (6)†	1 (3)†	6 (19)†	0 (0)†
Franck et al., 2002	22	23	5 (23)	10 (45)	7 (32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Kumta et al., 2002	19	21	5 (26)	0 (0)	5 (26)	2 (11)	2 (11)	0 (0)	0 (0)	3 (16)	0 (0)	2 (11)
Gebhart et al., 2001	53	56	25 (45)†	10 (18)†	6 (11)†	5 (9)†	0 (0)†	0 (0)†	0 (0)†	0 (0)†	10(18)†	0 (0)†
Schurman et al., 2000	50	50	18 (36)	14 (28)	5 (10)	6 (12)	2 (4)	2 (4)	0 (0)	0 (0)	3 (6)	0 (0)
Flinkkila et al., 1998	16	18	5 (31)	2 (13)	2 (13)	2 (13)	0 (0)	1 (6)	0 (0)	0 (0)	2 (13)	2 (13)
Muller-Farber et al., 1997	32	32	11 (34)	1 (3)	5 (16)	5 (16)	4 (13)	0 (0)	1 (3)	1 (3)	2 (6)	2 (6)
Dijkstra et al., 1996	37	38	19 (50)†	2 (5)†	3 (8)†	7 (18)†	1 (3)†	0 (0)†	1 (3)†	0 (0)†	4 (11)†	1 (3)†
Redmond et al., 1996	13	16	2 (15)	4 (31)	1 (8)	1 (8)	2 (15)	0 (0)	1 (8)	0 (0)	1 (8)	1 (8)
Ingman et al., 1994	15	15	4 (27)	3 (20)	2 (13)	0 (0)	3 (20)	0 (0)	1 (7)	0 (0)	0 (0)	2 (13)
Lancaster et al., 1988	52	57	20 (38)	17 (33)	4 (8)	3 (6)	1 (2)	1 (2)	2 (4)	2 (4)	1 (2)	1 (2)

Alvi et al. 2013 & Piatek et al. 2003 did not report primary tumor distribution of operated humeral metastasis cases.
-- = not reported, † = per fracture

Appendix 3: Surgical treatment characteristics

Author, year	Surgical treatment modality	Total (Impending) Pathological Fractures	Cement	Antegrade nailing	Proximal Humerus	Diaphysis	Distal Humerus	Type of implants
Alvi et al., 2013	IMN	14	--	--	--	--	--	Locked intramedullairy nail
Wedin et al., 2012	IMN	148	45 (30)	--	29	117	2	Locked intramedullairy nail
Laitinen et al., 2011	IMN	40	21 (53)	40 (100)	0	40	0	Synthes UHN
Piccioli et al., 2010	IMN	57	48 (84)	57 (100)	0	57	0	Synthes UHN
Pretell et al., 2010	IMN	23	0 (0)	23 (100)	0	23	0	Acumed Polarus nail, Synthes UHN, Smith & Nephew TriGen nail
Ofluogle et al., 2009	IMN	24	--	24 (100)	0	24	0	Acumed Polarus nail, Synthes PHN, Hipokrat C-75 nail
Sarahrudi et al., 2009	IMN	19	0 (0)	--	0	19	0	Synthes UHN, Howmedica Seidel nail, Sanatmetal AR-nail
Atesok et al., 2007	IMN	24	5 (21)	24 (100)	0	24	0	Synthes UHN
Hunt et al., 2006	IMN	11	6 (55)	--	0	11	0	Locked intramedullairy nail
Bauze et al., 2003	IMN	31	4 (13)	24 (77)	0	31	0	Austofix nail
Piatek et al., 2003	IMN	10	--	8 (80)	0	10	0	Russell-Taylor, bundle nail
Franck et al., 2002	IMN	23	0 (0)	15 (65)	0	23	0	Fixion expandable nail
Kumta et al., 2002	IMN	21	21 (100)	0 (0)	0	21	0	Ender rods
Gebhart et al., 2001	IMN	38	38 (100)	--	--	--	--	Hackethal nail, Rush rods, Howmedica Seidel nail
Flinkkila et al., 1998	IMN	18	--	18 (100)	0	18	0	Howmedica Seidel nail, Kuntscher nail, St-Pro nail
Dijkstra et al., 1996	IMN	18	0 (0)	11 (61)	0	18	0	Locked intramedullairy nail
Redmond et al., 1996	IMN	16	0 (0)	16 (100)	0	16	0	Biomet Uniflex nail
Ingman et al., 1994	IMN	15	0 (0)	3 (20)	0	15	0	Locked intramedullairy nail
Lancaster et al., 1988	IMN	46	31 (67)	--	--	--	--	Kuntscher nail, Rush rods, Ender rods
Wedin et al., 2012	PSF	21	18 (86)	NA	0	11	10	Plate-screw fixation
Weiss et al., 2011	PSF	63	63 (100)	NA	0	63	0	Plate-screw fixation
Siegel et al., 2010	PSF	24	24 (100)	NA	--	--	--	Synthes proximal humeral locking plate

Appendix 3: Surgical treatment characteristics (*continued*)

Author, year	Surgical treatment modality	Total (Impending) Pathological Fractures	Cement	Antegrade nailing	Proximal Humerus	Diaphysis	Distal Humerus	Type of implants
Sarahrudi et al., 2009	PSF	22	22 (100)	NA	0	22	0	Synthes DCP, Synthes LCP, Synthes Philos, Y-plate Synthes
Dijkstra et al., 1996	PSF	20	20 (100)	NA	0	20	0	Plate-screw fixation
Wedin et al., 2012	EPR	35	--	NA	35	0	0	Hemi-arthroplasty, total joint arthroplasty, modular tumor prosthesis
Piccioli et al., 2010	EPR	30	--	NA	30	0	0	Modular tumor prosthesis
Gebhart et al., 2001	EPR	16	--	NA	16	0	0	Proximal endoprosthesis
Schurman et al., 2000	DP	50	--	NA	0	50	0	Diaphyse prothesis
Muller-Farber et al., 1997	DP	32	32 (100)	NA	0	32	0	Diaphyse prothesis

IMN = intramedullary nailing; PSF = plate-screw open reduction and internal fixation; EPR = endoprosthetic reconstruction; DP = diaphysis prosthesis; NA = not applicable, UHN = unreamed humeral nail, PHN = proximal humeral nail; DCP = Dynamic Compression Plate; LCP = Locking Compression Plate. -- = not reported

Appendix 4: Local tumor progression primary tumor types

Author, year	Surgical treatment modality	Number of impending or pathological fractures	Local tumor progression (%)	Origin of primary tumor
Alvi et al., 2013	IMN	14	1 (7)	Head and Neck tumor
Wedin et al., 2012	IMN	148	0	0
Piccioli et al., 2010	IMN	57	0	0
Ofluogle et al., 2009	IMN	24	2 (8)	Kidney, Lung
Sarahrudi et al., 2009	IMN	19	1 (5)	--
Atesok et al., 2007	IMN	24	1 (4)	Kidney
Bauze et al., 2003	IMN	31	3 (10)	Kidney, Myeloma, Prostate
Piatek et al., 2003	IMN	10	1 (10)	Lung
Kumta et al., 2002	IMN	21	1 (5)	Lung
Dijkstra et al., 1996	IMN	18	0	0
Redmond et al., 1996	IMN	16	1 (6)	Lung
Wedin et al., 2012	PSF	21	0	0
Weiss et al., 2011	PSF	63	5 (8)	3 x Kidney, Colon, Unknown
Siegel et al., 2010	PSF	24	3 (13)	Kidney, Myeloma, Lymphoma
Sarahrudi et al., 2009	PSF	22	0	0
Dijkstra et al., 1996	PSF	20	1 (5)	--
Wedin et al., 2012	EPR	35	0	0
Piccioli et al., 2010	EPR	30	3 (10)	Kidney, 2 x Breast
Schurman et al., 2000	DP	50	1 (2)	--

IMN = intramedullary nailing; PSF = plate-screw open reduction and internal fixation; EPR = endoprosthetic reconstruction; DP = diaphysis prosthesis. -- = not reported