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Surgical treatment for pathologic fracture

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List of publications

This summary was based on the following publications, referred to by their Roman numerals:

I. Surgical treatment for skeletal breast cancer metastases; a population based study of 641 patients.
Rikard Wedin, Henrik C. F. Bauer and Lars-Erik Rutqvist.
Accepted in *Cancer*.

II. Survival after surgery for spinal and extremity metastases. Prognostication in 241 patients.
Henrik C. F. Bauer and Rikard Wedin.
Acta Orthopaedica Scandinavica 1995; 66 (2): 143-146.

III. Cytological diagnosis of skeletal lesions; fine needle aspiration biopsy in 110 tumours.
Rikard Wedin, Henrik C. F. Bauer, Lambert Skoog, Veli Söderlund and Edneia Tani.
Journal of Bone and Joint Surgery [Br] 2000; 82-B: 673-8

IV. Failures after operation for skeletal metastatic lesions of long bones.
Rikard Wedin, Henrik C. F. Bauer and Peter Wersäll.
Clinical Orthopaedics and Related Research 1999; (358): 128-139.

Abstract

Aim

To evaluate epidemiology, prognosis and diagnostics in metastatic bone disease and identify risk factors for failure after operation for pathologic fracture.

Patients

The study was based on patients treated for skeletal metastases, myeloma or lymphoma between 1986 and 1998 at the Oncology Service, Department of Orthopedics, Karolinska Hospital and on patients diagnosed with symptomatic skeletal metastases 1989-1994 in the Stockholm Region.

Epidemiology

641 breast cancer patients were diagnosed with symptomatic skeletal metastases 1989-1994. Based upon 1100 new primary breast cancer cases yearly, the overall risk of developing symptomatic skeletal metastases was 10–15%. One out of 5 patients with skeletal metastases required surgical treatment for skeletal complications.

Prognosis

The survival rate after surgical treatment for skeletal complications was 0.3 at 1 year and 0.008 at 3 years. Multivariate analysis based on 619 patients showed that complete pathologic fracture and soft tissue metastases were negative prognostic variables for 1-year survival after operation. Solitary skeletal metastasis, breast, prostate, kidney cancer, myeloma, and lymphoma were positive variables.

Diagnosis

Fine Needle Aspiration Biopsy (FNAB) was assessed in 110 patients for diagnostic accuracy and to which extent information about primary site of the metastatic carcinoma could be gained. There were 80 patients with metastatic carcinoma, 14 with lymphoma, and 16 with myeloma. FNAB offered correct diagnosis in 9 of 10 patients and also provided guidance in the search for the primary lesions. Hence, 27 of 30 myeloma or lymphomas were diagnosed by FNAB and in half of the patients with metastatic carcinoma the site of the primary tumor could be ascertained. For patients with a suspected skeletal metastasis the search for the primary tumor may preferably start with FNAB.

Surgical treatment

Risk factors for failure after operation for pathologic fractures were identified in 192 patients treated for 228 metastatic lesions of the long bones. 26 out of 228 procedures (11%) lead to failures necessitating reoperation. Long survival after surgery was the most important risk factor for failure of the reconstruction. Kidney cancer was the primary tumor associated with the highest rate of reoperations. Reoperations were more common in the femur than in the humerus. Reconstructions based on prosthetic as opposed to osteosynthetic devices appeared safer. There was a tendency for a high reoperation rate in hospitals with few treated patients.

Conclusion

To decrease the risk of reoperation, it is important to identify patients with a long expected survival. Patients with a good prognosis should be considered for wide resection and reconstruction as applied in primary malignant bone tumors.

Introduction

One of the reasons for initiating this project was the suspicion of a high failure rate in the surgical treatment for pathologic fracture. If a reoperation is a disappointment for an otherwise healthy patient, it is often a disaster for a gravely ill patient. The main aim of this thesis was to draw attention to this important clinical problem and the fact that principles of fracture treatment are different for pathologic and traumatic fractures.

Bone metastasis is a dreaded complication in malignant disease. The precise incidence is unknown. It has been estimated that half of all patients with malignant disease will acquire metastases and half of these will arise in the skeleton. With 40,000 new cases of malignant disease in Sweden each year approximately 10,000 patients will develop skeletal metastases. However, skeletal metastases may be asymptomatic and the incidence of clinically significant skeletal metastases is lower.

Bone metastases *per se* are seldom responsible for cancer mortality but often dramatically affect quality of life by causing pain, pathologic fracture, hypercalcemia, anemia and paraparesis. These complications often occur during the last months of life; however, some patients will survive for many years. It would be of clinical importance if this subgroup of patients could be identified since long-term survival has implications for the choice of treatment.

During recent years, more attention has been directed towards improved palliative care for cancer patients with skeletal metastases. Radiotherapy remains the mainstay for painful skeletal metastases, but treatment with hormone therapy, chemotherapy and bisphosphonates are also important treatment modalities. The application of surgical treatment for pathologic fracture has increased dramatically. At our Department, the yearly number of patients operated for pathologic fracture or paraparesis has tripled during the last decade. Home based care of terminally ill patients requires an active palliative management of pathologic fractures and there has been a change in attitude among oncologist and orthopedic surgeons, favoring surgical treatment.

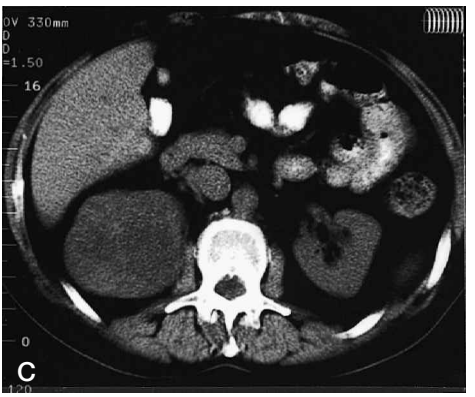
There are no prospective randomized studies of surgical treatment for pathologic fracture. Current treatment is based on retrospective analyses of single institution experience. The reported series comprise heterogeneous patient populations regarding types of primary cancer, extent of the metastatic disease, and location of the lesions. Furthermore, some patients are treated for complete fracture while others will have prophylactic stabilization for what is considered an impending fracture.

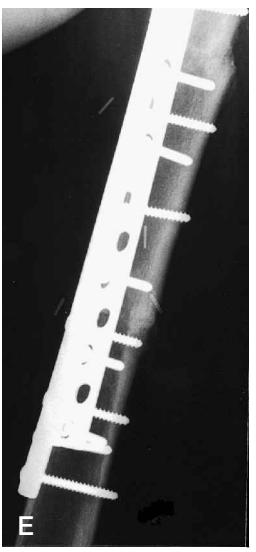
The aim of surgical treatment is to achieve immediate restoration of function while alleviating pain. The surgeon must take into consideration that pathologic fractures often will not heal and that bone destruction may proceed. There remains uncertainty whether to choose osteosynthetic devices or endoprostheses in pathologic fractures of the humerus and the femur. Estimation of the risk for fracture through a bone destruction and indications for prophylactic surgical treatment remain unclear. The role of post-operative radiotherapy needs to be defined as radiation decreases the risk of local tumor progression but increases bone-healing complications.

To improve the surgical treatment of cancer patients with pathologic fractures, the Scandinavian Sarcoma Group started the Skeletal metastasis registry in 1999. Criteria for inclusion are patients surgically treated for either impending or complete non-spinal fractures due to skeletal metastases. Orthopedic oncology centers as well as non-specialized orthopedic departments from 4 countries participate. The yearly accretion rate is at present approximated to 200 patients. Additional aims of the registry are to provide a scientific basis for treatment recommendations and to provide participating departments a tool for quality assessment as measured in terms of reoperation rate, operation morbidity and operation frequency for impending fractures.

Case report. A patient with a solitary bone destruction without other manifestations of metastatic disease presents a challenging diagnostic and therapeutic problem. The case report illustrates how the diagnosis can be rapidly achieved by cytology and radiology and that wide surgical resection of the lesion may be indicated in patients with long expected survival.

This 58 year-old previously healthy woman was referred because of gradually increasing load-related pain in her right thigh. Radiographs at the referring hospital revealed bone destruction in the diaphysis of the right femur (A and B). Fine needle aspiration biopsy revealed a metastatic carcinoma probably derived from the kidney. MRI found the primary tumor in the right kidney (C). The patient was operated 5 days later with wide excision of the bone tumor and reconstruction with an intercalary allograft fixed with two plates (D), followed by excision of the right kidney. At follow-up 10 months later, the patient has no recurrence and has regained normal function allowing dancing, swimming and use of her bicycle. Radiographs revealed that allograft incorporation was proceeding (E).





Patients

The study was based on patients diagnosed with or surgically treated for skeletal metastases, myeloma or lymphoma between 1986 and 1998 at the Oncology Service, Department of Orthopedics, Karolinska Hospital. In addition, breast cancer patients operated for skeletal complications at other Stockholm hospitals 1989–1998 were included (**I**).

I

In the epidemiological study, 641 patients diagnosed with symptomatic skeletal metastases 1989–1994 in the Stockholm Region were identified through the Breast Cancer Database.

II

The survival of cancer patients after surgical treatment for metastases to the spine or extremities was based on two consecutive patient series. The first series comprised 153 patients with extremity metastases surgically treated between 1986 and 1994 and the second 88 patients with spinal metastases operated between 1990 and 1994 (Bauer 1997). Many types of primary tumors were represented in both groups; breast cancer predominated in the extremity group and prostate cancer in the spinal group.

In this summary, the analysis of survival after surgical treatment for pathologic fracture or paraparesis was enlarged from the original 241 patients by including all 619 patients operated at our Department between January 1, 1986 to December 31, 1998.

III

444 patients were referred to our Department between 1990 and 1997 for diagnosis of skeletal lesions of unknown type. 110 of these patients diagnosed with metastatic carcinoma, myeloma or lymphoma formed the basis for this study of fine needle aspiration biopsy.

IV

The study of failures after surgical treatment for pathologic fractures of extremities was based on 192 patients treated surgically for 228 metastatic lesions from 1986 through 1995. This patient material is largely the same as the extremity series (**II**).

Epidemiology

Little is known about the incidence of symptomatic skeletal metastases or the frequency of skeletal complications necessitating surgical treatment. Previous clinical studies with large patient materials have been hospital and not population based and mostly related to clinical trials. Other studies were based on autopsy findings which are not necessarily related to clinical symptoms (Galasko 1981). The aim of this study (**I**) was to assess the prevalence of symptomatic bone metastases in a defined population of breast cancer patients.

Patients

Since 1976, the Stockholm Breast Cancer Study Group has kept a register of new cases of invasive breast cancer in the Stockholm region (population 1.8 million) (Oncologic Centre for the Stockholm-Gotland area 1999). The yearly accretion to the Breast Cancer Database from 1976 to 1994 was about 1100 patients (Fornander 1990).

We identified all patients in the Breast Cancer Database who were diagnosed with bone metastases during the 6-year period 1989–1994. The identified cases were linked with the Stockholm County Council Hospital Discharge Diagnosis Registry. Through this linkage we were able to identify patients who had been treated at any of the six orthopedic departments in the region, or at the only neurosurgical department 1989–1998.

Medical records were assessed regarding surgical treatment and reoperation rate. Survival times were estimated according to Kaplan-Meier. Comparisons of survival times were performed with the log rank test.

Results

There were 641 incident cases of bone metastases diagnosed during 1989 through 1994. The mean number of cases diagnosed each year was 107 (94–128). This figure may be compared with the yearly number of new cases reported to the database during the same period, *i.e.*, 1,147 (974–1,260) per year. The median follow-up time was 7 (4–10) years from the date of diagnosis of bone metastases for the 44 (7%) patients who remained alive at the end date of follow-up, January 31st, 1999. The 641 patients were all females with a median age of 57 (26–90) years. The median time from diagnosis of breast cancer to the diagnosis of bone metastases was 4 (0–22) years.

Among the 641 patients with bone metastases, the skeleton was the first site of relapse in 336 (52%) patients. Among the remaining 305 cases the bone metastases were preceded by loco-regional recurrences in 135 cases (21%), soft tissue metastases in 38 (6%), while 132 (21%) had multiple sites of first recurrence.

107 patients (17%) were surgically treated due to pathologic fracture or neurological complications. The operated patients did not differ from the 534 non-operated patients regarding clinical or histopathological characteristics of the primary tumor. The median survival time from the diagnosis of bone metastases was 22 months for the operated group *versus* 16 months for the non-operated. The median elapsed time from the date of diagnosis of skeletal metastases until surgical treatment for skeletal complications was 5 (0–88) months and the postoperative survival was 8 (0–100) months.

Comments

In post-mortem studies of patients who have died in breast cancer, skeletal metastases were found in 73% (Galasko 1981). In this population-based study of symptomatic breast cancer metastases the incidence was much lower. Studies based on clinical trials of adjuvant treatment will also report a higher incidence of skeletal metastases, as patients with low risk of developing metastatic disease will not be included in the trials.

According to the Stockholm Breast Cancer Database about 100 new cases of skeletal metastases were diagnosed yearly. This figure may be compared to the approximately 1,100 new breast cancer cases diagnosed in the area each year. However, non-coverage of patients with bony metastases in the breast cancer register probably also contributed to some extent. We estimate that about one fifth of all cases of symptomatic skeletal metastases were not included in the study. Hence, the overall risk of developing symptomatic skeletal metastases is 10–15%.

107 of the 641 patients (17%) developed skeletal complications leading to surgical treatment. Twenty of these (19%) were surgically treated at more than one site. This implies that there is a small fraction of breast cancer patients who have a great risk of developing skeletal complications.

Prognosis

Clinical features

In the epidemiological study (**I**), the survival of the 641 breast cancer patients presenting with skeletal metastases was 6 years after diagnosis of breast cancer and 2 years after first sign of relapse. The median survival from diagnosis of bone metastases was better for patients with loco-regional relapse (22 months), as compared to those with bone as the first site of metastases (15 months) or soft tissue relapse (12 months) (Figure 1).

The survival rate after surgical treatment for skeletal complications based on the whole series of 241 patients was 0.3 at 1 year, 0.15 at 2 and 0.008 at 3 years (**II**). There was no difference in the 1-year survival between the patients operated for spinal or extremity metastases. Hence, the metastatic site is not of major importance when deciding whether or not to operate. A complete pathologic fracture was related to shorter survival compared to patients without fracture in the extremity, but not in the spinal group. A long interval between diagnosis of the primary tumor and surgery was associated with a better survival rate in the spinal but not in the extremity group. The age of the patient did not influence survival.

Multivariate analysis showed that complete pathologic fracture, visceral or brain metastases and lung cancer were negative prognostic variables for 1-year survival. Solitary skeletal metastasis, breast and kidney cancer, myeloma, and lymphoma were positive variables.

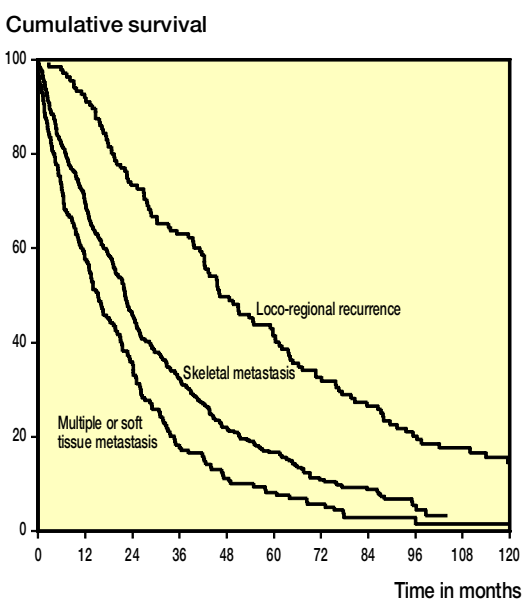


Figure 1. Survival curves of breast cancer patients based on first site of relapse.

Patients

These prognostic variables were reassessed in an enlarged patients series comprising all 619 patients operated for skeletal complications at the Department of Orthopedic Surgery, Karolinska Hospital 1986 to 1998 (Table 1).

Table 1. Clinical features of 619 patients operated for pathologic fracture or paraplegia 1986–1988

	n	%
Sex		
male	326	*53*
female	293	*47*
Site		
spine	224	*36*
pelvis	37	*6*
long bones	328	*53*
other	30	*5*
Site of primary tumor		
breast	162	*26*
prostate	137	*22*
kidney	89	*14*
myeloma	43	*7*
lung	40	*6*
unknown	25	*4*
others	123	*20*
Metastatic load		
solitary skeletal	98	*16*
multiple skeletal	320	*52*
non-skeletal also	198	*32*
History of cancer		
yes	520	*84*
no[a]	99	*16*

[a] Patients who present with pathologic fracture or epidural compression at diagnosis.

Table 2. Cox regression analysis of clinical features associated with 1-year survival after operation

Covariant	Coefficient	SD	*p*
Negative features			
Pathologic fracture	0.45	0.21	*0.03*
Soft tissue metastases	0.86	0.27	*0.002*
Positive features			
Myeloma/lymphoma	-2.01	0.39	*0.0001*
Kidney cancer	-1.51	0.34	*0.0001*
Breast cancer	-1.31	0.31	*0.0001*
Prostate cancer	-0.81	0.33	*0.01*
Solitary skeletal metastasis	-0.72	0.27	*0.008*

Results

Multivariate analysis based on all 619 patients showed that complete pathologic fracture and the presence of non-skeletal metastases remained as negative prognostic variables for 1-year survival but lung cancer did not (Table 2).

Solitary skeletal metastasis, breast and kidney cancer, myeloma, and lymphoma remained as positive variables in this larger patient material. In addition, patients with prostate cancer also proved to have better survival. There was still no difference in survival between patients operated for spinal or extremity metastases, but patients with pathologic fracture of the pelvis had a better 1-year survival (Figure 2).

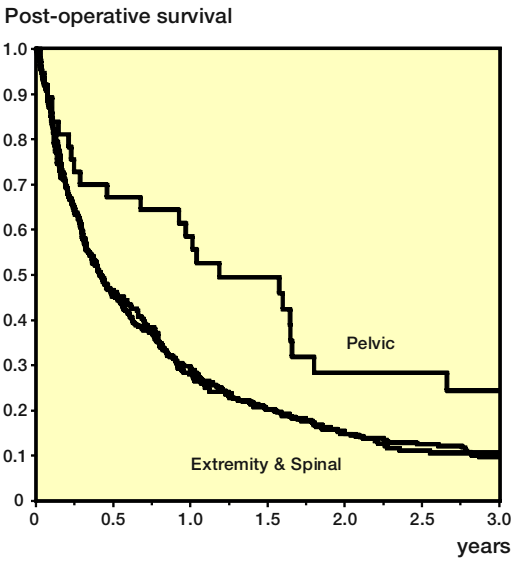


Figure 2. Survival after operation for pathologic fracture or paraparesis based on anatomical site.

Comments

This reassessment based on a large patient material shows that the identified prognostic factors remained valid. Only lung cancer lost significance as a negative prognostic feature in the multivariate but not in the univariate analysis. Prostate cancer also emerged as a positive factor for survival one year after surgery.

Patients operated for pathologic fractures of the pelvis, almost exclusively the acetabulum (Stark and Bauer 1996), survived longer than those operated for spine or extremity metastases (Figure 2). Such patients pose less of an urgent demand for surgical treatment than do patients with paraparesis or pathologic fracture of long bones. Hence, patients with fractures of the acetabulum proved to be selected for more favorable survival prognosis.

These findings show that simple clinical features can be used as a basis for pre-operative prognostication in patients with skeletal complications of metastatic disease. Tokuhashi et al. (1990) have proposed a scoring system for preoperative evaluation of prognosis in spinal metastases. Their prognostic criteria are largely similar to those found here, *i.e.* extent of metastatic disease, primary tumor and presence of pathologic fracture. They also included a grading of the neurological impairment and a performance status (Karnofsky 1949) in their scoring system. The Tokuhashi score has been validated but all such scoring systems are nevertheless biased by the fact that they are based on analysis of patients who have been selected for surgical treatment (Tokuhashi et al. 1994).

Prognostication based on clinical characteristics can be applied to select patients for wide excision and reconstruction. Although survival will probably not be improved by radical resection of solitary metastases, the morbidity associated with local failures can be reduced. The efficacy of other treatment modalities must also be taken into account; *i.e.* wide excision is often indicated in a solitary kidney cancer metastasis but not in a prostate cancer metastasis.

Long term survival after pathologic fracture in kidney cancer metastases is associated with major problems of failure of the reconstruction. DNA

flow cytometry has been applied as a prognostic tool in kidney cancer (Ljungberg et al. 1996). DNA flow cytometry has also been based on skeletal metastases of kidney cancer (Ljungberg et al. 1990). Patients with diploid (normal DNA content) metastases had longer survival after pathologic fracture than those with aneuploid. In the series of 619 patients operated at our Department, 89 had metastases of kidney cancer and DNA flow cytometry was obtained in 31 of these (unpublished). The 1-year survival was equal for patients with diploid and aneuploid metastases. However, long term survival was almost exclusively seen among patients with diploid lesions. Five of 13 patients with diploid lesions survived more than 3 years, as opposed to 1 of 17 with aneuploid metastases (p=0.06). A similar association was found in breast cancer, *i.e.* long-term survival was mostly seen in the group with diploid metastases (Figure 3). Unfortunately, DNA flow cytometric data was only available from 20% of all patients operated for pathologic fracture of breast cancer in our Department. The preliminary results warrant routine collection of tumor samples for DNA cytometry and for immunohistochemistry at the time of surgery for pathologic fracture.

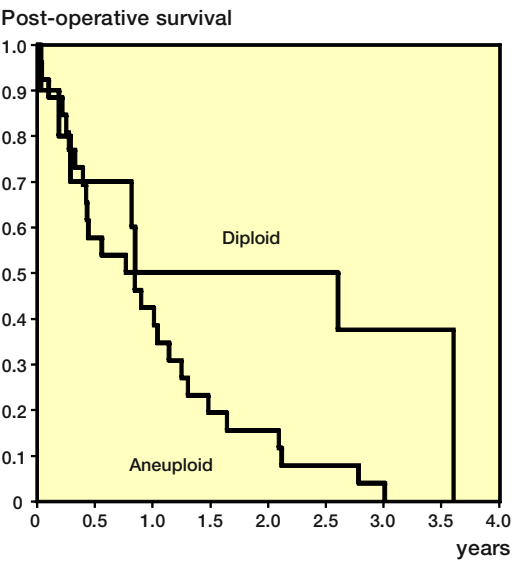


Figure 3. Survival after operation for pathologic fracture or paraparesis in patients with breast cancer. There were 10 patients with diploid metastases and 26 with aneuploid. All patients are dead except 3 with diploid metastases who are alive 1.5, 3.1 and 3.3 years after operation.

Diagnosis

A skeletal destruction in a patient without a prior history of malignant disease poses a diagnostic challenge and radiological features are seldom specific enough to allow a conclusive diagnosis. In metastatic disease knowledge about or identification of the primary tumor is of clinical importance since specific treatment may be available (Nottebaert et al. 1989, Didolkar et al. 1977). In the case of a lesion, which suggests metastatic disease, many clinicians would choose radiology to identify the primary tumor and biopsy of the skeletal lesion only if the primary tumor is not disclosed (Rougraff et al. 1993, Alcalay et al. 1995, Jacobsen et al. 1997). This strategy is based upon two assumptions. Firstly, the tissue obtained from the metastasis seldom provides information about the site of the primary tumor. Secondly, surgical biopsy is associated with significant morbidity like infection, bleeding, and contamination of surrounding tissues and discomfort associated with surgery.

Fine Needle Aspiration Biopsy (FNAB) for cytological diagnosis of bone lesions has so far only been used in some centers (Kreicbergs et al. 1996, Åkerman and Domanski 1998, Bommer et al 1997). It is a quick, atraumatic outpatient procedure readily performed in any skeletal location. The aim of the diagnostic study (**III**) was to assess to which extent FNAB allows a conclusive diagnosis of these lesions including information about primary site of the metastatic carcinoma.

Patients

Between 1990 and 1997, 444 patients were referred to the Orthopedic Oncology Service, Karolinska Hospital for diagnosis of skeletal lesions of unknown type. 119 proved to have metastatic carcinoma or myeloma/lymphoma. Nine patients were excluded, thus a total of 110 patients were included in the study. The series comprised 68 males and 42 females with a median age of 67 (4–87) years. The tumor sites were the pelvis (39), long bones (36), spine (20) and others (15).

Figure 4. CT-guided fine needle aspiration biopsy of a spinal tumor.

The FNAB was usually done under radiological guidance by a cytologist in co-operation with the radiologist. Occasionally CT guidance was used for vertebral or pelvic lesions (Figure 4). A 0.5 mm needle (25G) with stylet was used in most cases. Each aspirate was smeared on to slides, air-dried and stained with May-Grünewald-Giemsa (MGG) and material was also kept for immunocytochemistry.

The cytological diagnosis was compared to a consensus diagnosis based on radiology, clinical findings, histologic post-operative specimens as well as information from the Swedish National Cancer Registry. There were 80 patients with metastatic carcinoma, 14 patients with lymphoma, and 16 with myeloma. In 69 of the 80 patients with metastatic carcinoma, the primary tumor was identified in the lung (26), kidney (26), prostate (6), breast (2), and other sites (9). The primary site of malignancy was not found in 11 patients.

Results

FNAB offered correct diagnosis in more than 9 of 10 patients (Table 3). In the inconclusive or misleading cases the final diagnosis was made on histological material from surgical specimens and the diagnostic difficulties were of no major clinical consequences. Overall only 7 surgical biopsies were performed among the 110 patients.

Table 3. Cytological and final diagnoses

Final diagnoses	FNAB					
	Myeloma	Lymphoma	Carcinoma	Sarcoma	Inconclusive	Total
Myeloma	15				1	16
Lymphoma		12	1		1	14
Carcinoma			75	2	3	80

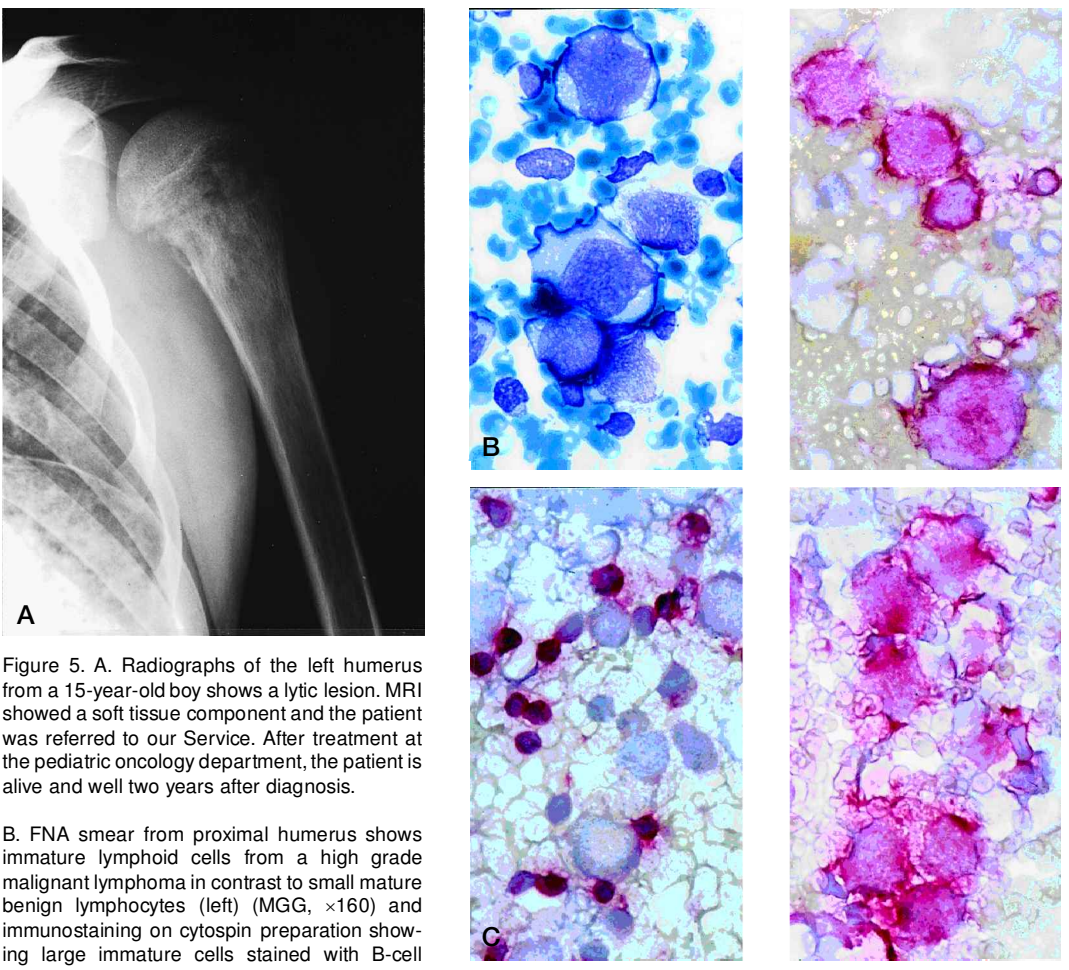


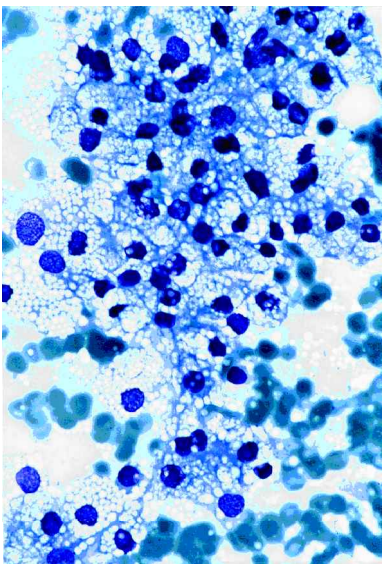
Figure 5. A. Radiographs of the left humerus from a 15-year-old boy shows a lytic lesion. MRI showed a soft tissue component and the patient was referred to our Service. After treatment at the pediatric oncology department, the patient is alive and well two years after diagnosis.

B. FNA smear from proximal humerus shows immature lymphoid cells from a high grade malignant lymphoma in contrast to small mature benign lymphocytes (left) (MGG, ×160) and immunostaining on cytospin preparation showing large immature cells stained with B-cell marker CD20 (right) (alkaline phosphatase, ×160).

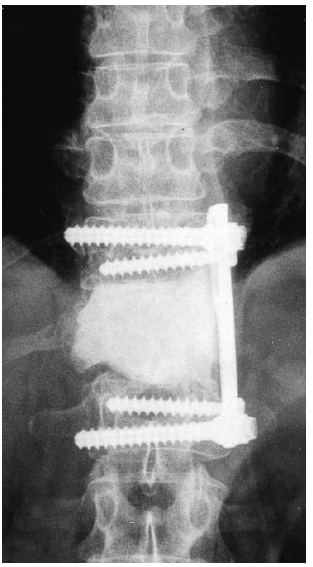
C. Immunostaining on cytospin preparation for T-cells (left) and large immature cells showing kappa light restriction (right) (alkaline phosphatase, ×160).

FNAB also provided guidance in the search for the primary lesions. Hence, 27 of 30 myeloma or lymphomas were diagnosed by FNAB (Figure 5) and in half of the patients with metastatic carcinoma the site of the primary tumor could be ascertained. Specifically, FNAB correctly identified the origin of the metastasis in 22 of the 26 patients who were found to have kidney cancer, in 13 of 26 patients with lung cancer and in 5 of 6 patients with prostatic carcinoma (Figure 6).

Figure 6. A. This 72-year-old woman had pain in the right hip and back for one year before diagnosis. Initial spinal radiographs were normal and she was treated with physical therapy. Finally a skeletal scintigraphy revealed an intense uptake in the 12th thoracic vertebra. Radiographs and MRI revealed a suspected solitary metastasis in the same vertebra.



B. FNAB smear shows metastatic kidney cancer characterized by a cluster of clear cells showing vacuolated large cytoplasm and rounded central nuclei (MGG, ×160).



C. The patient had severe pain but no neurological deficits. No other metastases were detected and the patient was treated surgically with nephrectomy and removal of the 12th thoracic vertebra from an anterior approach. Reconstruction with cement and a plate. She was reoperated 2.5 years later because of recurrent cord compression due to tumor progression and died 4 years after diagnosis.

Comments

The accuracy was high in suggesting the correct primary tumor in metastatic carcinoma of the kidney while guidance to the primary tumor was only possible in half of the lung cancer cases and rarely in metastatic carcinoma of other primary tumors. Kidney cancer will in most cases present with a typical cytomorphologic picture while other adenocarcinoma in general are more difficult to subclassify.

For patients with a suspected skeletal metastasis the search for the primary tumor may preferably be started with FNAB. The cytological diagnosis in combination with immunohistochemistry and radiology will in most cases be conclusive. Time consuming and costly investigations can be limited and surgical biopsy is only necessary if cytological diagnosis is inconclusive or fails to articulate with the radiological or clinical finding.

Surgical treatment

There is a high risk of failure after surgical treatment for pathologic fractures in skeletal metastases. The aim of the surgical reconstruction is to allow immediate and pain free weight bearing and be durable enough to last the lifetime of the patient even if the fracture does not unite and bone destruction proceeds.

In this study of surgical treatment (**IV**) risk factors for failure after operation for pathologic fractures were identified.

Patients

192 patients treated for 228 metastatic lesions of the long bones were included (**IV**). The breast was the most common site of primary tumor, followed by the kidney and the prostate. Femoral lesions predominated, followed by the humerus and the tibia. A complete fracture was evident in 141 (62%) of the lesions while 87 (38%) were operated for what was considered an impending fracture. There were 1% systemic and 10% local complications which shows that surgery is safe even in this group of seriously ill patients.

Results

26 out of 228 procedures (11%) lead to failures necessitating reoperation. The median time to reoperation was 8 months and the risk of reoperation increased linearly with time. Among the 26 reoperations, 4 were due to immediate failures (within 6 weeks of the operation), 6 to local tumor progression, 10 to non-union, and 5 to stress fracture of bone, and 1 to late dislocation of a humeral megaprosthesis and skin necrosis.

The median survival was 17 months after surgical treatment for pathologic fracture for the group of reoperated patients compared to 4 months for non-reoperated patients.

Kidney cancer was the primary tumor associated with the highest rate of reoperations, 8 of 34 cases (Figure 7). Reoperations were more common in the femur (13%) than in the humerus (5%). Reconstructions of the diaphyseal and distal femoral lesions failed in 20%, compared to the femoral head and neck in only 5%.

Among 54 endoprostheses, only 1 required reoperation (2%). Among 162 operations involving osteosynthetic devices 22 were failures (14%). Glide screw plates in the proximal femur failed in 8 of 43 cases (19%).

Comments

The mortality rate within one month of operation was 11%, which may call into question the indications for surgical treatment being too wide. Except in the obviously moribund patient, it is still not possible to accurately assess remaining survival; with narrower indications too many patients with pathological fractures may suffer unnecessarily.

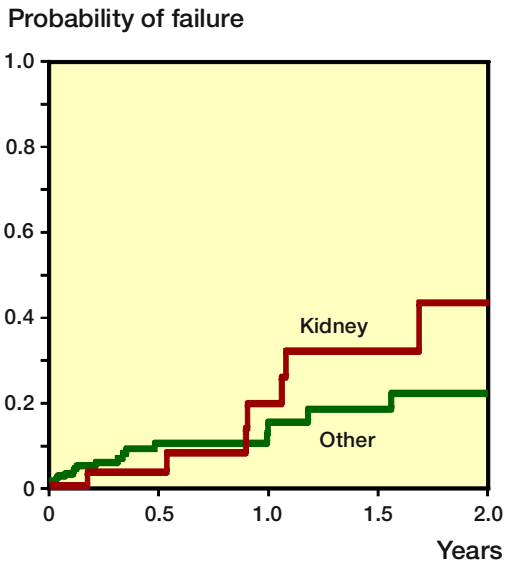


Figure 7. Reoperation rate comparing kidney cancer and other primary tumors, p = 0.4. The slope of the failure curve was the same for kidney cancer patients and for patients with other primary tumors. The high crude failure rate associated with kidney cancer was probably due to the longer survival time and not to local tumor features.

Table 4. Clinical features and reoperation rate

Factor Criteria	n	Crude failure rate n	%	Risk of reop. at 2 years [b]	p-value [a]
Age					
63 year	102	10	10	0.2	n. s.
> 63 year	126	16	13	0.4	
Site of primary tumor					
breast	83	8	10	0.2	n. s.
kidney	34	8	24	0.4	
prostate	29	3	10	0.1	
other	82	7	9	0.2	
Metastatic load					
solitary skeletal	29	6	21	0.3	n. s.
multiple skeletal	101	12	12	0.3	
visceral/brain	98	5	5	0.2	
Bone					
humerus	57	3	5	0.1	n. s.
femur/tibia	171	23	13	0.3	
Complete fracture					
yes	141	13	9	0.2	n. s.
no	87	13	15	0.4	
Reconstruction [c]					
synthesis	162	22	14	0.4	0.002
prosthesis	54	1	2	0	

[a] Mantel-Haenzel
[b] Kaplan-Meier
[c] 10 cases with cement only and two cases with no reconstruction excluded.

Figure 8. This 55-year-old man with kidney carcinoma sustained a pathologic fracture in September, 1997, treated with curettage, bone cement and a reconstruction nail. Postoperative radiotherapy was delivered. Two years later he suddenly experienced intense pain and radiographs showed nonunion and implant failure. He was reoperated with excision of proximal femur and reconstruction with a megaprosthesis, which he should have had primarily.

The increased risk of serious complications associated with long-stem prostheses and intramedullary nailing of pathologic fractures must also be taken into account (Persson and Bauer 1994, Kerr et al 1993, Pattersson et al. 1991).

Reconstructions based on prosthetic as opposed to osteosynthetic devices appeared safer (Table 4). There are several reasons why endoprosthetic replacement might be safer than osteosynthesis, especially in the trochanteric and subtrochanteric region. Endoprostheses are not dependent on fracture healing which is often poor in cancer patients due to systemic and local factors as well as radiotherapy (Gainor 1983, Bonarigo 1967, Cooley 1958). Endoprostheses are by design intended to replace bone and joints, whereas osteosynthetic implants are at best load sharing and will ultimately fail if the bone does not heal (Figure 8).

These findings were supported by the results of the epidemiological study of breast cancer metastases (**I**). Two of 14 reoperations involved endoprostheses while 7 of 27 osteosynthetic reconstructions of the proximal femur failed. These results based on operations at 6 different orthopedic departments support the use of endoprosthesis instead of osteosynthesis in the proximal femur.

Long survival after surgery was the most important risk factor for failure of the reconstruction. The risk for reoperation was almost 40 % for the few patients alive 2 years after the operation. To decrease the risk of reoperation, it is important to identify patients with a long expected survival. In patients with a good prognosis, wide resection and reconstruction as applied in primary malignant bone tumors should be considered (Figure 9). This is especially important in solitary lesions of tumors that are relatively insensitive to radiotherapy, *e.g.* kidney cancer.

The reoperation rate was also assessed at different hospitals in the Stockholm Region among breast cancer patients operated for skeletal complications (**I**). The total failure rate leading to reoperation was 11% (14/129). Half of the patients were treated at the Karolinska Hospital Orthopedic Oncology Service and half at 5 other orthopedic departments and the one neurosurgical department

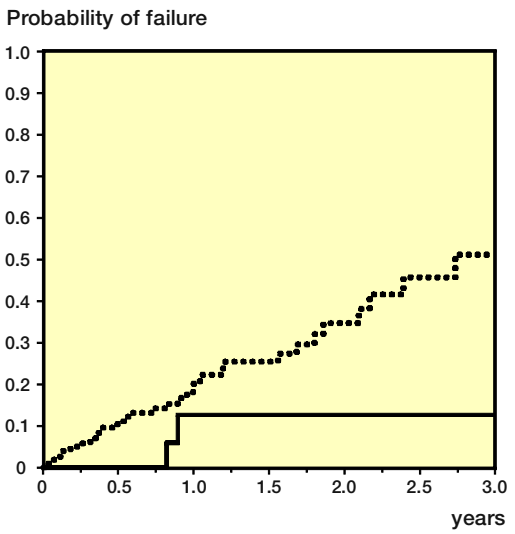


Figure 9. Reoperations for patients with pathologic fracture of the humerus or femur. Those operated with wide resection and reconstruction with megaprostheses or allografts (solid line) had a lower failure rate and longer survival (19 *versus* 4 months) than patients treated with intralesional stabilization (dotted line). It is thus possible to select a group of patients with long-term survival in whom major reconstructions are of benefit.

Figure 10. Distal humerus 6 weeks after surgical treatment with curettage, cement and a plate. The patient had not yet received radiotherapy for this metastasis of unknown origin and the radiograph already shows local tumor progression. The chosen method was not appropriate to ensue stability.

in the region. The reoperation rate at the Oncology Service was 0.06 as compared to 0.16 for the other 6 departments combined (p=0.1). There was a tendency for a high reoperation rate in hospitals with few treated patients. This may be due to inexperience both in identifying the etiology of the fracture and in the surgical treatment itself. Solutions to this problem include educational efforts and referral to specialized units in selected cases.

Postoperative radiotherapy

Radiotherapy is the treatment of choice in painful metastatic skeletal lesions unless fracture seems inevitable despite radiation. It is also routinely administered after operative treatment for pathologic fracture (Figure 10).

Uncertainties exist regarding indications for postoperative radiotherapy and the optimal dose schedule and timing that will provide adequate local tumor control without inhibiting bone healing (Bates 1992, Gainor 1983). A single fraction delivery of radiotherapy has been shown to provide equal pain relief as multiple fractions (Tong et al. 1982). However, it remains unclear to what extent skeletal complications after radiotherapy or local tumor progression is affected by different fractionation schemes. It is also unclear whether one fraction schedule is adequate for all tumor types.

In the study of surgical treatment (**IV**) radiotherapy was delivered pre-operatively (49) or post-operatively (87) in 136 of 228 cases. The reason for non-treatment may be attributed to short survival in many patients and to irradiation sensitivity since radiotherapy was common in breast cancer and myeloma while less common in kidney cancer. Most patients were treated with standard fractionation schedules of 4 Gy × 5 or 3 Gy × 10 starting within 3 weeks of the operation.

The reoperation rate in radiated fracture sites was 13% as compared to 10% in non radiated sites. Only 1 of the 6 failures due to local tumor progression had received radiotherapy and this was a case of kidney cancer, a type of tumor known to be radio-resistant. On the other hand, 8 of 10

non-unions and all 5 stress fractures occurred in patients who had received radiotherapy. Postoperative radiotherapy may decrease the risk of local tumor progression but was associated with an increased risk of stress fracture and non-union. However, only 13 of the 136 (10%) irradiated patients developed these complications. With increased use of endoprosthetic reconstructions complications to radiotherapy may become less of a problem.

Treatment recommendations

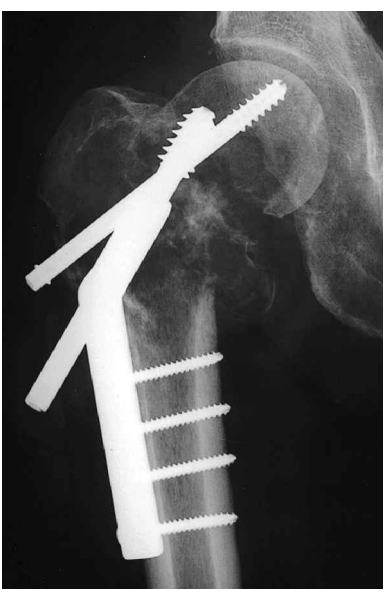
Since the aim of the surgical reconstruction is to allow immediate and pain free weight bearing, non-surgical treatment like orthoses and casts should seldom be considered even in terminally ill patients. Even if a fracture may heal with nonoperative treatment, the length of time required for healing of a pathologic fracture is inappropriate for patients with a limited life expectancy. Furthermore, it is difficult to provide radiotherapy to a patient with a painful non-stabilized fracture.

Indications for surgical treatment of impending fractures

Indication for surgical treatment of an impending fracture exists when fracture seems inevitable despite of radiotherapy. In these carefully selected cases there is much to gain by surgically stabilizing the fracture before the bone breaks. It is easier to stabilize the bone while it is still intact and it saves the patient from suffering a painful fracture. A patient with a life expectancy of less than two months rarely benefits from prophylactic stabilization. Indications for surgery increases with longer life expectancy and the less sensitive the tumor is to treatment such as radio-, chemo-, and hormonal therapy.

For example, metastases of kidney cancer are considered unresponsive to radio- or chemotherapy which strengthens the indication for surgical treatment (Veeth 1973) (Figure 11). Myeloma and lymphoma are radiosensitive tumors making surgical therapy less often needed.

The definition of an impending fracture and the indications for surgical treatment of these destructions is highly controversial. Criteria used to pre-



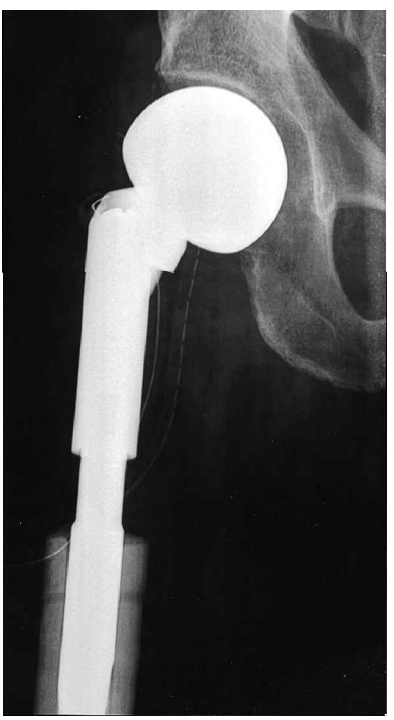


Figure 11. A. Proximal femur of a 49-year-old man with multiple skeletal metastases of kidney carcinoma. He was inappropriately treated with a glide screw plate device and a hip screw. Despite postoperative radiotherapy local tumor progression was obvious 8 months later. B. He was reoperated with a bipolar reconstruction prosthesis.

dict a pathologic fracture includes:

- A painful medullary lytic lesion resulting in endosteal reabsorption of 50% of the cortical thickness;
- painful lytic lesion involving the cortex, which is greater than the cross-sectional diameter of the bone;
- lesion producing functional pain after radiation therapy
- ny destruction in the area of the lesser trochanter of the femur.

None of these criteria (Harrington 1982, Br. Assoc. Surg. Oncol 1999, Healey 2000) has been validated in large patient series. Hence, the selection of patients for prophylactic stabilization is still based on clinical judgement.

Figure 12. 69-year-old woman diagnosed with breast cancer in June 1997. A solitary skeletal metastasis appeared in June 1998 and fractured three months later. She was operated on with curettage and an unreamed intramedullary nail followed by postoperative radiotherapy. Good function until the sudden breakage of the nail 14 months postoperatively due to nonunion of the fracture.

Orthopedic management

The management of pathologic fractures is different to standard fracture management, so all patients with a suspected pathologic fracture should be treated conservatively until the diagnosis has been confirmed. Radiographs of the entire length of the affected bone is essential so that other lesions, which may at a later stage develop into a fracture, are stabilized and included in the radiotherapy field.

Radiotherapy as well as cement and tumor present at the fracture site prevents fracture healing. Therefore the surgeon must assume that the fracture will not unite. A method of reconstruction should provide immediate stability and the fixation should aim to last the lifetime of the patient without the support of fracture healing (Figure 12). Reconstruction based on endoprosthesis appears to be safer than those based on internal fixation (**I**, Yazawa 1990). Long-stemmed cemented prostheses are commonly used to avoid further surgical treatment due to progressive disease within the affected bone.

Excision of tumor causing the pathologic fracture is an important part of the surgical procedure. The removal of tumor may be carried out in a vast majority of cases as an intralesional curettage and may be considered also in diaphyseal fractures when intramedullary devices are used. Preoperative embolization of large deposits of hypervascular tumors such as kidney and thyroid carcinomas may be indicated to reduce per-operative bleeding. Tumor material should always be sent for histo-pathologic diagnosis even in cases with a known primary tumor. A fracture may be caused by another primary or secondary malignancy as well as by non-malignant causes including radiotherapy, osteopenia or infection.

Humerus

In most proximal fractures, reconstruction with a cemented hemiprosthesis is the treatment of choice. In cases with more extensive destructions, resection of proximal humerus followed by a reconstruction prosthesis may be indicated. Diaphyseal fractures are best treated with an intramedullary nail locked with proximal and distal interlocking screws. In distal fractures plates and cement or an elbow prosthesis are used.

Femur

A pathologic fracture of the femoral neck does not unite (Galasko 1974). As in intertrochanteric fractures, either a cemented hemiprosthesis or a total

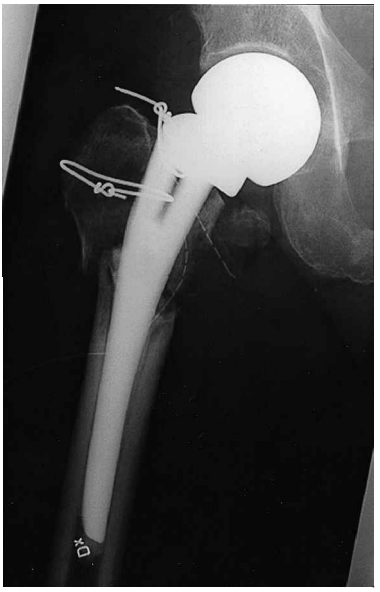


Figure 13. A. Radiograph showing an intertrochanteric fracture caused by a prostatic carcinoma in a 75-year-old man. B. He was surgically treated with a cemented hemiprosthesis.

hip reconstruction should be considered (Figure 13). Subtrochanteric fractures can either be treated with long stemmed prostheses or reconstruction nails. Prostheses are probably the safest method and in cases with large destructions a reconstruction prosthesis is indicated. Glide screw plate devices, with or without cement augmentation, are associated with a high risk of reoperation and should not be used (Figure 14).

Diaphyseal fractures are treated with interlocked intramedullary nails and local excision of the tumor should be considered. Because of the high frequency of non-unions, a reconstruction nail is recommended because of the stronger build. In distal fractures a retrograde nail, a reconstruction prosthesis or, sometimes, a glide screw plate device may be used.

Pelvis

Pathologic fractures of the pelvis are common but most do not require treatment. Fractures involving the acetabulum however may be very painful and frequently requires surgical treatment. A total hip arthroplasty combined with an acetabular reinforcement ring is a common method of reconstruction (Stark and Bauer 1996). In the most severe cases of destruction some authors (Nilsson et al. 2000, Kunisada and Choong 2000) recommend that in addition to total hip arthroplasty combined with an acetabular reinforcement ring, the destroyed ilium should be reinforced with threaded pins and cement according to Harrington (Harrington 1981).

Tibia

Diaphyseal fractures should be treated with interlocked intramedullary nails as in femur and humerus. Proximal and distal fractures are commonly treated with plates. A large destruction in the proximal tibia may require a reconstruction type prosthesis.

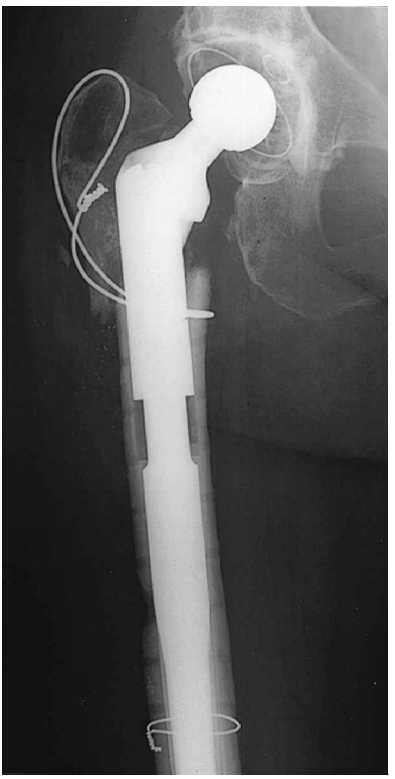


Figure 14. A. 60-year-old woman with breast carcinoma. She had previously received radiotherapy of the left proximal femur when she suffered a pathologic fracture in June 2000. She was surgically treated with a glide screw plate device. This image shows non-union and screw migration 6 months later.

B. She was reoperated with a reconstruction type of prosthesis.

Scandinavian Sarcoma Group Skeletal Metastasis Registry

Uncertainty remains whether to choose osteosynthetic devices or endoprostheses in pathologic fractures of the humerus and the femur. Estimation of the risk for fracture through bone destruction and indications for prophylactic surgical treatment remain unclear (Keene 1986, Crowninshield 1978). The role of post-operative radiotherapy needs to be defined as radiation decreases the risk of local tumor progression but increases bone-healing complications.

There are no prospective randomised studies of surgical treatment for pathologic fracture. Current treatment is based on retrospective analyses of single institution experience. The reported series comprise heterogeneous patient populations regarding types of primary cancer, extent of the metastatic disease, and location of the lesions. Furthermore, some patients are treated for complete fracture while others will have prophylactic stabilisation for what is considered an impending fracture.

The Scandinavian Sarcoma Group has since 1986 a well functioning registry of patients with primary skeletal and soft-tissue sarcomas in the Scandinavian countries as well as in Finland (Bauer et al. 2001). The skeletal metastasis registry was started 1999. Criteria for inclusion consists of patients surgically treated for either impending or complete non-spinal fractures due to skeletal metastases. In the future the aim is to expand the registry to also include cancer patients surgically treated for spinal cord compression. The registry may also be used to study other treatment modalities like radiotherapy.

The specific aims of the registry are:

1. to improve the surgical treatment of cancer patients with pathologic fractures
2. to provide a scientific basis for treatment recommendations
3. to provide participating departments a tool for quality assessment as measured in terms of reoperation rate, operation mortality and operation frequency of impending fractures.

SSG registration of surgically treated bone metstases (spine excluded), March 2001

Primary form

Use one set of forms for each operated bone metastasis

(complete before operation)

Patient identification

Sex: **1**: woman, **2**: man |___|

Hospital: ....

Diagnosis date |___|___|___|___|___|___|
(if doubt use middle of year)

Date of first
bone metastasis |___|___|___|___|___|___|

Primary tumor |___|
1: breast, **2**: lung, **3**: prostate, **4**: kidney
5: uterus, **6**: myeloma, **7**: lymphoma, **8**: unknown
9: other, specify ....

Has the op. metastasis been previously radiated |___|
0: no, **1**: yes

Hgb at referral: |___|___| mmmol/l
|___|___|___| gl/l

Pain & function: At operation or just before fracture

Pain from destruction site? |___|
1: no, **2**: load related, **3**: pain at rest,
4: 2 + 3, **5**: not known

If pain, for how many days before op.? |___|___|___|

Pain |___|
0: no, **1**: light, **2**: moderate, **3**: strong,
4: severe, **5**: not known

Analgesic |___|
1: no, **2**: peripheral/light, **3**: opioids, **4**: not known

Mobility |___|
1: walking without crutches, **2**: walking with crutches,
3: wheel chair, **4**: confined to bed, **5**: not known

STATUS at referral
(in case of fracture: just before the fracture)

Karnofsky performance |___|___|___|

Able to carry out normal activities		**good**
no limitations, no complaints	100%	
no limitations, minor symptoms	90%	
no limitations, some symptoms	80%	
Unable to work, able to self care		**moderate**
care for himself	70%	
require occasional assistance	60%	
considerable assist., frequent care	50%	
Unable to care for himself		**poor**
disabled, reuire special care	40%	
severely disabled, hospitalisation	30%	
very sick, hospitalisation, active support	20%	
moribund	10%	

Tokuhashi score (not compulsory):

1) Karnofsky score |___|
0: poor, **1**: moderate, **2**: good

2) Total number of skeletal metastases |___|
0: 4, **1:** 2–3, **2:** 1, **3:** not known

3) Organ metastasis |___|
0: not removable, **1:** removable, **2:** no metastasis known (CT-scan or ultrasound of abdomen)

4) Primary tumor |___|
0: lung, liver, pancreas
1: kidney, breast, prostate, uterus, other, unknown
2: thyroidea, lymphoma, myeloma

5) Fracture |___|
0: present, **2:** urgent
(*i.e.* diam. > 25 mm, > 50% of circumference)

Score |___|___|
3–5: expected survival < 7 months
0–2: expected survival < 3 months

SSG registration of surgically treated bone metstases (spine excluded), March 2001

Operation form

(complete after operation)

Patient identification

Date of operation |___|___|___|___|___|___|

Bone |___|
1: femur, **2**: humerus, **3**: tibia, **4**: pelvis
5: scapula, **6**: other, specify..... .....

A. Localisation in the operated bone: site of fracture or major destruction, if applicable

1: proximal (in femur: caput/collum) |___|
2: intertrochanteric (femur) |___|
3: subtrochanteric (femur) |___|
4: diaphysis |___|
5: distal |___|

B. Localisation in the operated bone: additional or minor destruction

1: proximal (in femur: caput/collum) |___|
2: intertrochanteric (femur) |___|
3: subtrochanteric (femur) |___|
4: diaphysis |___|
5: distal |___|

Side |___|
1: right, **2**: left

Main indication for surgery |___|
1: complete fracture
2: impending fracture
3: pain
4: other, specify..... .....

Operation method |___|___|
1: glide screw plate
2: plate
3: reconstrucution nail
4: intramedullary nail
5: hemiprosthesis
6: prosthesis, total joint replacement
7: prosthesis & acetabular reconstruction
8: tumor prosthesis
9: hip screws
10: allograft
11: other, specify..... .....

Operative strategy “surgical margin” |___|
1: curettage + cement,
2: curettage only,
3: stabilisation without tumor removal,
4: excision with wide margins,
5: other, specify..... .....

SSG registration of surgically treated bone metstases (spine excluded), March 2001

Follow-up form

(complete at 6 weeks, and 6 months after surgery or in case of reoperation or death)

Patient identification

Date |___|___|___|___|___|___|

Cytology #/i.d. |___|___|___|___|___|___|

Histology/PAD #/i.d. |___|___|___|___|___|___|

Karnofsky performance |___|___|___|

Able to carry out normal activities		**good**
no limitations, no complaints	100%	
no limitations, minor symptoms	90%	
no limitations, some symptoms	80%	
Unable to work, able to self care		**moderate**
care for himself	70%	
require occasional assistance	60%	
considerable assist., frequent care	50%	
Unable to care for himself		**poor**
disabled, reuire special care	40%	
severely disabled, hospitalisation	30%	
very sick, hospitalisation, active support	20%	
moribund	10%	

Pain |___|
0: no, **1**: light, **2**: moderate, **3**: strong, **4**: severe

Analgesic |___|
1: no, **2**: peripheral/light, **3**: opioids

Mobility |___|
1: walking without crutches, **2**: walking with crutches,
3: wheel chair, **4**: confined to bed

COMPLICATIONS

Date |___|___|___|___|___|___|

1: wound infection |___|
2: deep infection
3: prosthetic dislocation
4: nerve injury
5: systemic
6: other, specify..... .....

REOPERATION

Date |___|___|___|___|___|___|

Reperation method |___|___|
1: glide screw plate
2: plate
3: reconstrucution nail
4: intramedullary nail
5: hemiprosthesis
6: prosthesis, total joint replacement
7: prosthesis & acetabular reconstruction
8: tumor prosthesis
9: hip screws
10: allograft
11: other, specify..... .....

Reason |___|
1: non-union
2: local tumor progression
3: stress fracture of bone
4: immediate failure (within 6 weeks)
5: technical error
6: other, specify..... .....

DEATH

Date |___|___|___|___|___|___|

Reason |___|
1: due to cancer
2: other reason

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