# Pathological fractures of long bones due to bone metastases

Cover: *Girafe en feu*, Salvador Dali, 1936/1937, oil on panel, 35×27 cm
Kunstmuseum Basel, Switzerland
Öffentliche Kunstsammlung, Emanuel Hoffmann Foundation

Druk: Pasmans Offsetdrukkerij, Den Haag

CIP DATA KONINKLIJKE BIBLIOTHEEK, DEN HAAG

Dijkstra, Pieter Durk Sander
Pathological fractures of long bones due to bone metastases
Thesis, Rotterdam. -With ref.- With Summary in Dutch.
ISBN 90-9011034-8
NUGI 742
E-mail pdsdijk@knmg.nl

Subject headings: pathological fracture
cortical defects
long bones
internal fixation
prophylactic surgery
bone metastases
finite element modelling
torsion loads

# Pathological fractures of long bones due to bone metastases

Pathologische fracturen van lange pijpbeenderen als gevolg van botmetastasen

**Proefschrift**

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de Rector Magnificus
Prof. dr P.W.C. Akkermans M.A.
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
12 november 1997 om 13.45 uur

door

**Pieter Durk Sander Dijkstra**

geboren te Voorburg

Promotores : Prof. dr ir C.J. Snijders
dr T. Wiggers

Leden : Prof. dr ir L.J. Ernst
Prof. dr J. Jeekel
Prof. dr J.W.J.L. Stapert
Prof. dr J.A.N. Verhaar

Publication of this thesis was generously supported by grants from:
Stichting Anna Fonds
Nederlandse Vereniging voor Orthopaedische Traumatologie
Nederlandse Orthopaedische Vereniging
VVAA
Aesculap
Byk Nederland
Femto
Howmedica
Janssen-Cilag
Oudshoorn Chirurgische Techniek
Ortomed
Penders Orthopedische Schoentechniek
Schering Plough
Siemens
Smith & Nephew Nederland
Somas Orthopaedie
West Meditec

"That accident ruled every corner of the universe except
the chambers of the human heart"

*Snow falling on cedars*
David Guterson

*Ter nagedachtenis aan mijn vader*

# Contents

# Chapter 1

## General introduction

## General Introduction

Skeletal metastases are the most common form of malignant bone tumours and have probably occurred for many thousands of years.[1] Radiografic analysis of Egyptian mummies have shown cortical bone lesions very likely due to bone metastasis.[2] Skeletal metastases of the long bones have been found in a French specimen dated from 700 *ad.*[3] It was probably Wiseman in 1676 who first described 'rotting the bones under them' as the effects of skeletal metastases.[4] In 1824 Cooper described several cases of breast cancer with bone metastasis and development of actual pathological fractures.[5]

In three-quarters of the patients with skeletal metastases the primary tumour is mamma, bronchus, prostate and kidney carcinoma.[6,7] The incidence increases due to prolonged survival as a result of more effective treatment of the primary tumours.[8,9] With more than 61.000 new cases of cancer each year in the Netherlands, at least 7% to 27% of these patients develop a metastatic bone defect.[10,11] Pain is the main clinical sign of peripheral bone metastases in three-quarters of the patients.[12,13] In 5% to 10% an actual pathological fracture sustained (Figure 1).[14-16] Although patients with bone metastases usually die from organ failure due to disseminate cancer, skeletal metastases can greatly influence patient's quality of life.[17]

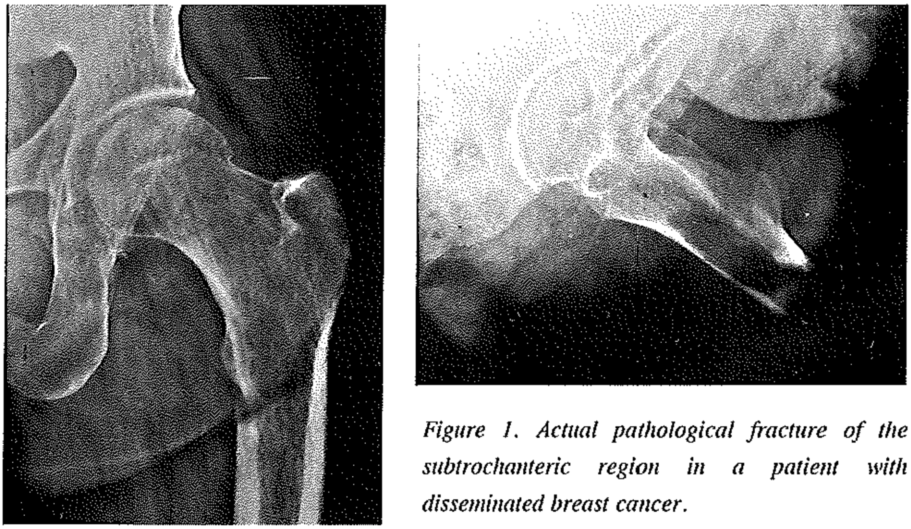


*Figure 1. Actual pathological fracture of the subtrochanteric region in a patient with disseminated breast cancer.*

A pathological fracture (also called secondary fracture or spontaneous fracture), first named by Grunert in 1905, has been defined as a fracture due to weakening of the bone structure by a pathological proces.[18,19] There are minimal forces on the long bones applied when a pathological fracture occurs.[20] This dramatic appearance was early described by Miller, in 1850, when he wrote 'on some slight exertion, as turning in bed, a bone broke'.[21] In a general hospital the incidence of a pathologic fracture is less than one percent of all types of fractures.[22] The pathological fractures are in majority due to bone metastasis.[23] In two-third of the patients the primary tumour is breast cancer. [17,24] Although most neoplastic cells that detach from the primary tumour and enter the vascular system do not survive, the cells that do survive have an affinity to metastasise to certain anatomical areas.[25,26] This is in bone metastasis most frequently involvement of blood cell formation areas.[27,28] The metastatic growth in bone is accompanied by increased bone destruction, increased bone formation, or both and is stimulated by tumour products and direct tumour cell reaction.[29] Osteolytic metastases are the predominant types of bone lesions in most cancers.[30] In breast cancer patients for instance, one-third of these patients developing metastasis will have bone metastasis at first recurrence, within 50% involvement of the extremity.[31] About 10 to 21% of these patients with skeletal metastases are at risk for a pathological fracture of the long bones.[32-34] The survival of these patients is highly variable.[35,36] However, after treatment of a pathological fracture in patients with skeletal metastases of the extremity of all kind of primary tumours the survival rate at 1 year is one-third.[37]

Treatment of pathological fractures due to bone metastasis by cast fixation or traction had little effect in relieving pain and enhancing mobility. In 1886 Leuzinger described a large variation in the clinical outcome of treatment in a series of 16 cases with actual pathological fractures of the femur due to bone metastasis of different primary lesions.[38] Radiotherapy was the first improvement of the fracture treatment by shortening the consolidation period.[39] Moulonguet wrote in 1937 'Osseous metastatique est beaucoup plus interessant par les problemes diagnostiques et therapeutiques qu'il pose'.[40] The next step was made by Haase in 1943, who first treated a pathologic fracture due to metastases of kidney carcinoma by intramedullary nailing.[41] In the following decades surgical treatment was improved by development of different techniques for osteosynthesis.[42,43] According to the

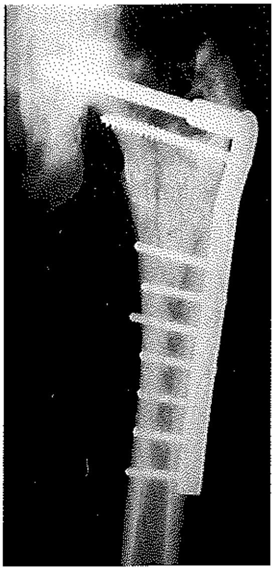


*Figure 2. Impending pathological fracture in the subtrochanteric region in a patient with bone metastasis due to breast cancer, treated with a dynamic condyl screw and bone cement.*

fracture surgery without a pathological lesion, the development of internal fixation in the diaphyseal pathological fractures were first based on intramedullary osteosynthesis, and later plate osteosynthesis.[23,44,45] Parrish and Murray introduced in 1970 the additional use of bone cement (methylmethacrylate), necessary for filling of the cavity after removing the tumour and for rigid stabilisation of pathological fractures with extensive destruction (Figure 2). [46-49] Revival of intramedullary nailing has been shown in the last two decades.[24,50] The introduction of cemented hemiarthroplasty of the proximal femur resulted in better treatment of the femoral neck fractures.[51,52] In all cases a biopsy specimen should be taken at the time of operation to confirm the nature of the lesion.[53]

Altough there are improved surgical, radiological and chemotherapeutic techniques in the management of secondary neoplastic deposits in the long bones, the problem rises whether and when prophylactic internal fixation should be carried out. The benefits of surgical treatment of an impending pathological fracture of the long bones was first described by Griesmann and Schüttemeyer in 1947.[42] Before the guidelines to prophylactic surgical treatment were developed, the usefulness of this treatment was already confirmed.[44,54,55] Nowadays, prophylactic fixation of fractures is generally preferred instead of treatment of actual fractures, because of important advantages; quick relief of pain, earlier mobility, decreased hospital stay and reduction of operative complications.[56,57] Modern aneasthesia makes surgery possible in these patients with often poor general condition.[58] Although there is a lot of contradiction in the guidelines to prophylactic treatment of the long bones, there are four main criteria used in clinical practice: 1] a lesion of 25mm or larger, 2] circumferential cortical destruction of 50% or more, 3] a lytic lesion, 4] persistent pain. [44,46,56,57,59-63] These guidelines arose from several, often small, retrospective clinical studies. Neither guideline has been confirmed by in vitro studies on human specimen.

As the number of people with osteoporosis and the number of people with cancer in the population increases, the incidence of pathological fracture is likely to rise. Furthermore, advances in cancer therapy allow longer survival for these patients. So a reliable method for predicting which patients require prophylactic treatment of an impending pathological fracture can improve their quality of life and can prevent unnecessary surgery.

The aim of this thesis is to provide guidelines for prophylactic surgery of impending pathological fractures in the long bones, to develop a finite element model to predict this fracturing risk and to compare different operation techniques. To this extend the following six studies were performed:

A description of a population of 199 patients with impending or actual pathological fractures due to bone metastases of the long bones, by measures of pain relief, mobilisation, short and longterm complications and survival after surgical treatment (*Chapter 2*).

A comparison of intramedullary nail and AO plate osteosynthesis with adjunctive bone cement in the treatment of pathological fractures of the humeral shaft (*Chapter 3*).

Prediction of fracturing by the measurements of different parameters of metastatic lesions in the subtrochanteric region of the femur , using radiografics (*Chapter 4*).

In vitro experiments on human femora to analyse the torsional strength reduction by longitudinal cortical defects and the occurrence of 'stress risers' and 'open section' effects (*Chapter 5*).

Evaluation of strength reduction by cortical defects on human femora in torsinal loading estimated by surgeons and in vitro experiments by using radiographs and computed tomography (*Chapter 6*).

Development of a finite element model for fracture risk assessment for patients with cortical defects of the femur (*Chapter 7*).

General discussion and clinical implication of the results of these studies (*Chapter 8*).

**References**

1 Strouhal E. Tumors in the remains of the ancient Egyptians. Am J Phys Antrop 1976; 45: 613-620.

2 Wells C. Ancient Egyptian patholgy. J Laryngol Otol 1963; 77:261-265.

3 Soulie R. Un cas de metastases craniennes de carcinoma datant du Bronze Ancien, typologie, des lesions, observations paleopathologiques analogues en Europe centrale et occidentale. Caen: Paleopathology Association 3rd European Meeting 1980: 239-253.

4 Wiseman R. Several chirurgical treatises. London, Royston. 1676.

5 Cooper A. Lectures on diseases of the breast. Lancet 1824; 2: 710-725.

6 Fitts WT, Roberts B, Ravdin IS. Fractures in metastatic carcinoma. Am J Surg 1953; 85:282-287.

7 Galasko CSB. Skeletal metastases. Cambridge. Butterworth & Co, Ltd 1986: 14-27.

8 Albright JA, Gillspie TE, Butaud TR. Treatment of bone metastases. Semin Oncol 1980; 7: 418-434.

9 Friedlaender GE, Johnson RM, Brand RA et al. Treatment of pathological fractures. Conn Med 1975; 39: 765-772.

10 Visser O, Coebergh JWW, Schouten LJ. Incidence of cancer in the Netherlands 1993. Fifth report of the netherlands cancer registry. Association of Cancer centra. Utrecht 1996: 1-4.

11 Tubiana-Hulin M. Incidence, prevalence and distrubition of bone metastases. Bone 1991; 12:S9-S10.

12 Front D, Schenck SO, Frankel A, Robinson E. Bone metastases and bone pain in breast cancer. Are they closely associated? J Am Med Assoc 1979; 242: 1747-1748.

13 Schutte HE. The influence of bone pain on the results of bone scans. Cancer 1979; 44: 2039-2043.

14 Higinbotham NL. The management of bone tumors. Surg Clin North Am 1951; 31: 317-323.

15 Staley C. Sletal metastases in cancer of the breast. Surg Gyn Obstet 1956; 68: 683-688.

16 Johnston AD. Pathology of metastatic tumors in bone. Clin Orthop 1970; 73: 8-12.

17 Galasko CSB. The management of skeletal metastases. Royal Coll Surg Edin 1980; 25: 143-161.

18 Grunert. Über pathologische Frakturen (Spontanfrakturen). Deutsch Zeitsch Chirurg 1905; 76: 254 .

19 Dorland WAN. Dorland's illustrated medical dictionary. Philadelphia: WB Saunders Co 1988: 661.

20 Hipp JA, McBroom RJ, Cheal EJ, Hayes WC. Structural consequences of endosteal metastatic lesions in long bones. J Orthop Res 1989; 7: 828-837.

21 Miller J. The principles of surgery, Edinburgh, Adam and Black, 1850: 323.

22 Walcher K, Dorn W. Die operative Behandlung der Spontanfrakturen. Arch Orthop Trauma Surg 1973; 77:315-329.

23 Bickel WH, Barber JR. Pathologic or spontaneous fractures. G P 1951; 3: 41-52.

24 Yazawa Y, Frassica FJ, Chao EYS et al. Metastatic bone disease: a study of surgical treatment of 166 pathologic humeral and femoral fractures. Clin Orthop 1990; 251: 213-219.

25 Springfield DS. Mechanisms of metastasis. Clin Orthop1982; 169: 15-19.

26 Fidler IJ, Gersten DM, Hart IR. The biology of cancer invasion and metastasis. Adv Cancer Res 1978; 28: 149-250.

27 Paget S. The distribution of secondary growths in cancer of breast. Lancet 1889; 1: 571.

28 Berrettoni BA and Carter JR. Mechanisms of cancer metastasis to bone. J Bone Joint Surg 1986; 68(Am): 308-312.

29 Nielsen OS, Munro AJ, and Tannock IF. Bone metastases: Pathophysiology and management policy. J Clin Oncology 1991; 9:509-524.

30 Stoll BA. Natural history, prognosis, and staging of bone metastases. In Stoll Ba ans Parbhoo S (eds): Bone metastases: Monitoring and Treatment, NY, Raven, 1983: 1-20.

31 Kamby C, Vijborg I, Daugaard S, et al. Clinical and radiologic characteristics of bone metastases in breast cancer. Cancer 1987; 60: 2524-2531.

32 Miller F, Whitehill R. Carcinoma of the breast metastatic to the skeleton. Clin Ortop 1984; 184: 121-127.

33 Malawer M, Delaney TF. Treatment of metastatic cancer of the bone. In: Devita VTJ (ed): Cancer: Principles and practices of Oncology. Lippincott, New York 1986; 2298-2315

34 Sherry HS, Levy RN, Siffert RS. Metastatic disease of bone in orthopedic surgery. Clin Orthop 1982; 169: 44-52.

35 Henderson IC. Breast cancer. N Eng J Med 1980; 302: 78-90.

36 Marcove RC, Yang DJ. Survival times after treatment of pathologic fractures. Cancer 1967; 20: 2154-2158.

37 Bauer HCF, Wedin R. Survival after surgery for spinal and extremity metastases. Acat Orthop Scand 1995; 66: 143-146.

38 Leuzinger. Die Knochenmetastasen bei Krebs. Thesis. Zürich. 1886.

39 Kohler A. Die Behandlung pathologischer Frakturen mit Röntgenstrahlen. Deuts med Wochenschr 1921. 741-744 .

40 Moulonguet P. Épithélioma osseux métastasique. Traité de chirurgie orthopédique. Ombrédanne L et Mathieu P. Masson et cie. Paris 1937: 448-450.

41 Haase W. Der Kuntscher-Nagel bei Spontanfraktur durch Hypernephrom-metastase. Zentralbl Chir 1943; 35: 1266-1268.

42 Griesmann H, Schüttemeyer W. Weitere Erfahrungen mit der Marknagelung nach Kuntscher an der Chirurgischen Universitatsklinik Kiel. Chirurg 1947; april: 17-18.

43 Ehrenhaft JL and Tidrick RT. Intramedullary bone fixation in pathologic fractures. Surg Gyn Obstet 1949; 88: 519-527.

44 Francis KC. Prophylactic internal fixation of metastatic osseous lesions. Cancer 1960; 13: 75-76.

45 Mickelson MR, Bonfiglio M. Pathological fractures in the proximal part of the femur treated by Zickel-Nail fixation. J Bone Joint Surg (Am) 1976; 58: 1067-1070.

46 Parrish FF and Murray JA. Surgical treatment for secondary neoplastic fractures. J Bone Joint Surg 1970; 52(Am): 665-686.

47 Harrington KD, Johnston JO, Turner RH and Green DL. The use of methylmethacrylate as an adjunct inthe internal fixation of malignant neoplastic fractures. J Bone Joint Surg 1972; 54(Am): 1665-1670.

48 Harrington KD, Sim FH, Enis JE, Johnston JO, Dick LM, Gristina AG. Methylcrylate as an adjunct in internal fixation of pathological fractures. J Bone Joint Surg 1976; 58(Am): 1047-1054.

49 Yablon IG, Paul GR. The augmentative use of methylcrylate in management of pathological fractures. Surg Gyn Obst 1967; 143: 177-181.

50 Stapert JW, Geesing CL, Jacobs PB, de Wit RJ, et al. First experience and complications with the long Gamma nail. J Trauma 1993; 34: 394-397.

51 Ray AK, Romine JS and Pankovich AM. Stabilization of pathological fractures with acrylic cement. Clin Orthop 1974; 101: 182-185.

52 Galasko CSB. Pathological fractures secondary to metastatic cancer. J R Coll Surg Edinb 1974; 19: 351-362.

53 Habermann ET and Lopez RA. Metastatic disease of bone and treatment of pathological fractures. Ortop Clin North Am 1989; 3:469-486.

54 Altman H. Intramedullary nailing for pathologic impending and actual fractures of the long bones. Bull Hosp Joint Dis 1952; 13: 239-251.

55 Mclaughlin HL. Intramedullary fixation of patholgic fractures. Clin Orthop 1953; 2:108-114.

56 Fidler M. Prophylactic internal fixation of secondary neoplastic deposits in long bones. Brith Med J 1973; 1: 341-343.

57 Harrington KD. New trends in the management of the lower extremity metastases. Clin Orthop 1982; 169: 53-61.

58 Pedersen T, Elias K, Henriksen E. A prospective study of mortality associated with anaestesia and surgery: risk indicators of mortality in hospital. Acta Anaest Scand 1990; 34: 176-182.

59 Fidler M. Incidence of fracture through metastases in long bones. Acta Orthop Scand 1981; 52: 623-627.

60 Menck H, Schulze S, Larsen E. Metastasis size in pathologic femoral fractures. Acta Orthop Scand 1988; 59: 151-154.

61 Mirels H. Metastatic disease in long bones: a proposed scoring system for diagnosing impending pathologic fractures. Clin Orthop 1989; 14: 513-525.

62 Beals RK, Lawton GD, Snell WE. Prophylactic internal fixation in metastatic breast cancer. Cancer 1971; 28: 1350-1354.

63 Zickel RE, Mouradian WH. Intramedullary fixation of pathological fractures and lesions of the subtrochanteric region of the femur. J Bone Joint Surg 1976; 58(Am): 1061-1066.

# Chapter 2

# Impending and actual pathological fractures in patients with bone metastases of the long bones

## A retrospective study of 233 surgically treated fractures

PDS Dijkstra[1], T Wiggers[2], BN van Geel[2] and H Boxma[1]

Department of Surgery[1], South Municipal Hospital, Department of Surgical Oncology[2],
Daniel den Hoed Cancer Center, Rotterdam, The Netherlands

*Eur J Surg 1994; 160: 535-542*

## Introduction

Malignant metastatic tumours are the most common neoplastic tumours of bone[39], more than 80% follow carcinomas of the breast, prostate, bronchus or kidney.[15,22,40] Postmortem examination of various carcinomas has shown skeletal metastases in 27% of patients.[1] In patients with disseminated breast cancer, radiographic evidence of bone metastases can be found in 30% - 60%; about 80% have bone metastases at necropsy.[1,11,34] Most bone metastases are located in the axial skeleton: spine, pelvis, ribs, sacrum, skull, scapula and sternum.[22,36] The femur is the most common site in the peripheral skeleton followed by the humerus.[33] Tibia, foot, and radius are less commonly involved, and metastases of the ulna or hand are rare.[35] The proximal parts of the long bones are most likely to be affected. Pathological fractures nevertheless occur in only 1% - 2% of patients with malignant disease.[19,29] Peripheral bone metastases can be asymptomatic, particularly in prostatic cancer. If they are symptomatic, pain, usually at night or during physical stress, is the main clinical sign in about 75% of patients.[17,46]

Metastases of the long bones progress to pathological fractures in about a quarter of cases,[2,10] but the chance of them doing so if they are in the proximal femur is much higher (40% - 60%). Between 30% and 40% of femoral fractures are in the subtrochanteric region and 25% - 33% in the femoral neck.[24,50]

Pathological fractures are not lifethreatening but can greatly influence the patient's quality of life. The goals of palliative treatment are to achieve rapid relief of pain, reduce anxiety and depression in these already sick patients, facilitate nursing care, and restore the function of the limb. Rigid fixation with adjuvant bone cement for immediate stability and pain relief, even in the face of extensive and wide spread bone destruction, is valuable.[13,16,21,24,25,38,48,50,51] In addition, impending pathological fractures can be predicted and treated prophylactically.[2,3,14,47]

## Patients and methods

The medical records of 199 patients with 233 surgically treated metastatic bone lesions, treated at the Daniel den Hoed Cancer Center in coorporation with the South

Municipal Hospital over a 12 year period (1978-1990), were consecutively and retrospectively studied (Table 1). By themself, age and limited life expectancy were not contra-indications for operation. Patients who had previous had surgical treatment for bone metastases were included in the study.

*Table 1. Description of 199 patients with 233 pathological fractures.*

| | | Number (%) |
|---|---|---|
| Sex | Male | 41 (21) |
| | Female | 158 (79) |
| Age | Mean | 61 |
| | (range) | (21-84) |
| No of fractures | Total | 233 (100) |
| | Actual | 161 (69) |
| | Impending | 72 (31) |
| No of femoral fractures | Total | 191 (82) |
| | Actual | 123 (64) |
| | Impending | 68 (36) |
| | Bilateral | 16 (8) |
| No of humeral fractures | Total | 36 (15) |
| | Actual | 34 (94) |
| | Impending | 2 (6) |
| | Bilateral | 1 (3) |
| No of tibial fractures | Total | 6 (3) |
| | Actual | 4 (67) |
| | Impendig | 2 (33) |

Bone metastases from four primary tumours accounted for 80% of the fractures (Table 2) and the association was confined histologically in 193 cases (83%). In most of the remaining, post irradiation effects were found.

Conventional anteroposterior and lateral radiographs were routinely taken of the complete long bone. When in doubt (in cases of impending fractures), this was followed by tomography. The decision to give prophylactic treatment was based on at least one of the following criteria: a lytic lesion of more than 2.5 cm, circumferential cortical destruction of 50% or more, or persistent or increasing pain at the metastasis that was not improved after radiotherapy.[2,14,24,27,32,34,41] Half the patients had radiotherapy before operation (mean 27 Gy). Patients were given intravenous antibiotic prophylaxis (flucloxacillin combined with an aminoglycoside) and prophylatic anticoagulation.

The aim of operation was to fix the fracture rigidly with bone cement. In 91% of the cases Polymethylmethacrylate (PMMA) was used. After reposition, the normal bone above and below the lesion was fixed to the implant and after curettage, the defect was filled with cement. When the cement had hardened the cast was fixed to the plate with additional screws. We were more concerned with biomechanical stability than with bone healing. The selection of internal fixation devices or prosthetic implants depended on the site and pattern of bone destruction.

The indication for postoperative radiotherapy was recurrent local pain, but patients who had had a cemented hemi-arthroplasty were never given postoperative radiotherapy. During the remainder of their lives a quarter of the patients were given a mean of 21 Gy for pain. We monitored all patients, except 4, for at least 12 months or until death.

An objective evaluation of pain relief was made from the amount of analgesics that were required after postoperative healing.[3,24,25] Patients who survived less than six weeks were excluded because they used analgesics indefinitely. Objective pain relief was classified as excellent (no regular analgesics), good (regular non-narcotic drugs), fair (regular narcotics to relieve pain) and poor (no relief of pain even with narcotic analgesics). For a subjective evaluation of pain relief the patients reported only the pain in the treated limb. Subjective pain relief was evaluated from the casenotes six to eight weeks after operation. Postoperatively, patients with an endoprothesis were mobilised after five days and patients with an internal osteosynthesis after one day. Moderate to good function was defined in the lower extremity as partial or full weight bearing, and in the upper extremity when it could be freely used .

Survival curves were calculated using the Kaplan-Meier method. The Kruskal-Wallis test was used to assess the significance of differences in blood loss and operation time, and the Spearman test for the correlation between both items. The logrank test for comparing times between primary treatment and the development of fractures, and Fisher's exact probability test for differences in mobilisation and pain relief.

*Table 2. Site of primary tumour*

| Site | Femur | Humerus | Tibia | Total |
|---|---|---|---|---|
| Breast | 125 | 20 | 0 | 145 |
| Kidney | 9 | 3 | 4 | 16 |
| Multiple meyloma | 10 | 1 | 0 | 11 |
| Bronchus | 10 | 1 | 0 | 11 |
| Gastrointestinal tract | 7 | 1 | 0 | 8 |
| Prostate | 7 | 0 | 0 | 7 |
| Sarcoma | 4 | 2 | 1 | 7 |
| Female genital tract | 3 | 2 | 1 | 6 |
| Urological tract | 5 | 1 | 0 | 6 |
| Lymphoma | 1 | 2 | 0 | 3 |
| Upper respiratory tract | 3 | 0 | 0 | 3 |
| Skin | 2 | 0 | 0 | 2 |
| Thyroid | 2 | 0 | 0 | 2 |
| Unknown | 3 | 3 | 0 | 6 |
| Total | 191 | 36 | 6 | 233 |

## Results

### *Interval between diagnosis of primary tumour and fracture*

The interval between the diagnosis of the primary tumour and the first pathological fracture varied from none to 28 years (median 37 months). Patients with breast cancer had a much longer median interval compared with the other primary tumour (45 compared with 13 months). There was no difference in intervaltime between

*Table 3. Use of implant devices and bone cement in 123 actual and 68 impending femoral fractures. The number that required supplementary bone cement are given in parentheses.*

| Implant device | Head neck | Inter-trochanteric | Sub-trochanteric | Diaphysis | Supra-condylar | Total |
|---|---|---|---|---|---|---|
| Nail | 0 | 0 | 6 (1) | 7 (0) | 0 | 13 (1) |
| Endoprothesis | 46 (44) | 4 (4) | 2 (1) | 0 | 0 | 52 (49) |
| Dynamic hip screw | 3 (3) | 5 (4) | 7 (7) | 0 | 0 | 15 (14) |
| Angled plate | 5 (5) | 14 (12) | 53 (52) | 5 (5) | 7 (7) | 84 (81) |
| ORIF plate | 0 | 0 | 7 (6) | 19 (18) | 1 (1) | 27 (25) |
| Total | 54 (52) | 23 (20) | 75 (67) | 31 (23) | 8 (8) | 191 (170) |

actual and impending fractures. In about 10% of the cases the pathological fracture was the first sign of malignant disease (n= 19).

### *Distribution of lesions and type of devices*

The methods of treatment of the 191 femoral fractures are shown in Table 3. Supplementary bone cement was used in 89% (n=170) of the different devices. In 35 of the 36 fractures of the humerus AO-plates were supplemented with bone cement; two of the 36 fractures were impending. Four of the six tibial fractures were actual and two were impending, and five were treated with cemented AO-plates.

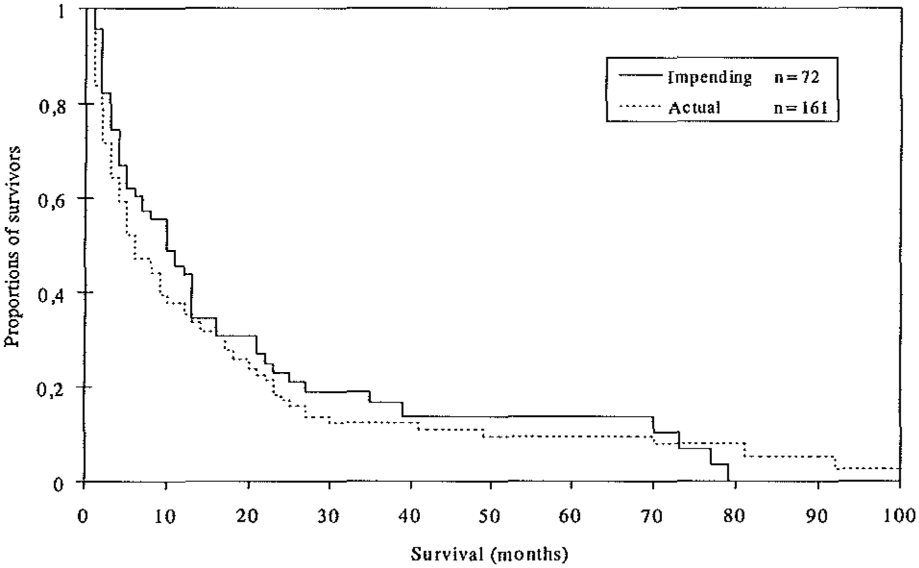


*Figure 1. Kaplan Meier survival curve of actual and impending pathological fractures at all sites*

### *Survival*

None of the patients died during operation, though 43 died postoperatively (18%). Most of them were in poor general condition. Survival analysis showed an overall survival of 55% at six months and 40% at 12 months; 25 were alive after two years. Surgical treatment of impending pathological fractures was associated with a slightly but not significantly better survival rate than actual fractures (Figure 1). Patients with multiple myeloma (n=11) had the best prognosis, four being alive after 18 months; two of the 11 patients with lung cancer had died after three months (Figure 2). Half of the patients with fractures of the tibia, femur, and humerus died within 16.5, 9,and 4.5 months, respectively.

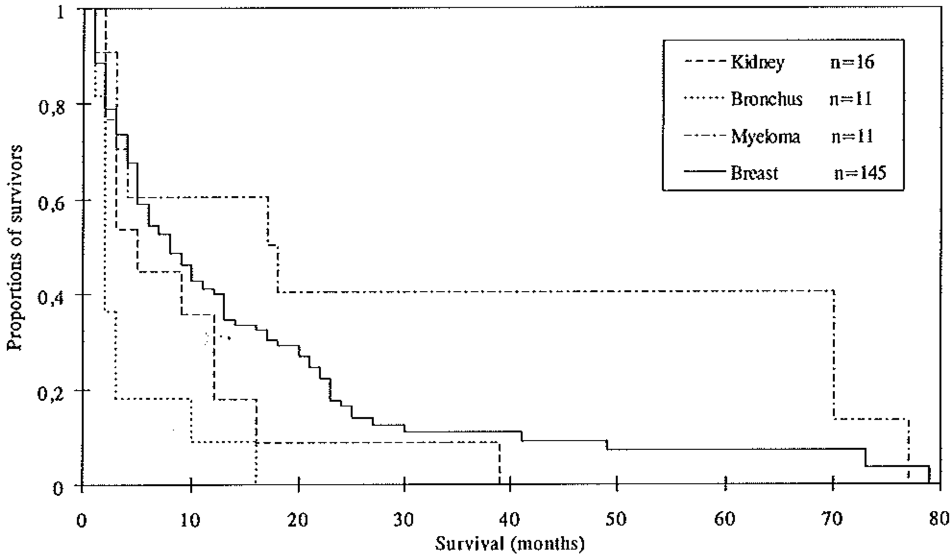


*Figure 2. Kaplan Meier survival curve of pathological fractures at all bone sites correlated with site primary tumour*

## *Pain Relief*

Objective pain relief was excellent to good in 159 patients (84%) (Table 4), and poor in two. This coincided with the subjective assessment of relief of pain. In general, adequate pain relief could achieved in most patients with no difference between those with impending and actual fractures.

*Table 4. Objective and subjective relief of pain six weeks after operation. Percentages in parentheses.*

| | | Actual | Impending | Total |
|---|---|---|---|---|
| Subjective relief of pain | Excellent | 67 (54) | 41 (63) | 108 (57) |
| | Good | 39 (31) | 12 (19) | 51 (27) |
| | Fair | 18 (14) | 11 (17) | 29 (15) |
| | Poor | 1 (1) | 1 (1) | 2 (1) |
| Objective relief of pain | Excellent | 87 (70) | 47 (72) | 134 (70) |
| | Good | 31 (25) | 15 (23) | 46 (24) |
| | Fair | 4 (3) | 1 (2) | 5 (3) |
| | Poor | 3 (2) | 2 (3) | 5 (3) |

### *Mobilisation and function*

Moderate to good function of the limb was achieved in 182 of the 233 cases (78%), and in 32 of the 36 pathological fractures of the humerus (89%). Despite good arm function four had a poor function of the hand because of damage to the radial nerve. Of the 191 fractures of the femur, ability to walk was regained after 145 operations (76%), and 116 were fully weight bearing within about a month. Nineteen cases were confined to a wheelchair. Twenty-seven cases were bedridden, mostly as a result of poor general condition, a second pathological fracture, or progressive neurological dysfunction (Table 5). Weightbearing was not achieved after 11 operations because of inadequate fixation (6%). Three of the six patients treated for tibial fractures were able to walk within five weeks after operation. Two patients (who died within six weeks after operation) had already mobilised with crutches, and one remained bedridden after a new actual fracture elsewhere. Sixty-three of the 70 patients with impending fractures of the lower extremities achieved weightbearing (90%), two were in wheelchairs and five were bedridden. Patients with impending fractures walked after a mean of 12 days, and those with actual fractures a mean of 18 days.

*Complications*

These debilitated patients had many operative and postoperative complications. The median operative blood loss was high (femoral 700 ml, humeral 500 ml and tibial fractures 900 ml ( $P<0.05$)). Bleeding was often related not only to the type of primary tumour (kidney and multiple myeloma ( $P<0.005$)) but also to the device used (angled blade and dynamic hip screw ( $P<0.0005$)) and the operation time (Rho=0.55, $P<0.0005$). There was no significant difference in blood loss between impending and actual fractures. Common local complications were deep wound infection (3%), in one patient after of a cemented hemi-arthroplasty and five after

*Table 5. Ambulatory status of 197 pateints with pathological fractures of lower extremity. Percentage in parentheses.*

| Ambulatory status | Actual | Impending | Total |
|---|---|---|---|
| Full weight bearing | 67 (54) | 50 (71) | 119 (60) |
| Partial weight bearing | 18 (14) | 13 (19) | 31 (16) |
| Wheelchair | 17 (14) | 2 (3) | 19 (10) |
| Bedridden | 23 (18) | 5 (7) | 28 (14) |

*Table 4. Local and systemic complications after operation in all 233 patients.*
** In one case together with paresis of ulnar nerve.*

| Complications | | Number (%) |
|---|---|---|
| Local | Deep wound infection | 6 (3) |
| | Deep wound dehiscence | 5 (2) |
| | Deep wound haematoma | 2 (1) |
| | Radial nerve paresis* | 2/36 (6) |
| | Radial nerve paralysis | 2/36 (6) |
| Systemic | Thrombosis of treated extremity | 3 (1) |
| | Thrombosis of extremity not treated | 2 (1) |
| | Sepsis | 4 (2) |
| | Rebleeding | 11 (5) |
| | Pulmonary emboli | 6 (3) |
| | Other pulmonary | 24 (10) |
| | Cardiac | 11 (5) |

implantation of AO-plates supplemented with bone cement (half were in the humerus). The two deep wound haematomas required re-exploration. Four patients had losser impairment of the function of the radial nerve, in three of whom it was transient. Three patients had deep venous thromboses of the operated extremity. Cardiac and pulmonary problems were common (Table 6).

### *Failure of fixation*

Of the 233 cases treated fractures the initial device failed in 26 (11%). The probability of the implant failure (Kaplan Meier survival test) increased in a linear manner over time to about 40% at 60 months. The probability of failure for endoprotheses and angled blades in the femur was 10% and 70% at four years, respectively (Figure 3). The types of failure are shown in Table 7.

*Table 7. Short-term and long-term failure of fixation after initial operation. Cases in which an endoprothesis were inserted are shown in parentheses*

| Complication | Short-term | Long-term | |
|---|---|---|---|
| | <7 weeks | 7-52 weeks | >52 weeks |
| Dislocation | 2 (2) | 0 | 0 |
| Loosening | 0 | 1 | 4 (2) |
| Fatigue break | 0 | 3 | 3 |
| Penetration of cortex | 1 | 0 | 1 |
| Refracture at the end of fixation device | 5 | 4 (1) | 2 |
| Total | 8 (2) | 8 (1) | 10 (2) |

## Discussion

The distribution of primary tumours in our study compares well with those in other studies.[3,6,16,24,25,50]

Rigid internal fixation with adjuvant PMMA bone cement after curettage of metastases to provide immediate stability is more important than to achieve union,

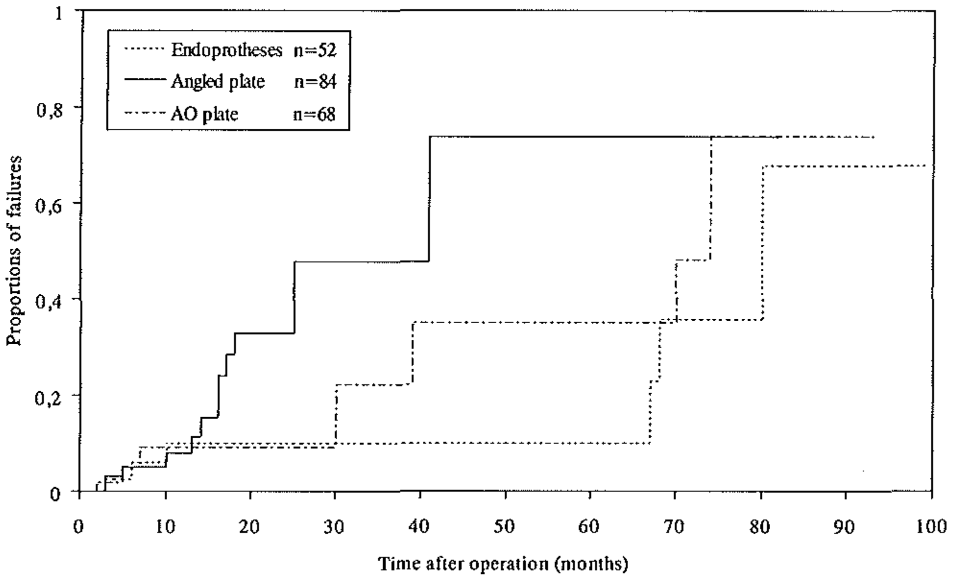


*Figure 3. Probability of failure of fixation after initial treatment of all pathological fractures*

and PMMA bone cement is valuable for this kind of operation.[5,6,8,9,16,24,25,34,42,44] Bone healing has, however, been reported in 64 to 89% of patients who received irradiation (less than 30 Gy) and who survived for more than three months after the operation.[3,18,21,25] Possible bone union depends on the primary tumour, on the anticipated length of survival of the patient, on the site and degree of osseous destruction, and on the radiosensitivity of the metastasis; the management of the fracture also plays a part.[24,49]

After surgical treatment of pathological fractures with internal bone fixation and bone cement, the proper timing of irradiation is controversial. The initial response of bone to irradiation is transient local osteoporosis during the second week after the course.[27] Irradiation of a fractured bone can lead to impaired healing, because irradiation suppresses the chondrogenetic phase of secondary ossification.[4,12,26,28] The anticipated radiosensitivity of the metastatic lesions varies depending on the primary tumour from moderate for breast cancer to low for pulmonary cancer.[27,45] There is, to our knowledge, no comparative study on internal fixation with or without postoperative irradiation. These arguments, in combination with the results gained from our policy of restricting irradiation to patients with recurrent pain (26%), support our practice that rigid internal fixation with bone cement after curettage of a metastatic lesion should not routinely be followed by irradiation.

Our policy is directed to surgical treatment of a pathological fracture before it actually happens. Experiments have shown that prophylactic intramedullary nailing of an impending pathological fracture does not increase dissemination of tumour cells. The same study showed that actual pathological fractures can increase spread of tumour cells appreciably.[7] The criteria for prophylactic osteosynthesis are, however, not well established and there is a true risk of "overtreating" metastatic bone lesions that will never progress to fractures.

Relief of pain is reported after surgical treatment in 80% to 98% of the patients.[3,23,25,38,50] In only one report were the criteria for pain relief defined, and the authors reported excellent to good pain relief in 97% of patients.[24] According to the same criteria, good relief of pain was achieved in 84% of our patients.

Function was restored to the upper extremity in 90% , and 76% were able to walk after operation; these results are similar to those reported alsewhere.[24,25,31,50] Most of the patients who had fractures of the lower limb were able to walk with full weightbearing, which we think is a good result.

Despite the often highly vascular metastatic tissue, in particular in renal cell carcinoma or multiple myeloma, only two of the 233 cases developed deep wound haematoma (1%). Blood loss during operation was high, however, we now embolise metastatic lesions originating from renal cancer before we operate. The haemostatic effect of bone cement on the curetted cavity may have contributed to the low incidence of bleeding after the operation. In only one of the four patients with dysfunction of the radial nerve, was this not caused by neurapraxy. During operation, no surgical lesions of the radial nerve were found. Hyperthermia caused by polymerisation of bone cement could be associated with destructive effects on the nerve. We now pay special attention to adequate cooling of the bone cement.

The mean survival in our group of 199 patients was 8.1 months, which compares well with other authors who have reported mean survival times of 3.2 to 15.6 months in groups of patients varying in selection criteria for operation, primary tumour site, extent and location of metastatic bone lesions.[3,20,23,24,25,34,37,43,50]

The success of fixation depended on the site, on the extention of destruction caused by the bone lesion, as well as on the device used. In the patients with lesions of the humerus, two of three failures were related to deep wound infection. Resection of the entire metastasis, as done before implantation of an endoprothesis, increased the likelihood of good fixation. Our failure of about 9% compares favourably with the results for the treatment of non-pathological femoral neck fractures.[30] Failed fixation of a lower extremity occured in 23 of our 197 patients (12%). Of particular concern was longterm failure caused by fatigue breaking, loosening of the device, penetration of the femoral head by the plate, and refracturing of bone at the distal end of the angled blade plate. About 60% of the failed fixations in femoral lesions were in the subtrochanteric region. Others have reported failure in the same region of 23% as a result of eccentric loadsharing of the angled blade plate resulting of a maximal stress at the weakest point: the position of the first screw hole.[50] The torque and shear forces on the plate at the subtrochanteric region can not entirely be relieved by the pressure of PMMA bone cement within the medullary canal. Fatigue breaks of a plate can easily be treated by inserting a new one, and fractures at the distal end of the plate of an endoprosthesis can be managed by an additional plate. More diffuse metastases should either be replaced by an interlocking nail or by a longer plate.

Osteosynthesis preserving joint and muscular insertion allows fast recovery of function without shortening or rotation of the limb. Immobilisation of the patient after osteosynthesis is not needed and most patients can quickly be mobilised. Curettage with tumour-free margins and bone cement is in general sufficient for local control of tumours. Because it is difficult to assess life expectancy of patients, the risks associated with an operation are justified for nearly every patient with a pathological fracture when one considers the quick relief of pain, the return to walking, and restored limb function, as well as the facilitated nursing care and psychological benefit for the patients.

## References

1 Abrahams HL, Spiro R, Goldstein N. Metastases in carcinoma. Analysis of 1000 autopsied cases. Cancer 1950; 3:74-85.

2 Beals RK, Lawton GD, Snell WE. Prophylactic internal fixation in metastatic breast

cancer.Cancer 1971; 28:1350-1354.

3 Behr JT, Dobozi WR, Badrinath K. The treatment of pathologic and impending pathologic fractures of the proximal femur in the elderly. Clin Orthop 1985; 198:173-178.

4 Bonarigo BC, Rubin P. Nonunion of pathologic fracture after radiation therapy. Radiology 1967; 88:889-898.

5 Borel Rinkes IHM, Wiggers T, Bouma WH, van Geel AN, Boxma H. Treatment of manifest and impending pathologic fractures of the femoral neck by cemented hemiarthroplasty. Clin Orthop 1990; 260:220-223.

6 Bouma WH. The surgical treatment of patients with pathological and impending pathological fractures. Thesis, Amsterdam, 1981. Bronder Offset, Rotterdam, 1981.

7 Bouma WH, Mulder JH, Hop WC. The influence of intramedullary nailing upon the development of metastases in the treatment of an impending pathological fracture: an experimental study. Clin Exp Metastasis 1983; 1:205-212.

8 Cameron U, Jacob CBR, Macnab I, Pilliar RM. Use of polymethyl-methacrylate to enhance screw fixation in bone. J Bone Joint Surg 1975; 57A:655-656.

9 Chan PYM, Norman A. Hyperthermia (HT) effects of methylmethacrylate (MM) in bone metastases. Proc Am Assoc Cancer Res 1979; 20:299-305.

10 Clain A. Secondary malignant disease of bone. Br J Cancer 1965; 19:15-29.

11 Coleman RE, Rubens RD. The clinical course of bone metastases from breast cancer 1987.Br. J. Cancer; 55:61-66.

12 Colyer RA. Surgical stabilization of pathological neoplastic fractures. Curr Prob Cancer. Year book medical publishers, 1986, pp120-168.

13 Douglass JO. Treatment of pathological of long bones excluding those due to breast cancer. J Bone Joint Surg 1976;58A:1055-1060.

14 Fidler M. Prophylactic internal fixation of secondary neoplastic deposits in long bones. Brith Med J 1973; 1:341-343.

15 Fitts WT, Roberts B, Ravdin IS. Fractures in metastatic carcinoma. Am J Surg 1953; 85:282-287.

16 Friedl W. Indication, management and results of surgical therapy for pathological fractures in patients with bone metastases. Eur J Surg Oncol 1990; 16:380-396.

17 Front D, Schenck SO, Frankel A, Robinson E. Bone metastases and bone pain in breast cancer. Are they closely associated? J Am Med Assoc 1979; 242:1747-1748.

18 Gainor BJ, Buchert P. Fracture healing in metastatic bone disease. Clin Orthop 1983; 178:297-302.

19 Galasko CSB. Skeletal metastases and mammary cancer. Ann R Coll Surg Engl 1972; 50:3-28.

20 Galasko CSB. Pathological fractures secondary to metastatic cancer. J R Coll Surg Edinb 1974; 19:351-362.

21 Galasko CSB. The management of skeletal metastases. Royal Coll Surg Edin 1980; 25:143-161.

22 Galasko CSB. Skeletal metastases. Cambridge. Butterworth & Co, Ltd 1986. pp14-27.

23 Gebhart M, Roman A, Ghanem G, Lejeune F. Surgical treatment of bone metastases of the peripheral skeleton: a review of 33 cases. Europ J Surg Oncol 1989; 15:520-529.

24 Habermann ET, Sachs R, Stern RE, Kirsch DM, Anderson WG. The pathology and treatment of metastatic disease to the femur. Clin Orthop 1982; 169:70-82.

25 Harrington KD, Sim FH, Enis JE, Johnston JO, Dick LM, Gristina AG. Methylmethacrylate as an adjunct in internal fixation of pathological fractures. J Bone Joint Surg 1976; 58A:1047-1054.

26 Harrington KD. New trends in the management of the lower extremity metastases. Clin Orthop Rel Res 1982; 169:53-61.

27 Harrington KD. Orthopaedic management of metastatic bone disease. St Louis, CV Mosby 1988, pp83-94, pp283-307.

28 Howland WJ, Loeffler RK, Starchman DE, Johnson RG. Postirradiation atrophic changes of bone and related complications. Therapeutic Radiology 1975; 117:677-685.

29 Johnston AD. Pathology of metastatic tumors in bone. Clin Orthop 1970; 73:8-12.

30 Johnston CE, Ripley LP, Bray CB, Shaffer LW, et al. Primary endoprosthetic replacement for acute femoral neck fractures: A review of 150 cases. Clin Orthop 1982: 123-127.

31 Katzner M, Schvingt E. Métastases oseouses des cancers du sein: Traitement chirurgical de 228 localisations aux membres. Chirurgie 1989; 115:741-750.

32 Keene JS, Sellinger DS, McBeath AA, Engber WD. Metastatic breast cancer in the femur: a search for the lesion at risk of fracture. Clin Orthop 1986; 203:282-288.

33 Knutson CO, Spratt JS. The natural history and management of mammary cancer metastatic to the femur. Cancer 1970; 26:1199-1203.

34 Lane JM, Sculco TP, Zolan S. Treatment of pathological fracture of the hip by endoprosthetic replacement. J Bone Joint Surg 1980; 62A:954-959.

35 Leeson MC, Makley JT, Carter JR. Metastatic skeletal disease: distal to elbow and knee. Clin Orthop 1986; 206:94-99.

36 Lenz M, Freid JR. Metastases to the skeleton, brain and spinal cord from cancer of the breast and the effects of radiotherapy. Ann Surg 1931; 93:278-293.

37 Levy RN, Sherry HS, Siffert RS. Surgical management of metastatic disease of bone at the hip. Clin Orthop 1982; 169:62-69.

38 Lewallen RP, Pritchard DJ, Sim FH. Treatment of pathologic fractures or impending fractures of the humerus with Rush rods and metylmethacrylate: experience with 55 cases in 54 patients, 1968-1977. Clin Orthop 1982; 166:193-198.

39 Lote K, Walloe A. Bjersand A. Bone metastasis : Prognosis, diagnosis, and treatment. Acta Radio Oncol 1986; 25:227-232.

40 Marcove RC, Yang DJ. Survival times after treatment of pathologic fractures. Cancer 1967; 20:2154-2158.

41 Menck H, Schulze S, Larsen E. Metastasis size in pathologic femoral fractures. Acta Orthop Scand 1988; 59:151-154.

42 Murray JA, Bruels MC, Lindberg RD. Irradiation of polymethylmethacrylate. J Bone Joint Surg 1974; 56A:311-312.

43 Rosenberger J, Zieren HU. Die Therapie maligner pathologischer Frakturen. Ergebnisse einer retrospektiven Untersuchung. Unfallchirurg 1989; 15:279-284.

44 Ryan JR, Begeman PC. The effects of filling experimental large cortical defects with methylmethacrylate. Clin Orthop 1984; 185:306-310.

45 Schocker JD, Brady LW. Radiation therapy for bone metastasis. Clin Orthop 1982: 169:38-43.

46 Schutte HE. The influence of bone pain on the results of bone scans. Cancer 1979; 44:2039-2043.

47 Sherry HS, Levy RN, Siffert RS. Metastatic disease of bone in orthopedic surgery. Clin Orthop 1982; 169:44-52.

48 Sim FH, Daugherty TW, Ivins JC. The adjunctive use of methylmethacrylate in fixation of pathological fractures. J Bone Joint Surg 1974; 56A:40-48.

49 Sim FH.Diagnosis and management of metastatic bone disease: a multidisciplinary approach. New York, Raven Press 1988. pp165.

50 Yazawa Y, Frassica FJ, Chao EYS et al. Metastatic bone disease: a study of surgical treatment of 166 pathologic humeral and femoral fractures. Clin Orthop 1990; 251:213-219.

51 Zickel RE, Mouradian WH. Intramedullary fixation of pathological fractures and lesions of the subtrochanteric region of the femur. J bone Joint Surg 1976; 58A:1061-1066.

# Chapter 3

## Treatment of pathological fractures of the humeral shaft

### A retrospective study among intramedullary nail and AO plate osteosynthesis with adjunctive bone cement

PDS Dijkstra[1], JWJL Stapert[2] , H Boxma[1] , and T Wiggers[3]

Departments of Surgery of the South Municipal Hospital[1], the Medical Spectrum Hospital[2], Enschede, and of the Daniel den Hoed Cancer Center[3], Rotterdam, The Netherlands

*Eur J Surg Onco 1996; 22: 621-626*

## Introduction

Pathological fractures caused by metastatic malignant disease have increasing interest in recent years. The humerus is the second involved bone, accounting for 16% - 39% of cases with actual or impending pathologic fractures of the long bones.[1-7] In the literature the humerus has received lesser attention then the femur. Pathological fractures are not life threatening by themselves, but pain and loss of arm function have devastiting effects on the patient's quality of life.

In contrast to treatment of the non-pathologic fracture of the humerus, conservative management of a pathologic fracture is not advised because of the high incidence of non-union and the poor relief of pain.[8-11] Rapid functional recovery with pain relief is best achieved with surgical stabilization. Basically, there are two techniques for internal fixation: plate with adjunctive bone cement and the use of an intramedullary (locking) nail. Plate osteosynthesis in combination with bone cement has shown its benefits in early painless restoration of function of the limb.[1,2,12] Revival of intramedullary fixation techniques in recent years has been remarkable and has several biomechnical and technical advantags in the treatment of actual and impending pathologic fractures.[13,14]

The purpose of this retrospective study is to analyse the results of two different surgical treatment protocols (plate fixation with adjunctive bone cement vs intramedullary locking nailing) for humeral shaft fractures due to bone metastases, with particular emphasis on complications, restoration of function, and relief of pain.

## Patients and Method

Over an 11 year period (1983 - 1993), data were collected by reviewing all files and radiografics of 37 consecutive patients treated surgically at the Daniel den Hoed Cancer Center in cooperation with the South Municipal Hospital Rotterdam and the Medical Spectrum Hospital Enschede with 11 impending and 27 pathologic fractures of the humeral shaft (Table 1). All patients were followed up for at least 6 months or until death. Conventional anteroposterior and lateral radiographs were routinely taken of the full humeral length. Age and limited life expectancy, by themself, were no contra-indications for operation.

The decision to give prophylactic treatment was based on at least one of the following criteria: a lytic lesion of more than 2.5 cm, circumferential cortical destruction of 50% or more, or persistent or increasing pain not improving after radiotherapy.[5,7,15,16]

*Table 1. Description of patient population.*

| | | Nail | Plate | Total (%) |
|---|---|---|---|---|
| Sex | Male | 6 | 5 | 11 (30) |
| | Female | 11 | 15 | 26 (70) |
| Age | Mean | 68 | 63 | 65 |
| | (range) | (43-78) | (47-89) | (43-89) |
| No of fractures | Actual | 11 | 16 | 27 (71) |
| | Impending | 7 | 4 | 11 (29) |
| | Bilateral | 1 | 0 | 1 (3) |
| Diaphysis | Proximal | 4 | 8 | 12 (32) |
| | Mid | 14 | 10 | 24 (63) |
| | Distal | 0 | 2 | 2 (5) |

Two different surgical techniques were performed depending on the surgeons preference, determinated by experience of the surgeon with nailing or plating. In one group, after open reduction, a plate was applied above and below the lesion. The tumour was excised, the defect was filled with bone cement. Additional screw fixation was used after hardening of the cement. In the other group, after reduction, antegrade or retrograde (un)reamed nail was introduced with proximal and/or distal locking. The different intramedullary nailing procedures was dependent on the kind of fracture. The aim in both groups was to fix the fracture rigidly, and not to achieve bone healing.

The following items were studied: the date of diagnosis, site and type of the primary tumour, site and kind of pathologic lesions, time and amount of radiotherapy, pain and use of analgesics before and after treatment, postoperative arm function, date of operation, surgical technique, peroperative blood loss, operation time, local and systemic complications, eventual reoperation, hospitalization time, and date at the time of death or last follow-up.

Objective pain relief was evaluated by the amount of analgesics required 1 month after operation: objective pain relief was classified as excellent (no pain and no regular analgesics), good (no pain with regular non-narcotic drugs), fair (narcotics to relieve pain), and poor (no relief of pain even with narcotics).[3,6,10,15] Subjective pain relief was evaluated from the pain reported in patients files 4 weeks after operation.

The function of the arm was classified as excellent (essentially normal function), good (slight impairment of function with normal activities of daily living), fair (limited use), and poor (inability to use the extremity).

Survival curves were calculated using the Kaplan-Meier method and logrank test. The Mann-Whitney test was used for nonpaired analyses of two groups, and the Fisher Exact test for one'case in different groups.

## Results

The primary tumour leading to bone metastases in the humerus in 75% of the patients were: breast carcinoma, hypernephroma, bronchus carcinoma, and multiple myeloma (Table 2).

One-third of the patients had radiotherapy before operation (mean 17 Gy). The indication for postoperative radiotherapy when a plate osteosynthesis was performed was recurrent local pain (n=5). In contrast, if there had been no radiotherapy applied previously (n=5) the group with intramedullary locking nail usually received postoperative radiotherapy (n=7, mean 13 Gy). This was applied to the operation site in the early postoperative period, between 1 - 4 weeks after operation. Radiotherapy was withheld if the patient's general condition had deteriorated to the point that further treatment was considered inappropriate. The median interval between diagnosis of impending or actual fracture and operation was 9 days. Twenty lesions in 20 patients were treated with plate osteosynthesis and bone cement (Figure 1, Table 1). Different nail devices were used to treat 18 humeri in 17 patients. The ntegrade nail without bipolar static locking was used in 2 cases, the interlocking nail with antegrade procedure in 9 humeri, and a retrograde operation in 7 cases

*Table 2. Site of primary tumour*

| Site | Nail | Plate | Total |
|---|---|---|---|
| Breast | 11 | 8 | 19 |
| Kidney | 2 | 5 | 7 |
| Bronchus | 2 | 1 | 3 |
| Multiple meyloma | 2 | 0 | 2 |
| Urological tract | 1 | 1 | 2 |
| Prostate | 0 | 1 | 1 |
| Sarcoma | 0 | 1 | 1 |
| Female genital tract | 0 | 1 | 1 |
| Lymphoma | 0 | 1 | 1 |
| Unknown | 0 | 1 | 1 |
| Total | 38 | 18 | 20 |

(Figure 2). Adjunctive bone cement wasn't used in nail fixation. Objective and subjective good to excellent relief of pain was achieved in plate fixation in 80% and 95%, and in nail fixation in 78% and 88%, respectively (Table 3). Recurrent local pain after one month occurred in two patients with nail fixation and in five patients with plate fixation. Restoration of function of the arm was good to excellent in patients treated with plate fixation in 19 cases (95%), and with nail

*Table 3. Objective and subjective relief of pain and restoration of function of the arm after operation. Percentages in parentheses*

| | | Nail | Plate | Total |
|---|---|---|---|---|
| Subjective relief of pain | Excellent | 8 (44) | 5 (25) | 13 (34) |
| | Good | 8 (44) | 14 (70) | 22 (58) |
| | Fair | 1 (6) | 1 (5) | 2 (5) |
| | Poor | 1 (6) | 0 (0) | 1 (3) |
| Objective relief of pain | Excellent | 3 (17) | 10 (50) | 13 (34) |
| | Good | 11 (61) | 6 (30) | 17 (45) |
| | Fair | 2 (11) | 4 (20) | 6 (16) |
| | Poor | 2 (11) | 0 (0) | 2 (5) |
| Function | Excellent | 9 (50) | 11 (55) | 20 (52) |
| | Good | 8 (44) | 8 (40) | 16 (43) |
| | Fair | 1 (6) | 1 (5) | 2 (5) |
| | Poor | 0 (0) | 0 (0) | 0 (0) |

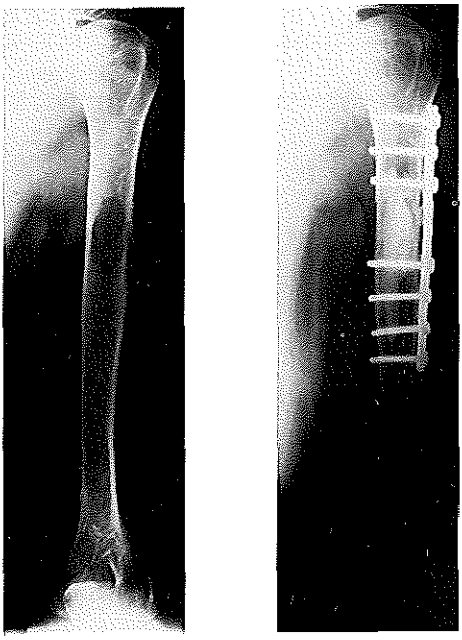


*Figure 1. Patient with impending pathological proximal shaft fracture treated with plate osteosynthesis with adjunctive bone cement.*

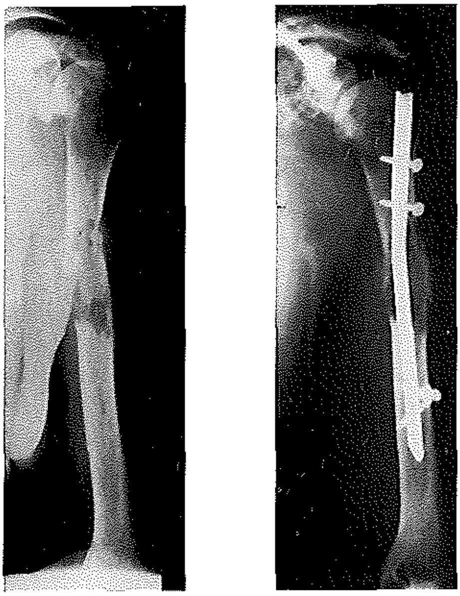


*Figure 2. Actual proximal shaft fracture treated with a intramedullary nail with bipolar static fixation.*

fixation in 16 cases (94%) (Table 3). In both treatment groups the function was scored fair in one case because of local tumour progression. Patients treated with nail fixation have a lower median operative blood loss (300ml) than patients with plate osteosynthesis (500ml)($P<0.05$). In plate fixation three patients developed local complications related to operative treatment. One patient had transient radial nerve paresis with subsequent total recovery, excellent relief of pain and a good armfunction, one patient had haematoma and wound dehiscence, and in one patient rebleeding. Wound haematoma occurred in one patient as local complication after nail fixation. Extended spread of primary disease was the main cause of systemic complications (Table 4).

*Table 4. Local and systemic complications after operation*

| Complications | | Nail | Plate | Total |
|---|---|---|---|---|
| Local | Wound dehiscence | 0 | 1 | 1 |
| | Wound haematoma | 1 | 1 | 2 |
| | Radial nerve paresis | 0 | 1 | 1 |
| | Rebleeding | 0 | 1 | 1 |
| Systemic | Primary tumour | 2 | 3 | 5 |
| | Sepsis | 0 | 1 | 1 |
| | Cardiac | 1 | 0 | 1 |

In one patient with plate fixation local tumour progression resulted in failure of fixation (Table 5). Eventually, after 6 months a fore-quarter amputation was necessary. After initial nail fixation all failure of fixation developed within 9 days. In two patients reamed nails without bipolar static locking were used. Angulation occurred in one case and rotation instability in the other. In another patient refracture at the site of introduction of a nail with bipolar static locking was treated with additional cerclage wiring. Because of poor relief of pain the wiring was removed and 2 additional plate's were applied.

*Table 5. Failure of fixation after operation*

| Complication | Nail | Plate | Total |
|---|---|---|---|
| Angulation | 1 | 1 | 2 |
| Rotation | 1 | 0 | 1 |
| Refracture at the end of fixation device | 1 | 0 | 1 |

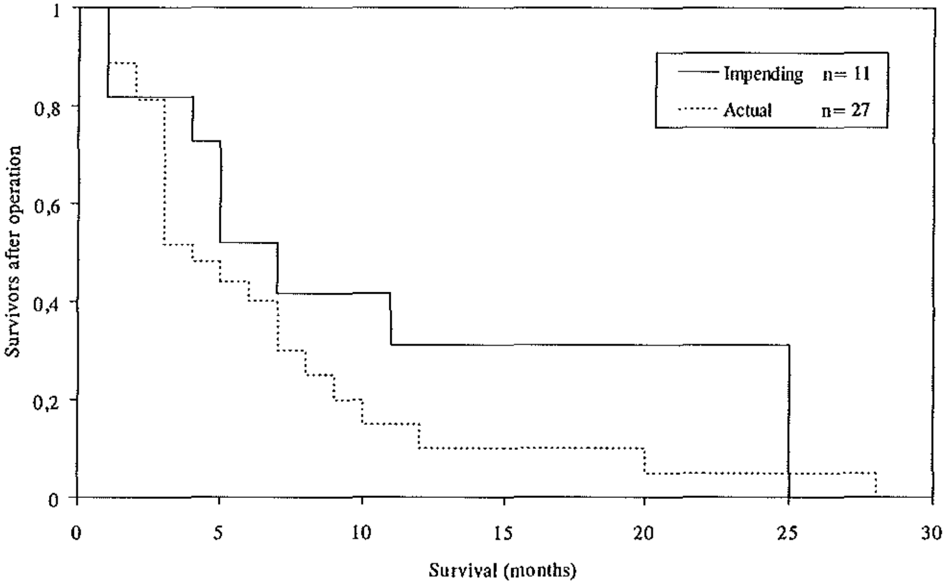


*Figure 3. Survival analysis of impending and actual pathological fractures*

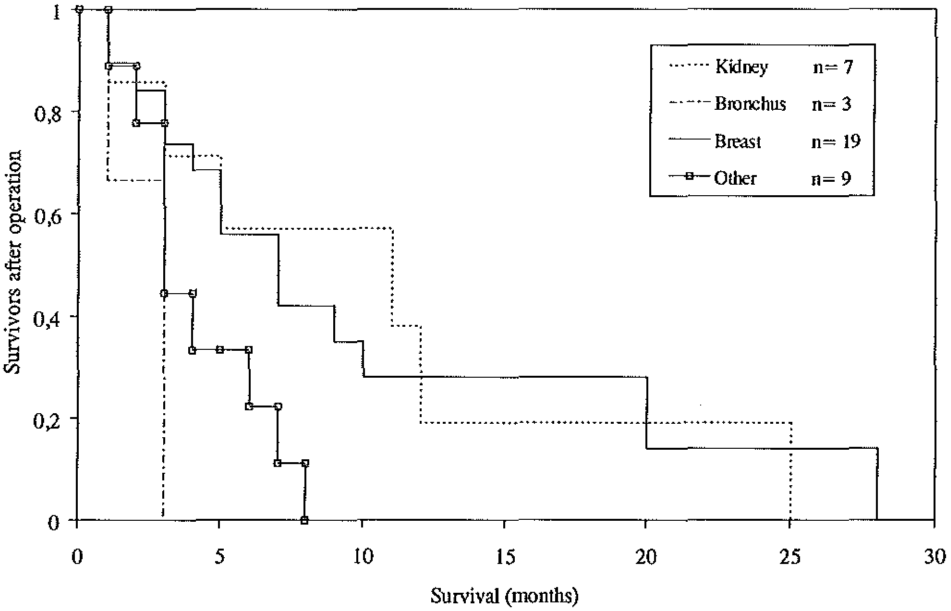


*Figure 4. Survival analysis of sites of primary lesions after operation*

The median hospital stay in plate and in nail fixation was 14 days and 9 days, respectively. None of the patients died as a result of the operative procedure. Survival analysis showed an overall survival of 61% at three months (n=31) and 44% at six months (n=16), six were alive after one year. No significant difference in survival rate were associated with the methods of treatment, nor with the operation indication (Figure 3). The survival rate after operation is highly influenced by the site of the primary lesion ($P<0.005$)(Figure 4).

## Discussion

The mean survival after a pathologic humerus fracture in 37 patients was 4.8 months, which is less in comparison with other authors who reported mean suvival of 9.6 to 15.4 months. We believe that this is the result of different criteria for selection, criteria for operation, primary tumour site, number of impending fractures, and non use of survival rate analysis. Katzner et al., however, reported a survival rate of 33% at 6 months after operation using Kaplan-Meier survivorship analysis.[3,4,10,17] In contrast to the reports of Harrington et al. and Hardman et al. we found no evidence of prolonged postoperative survival after prophylactic treatment.[3,18] A survival expectancy of 6 weeks or less, as mentioned by Parrish and Murray, should not be used as selection criteria because even terminally ill patients with a short life expectancy could benefit from internal fixation.[1,5]

Lesions smaller then 2.5 cm or involvement of 50% or more of the circumferential cortex were intially treated successfully with irradiation alone. Our policy is directed to prophylactic internal fixation of a pathological fracture before it actually happens because this prevents severe pain of an actual fracture, is technically easier, and has a lesser incidence of surgical complications.[3,5,10,13] Not only the measurements of the bone lesions should be taken into account as prophylactic surgery is performed but also the analysis of how essential functioning of the upper limb is in activities in daily life.

The humerus has a relatively small cortical mass. This, together with specific biomchanics of the humeral bone to torsional loading, commonly results in fractures of the middle third of the humeral shaft.[19] Katzner et al. reported that 50% of the 33 humeral shaft fractures were located at the proximal third region. In our series 63%

of the 38 humeral fractures affected the mid third of the shaft.[4]

Two advantages of intramedullary nailing are reduced blood loss and lower local complication rate because the fracture site and majority of the soft tissue remain untouched. Furthermore, compared to plate fixation, intramedullary nailing can create stabilization of the whole bone.[20] In case of multiple metastases, special attention should be given to prevent refracturing during operation. This was seen in one patient after nail insertion. A major pitfall of the antegrade use of interlocking nail fixation is impingment of acromion during shoulder abduction. It is essential that the tip protrudes deep into the humeral cortical head. In the present study all nail fixation without bipolar static locking resulted in failure of fixation. We recommend the use of nail fixation with bipolar static locking in treatment of pathological fractures.

Hoare showed in 1968 that tumour cells can be detected in the blood at the time of intramedullary nailing in pathologic fractures.[21] This could raise the issue of possible dissemination of systemic metastasis during the operation. However, because of short survival time of these patients, this appears not to influence the disease outcome.[3,22,23]

In general, radiotherapy is given postoperative routinely. However, there are arguments that support our experience that plate fixation with bone cement after curretage of metastatic lesion should not routinely be followed by irradiation:[1] A radioinsensitive tumour is not uncommon.[24] The initial respons of bone to irradiation is transient local osteoporosis during the second week after initiation.[24] Radiotherapy can lead to impaired healing because irradiation suppresses the chondrogenetic phase of secondary ossification.[25,26,27] Furthermore, the additional effect of the use of bone cement to provide an immediately stability, and tumournecrosis caused by hyperthermia should be considered.[28,29] Intramedullary nailing should be followed by radiotherapy for proper local tumor control.

In our series, operative treatment generally provided good early subjective and objective relief of pain and sufficient return to function to allow use of extremity for activities of daily living in 92%, 79%, and 95% respectively. No significant differences were found between both methods in these results. Similar to our findings, good relief of pain and function was also obtained in almost all patients treated with internal fixation by Perez et al. (n=9), Douglass et al (n=8), Katzner et al. (n=45), and Lewallen et al. (n=55).[4,6,8,17] No significant difference in local and systemic complications were found. Temporarely radial nerve paresis occured in one patient with plate osteosynthesis, based on neuropraxia. Highly vasculair tumours, like renal carcinoma, can result in extreme blood loss during and after operation. If such a patient should be treated, preoperative arterial embolization should be considered.[1,12] Besides the advantage of reduced blood loss during operation by using intramedullary nailing no other difference in outcome were found between both groups.

The procedures of osteosynthesis are not technically difficult, but because there are different degrees of bone destruction, levels of involvement, life expectancy, and experiences of the surgeon, each case must be individualized. Although in present study no difference in indication for the type of operation was found, we advocated in diffuse or multiple bone lesions intramedullary locking nail without resection of metastasis and according to the general condition followed by irradiation of the affected bone. To come to a more clear definition for plating or nailing osteosynthesis of pathological humeral fractures, a prospective randomized trial is needed.

In conclusion, we believe that nearly all patients with an impending or actual pathologic fracture of the humeral shaft are likely to benefit from rigid internal fixation with an appropiately selected device, in plate osteosynthesis with adjunctive bone cement and local irradiation as needed, and in intramedullary interlocking nail with postoperative local irradiation therapy.

## References

1 Dijkstra PDS, Wiggers T, van Geel AN, et al. Treatment of impending and actual pathological fracture in patients with bone metastases of the long bones. Eur J Surg 1994; 160:535-542

2 Friedl W. Indication, management and results of surgical therapy for pathological fractures in patients with bone metastases. Eur J Surg Oncol 1990; 16: 380-396

3 Harrington KD, Sim FH, Enis JE, et al. Methylacrylate as an adjunct in internal fixation of pathological fractures. J Bone Joint Surg 1976; 58A: 1047-1055.

4 Katzner M, Schvingt E. Métastases oseuses des cancers du sein. Traitement chirurgical de 228 localisations aux membres. Chirurgie 1989; 115: 741-750.

5 Parrish FF, Murray JA. Surgical treatment for secondary neoplastic frcatures. A retrospective study of ninety-six patients. J Bone Joint Surg 1970; 52(A): 665-686.

6 Perez CA, Bradfield JS, Morgan HC. Management of pathologic fractures. Cancer 1972; 29: 684-693.

7 Yazawa Y, Frassica FJ, Chao EYS, et al. Metastatic bone disease. Clin Orthop Rel Res 1990; 251: 213-219.

8 Douglass HO, Sukhla SK, Mindell E. Treatment of pathological fractures of long bones excluding those due to breast cancer. J Bone Joint Surg 1976; 58A: 1055-1060.

9 Gainor BJ, Buchert P. Fracture healing in metastatic bone disease. Clin Orthop Rel Res 1983; 178: 297-302.

10 Lancaster JM, Koman LA, Gristina AG, et al. Pathologic fractures of the humerus. South Med J 1988; 81: 52-55.

11 Mast JW, et al. Fractures of the humeral shaft. A retrosprctive study of 240 adult fractures. Clin Orthop Rel Res 1975; 112: 254-260.

12 Habermann ET, Lopez RA: Metastatic disease of bone and treatment of pathological fractures. Orthop Clin North Am 1989; 20: 469-486.

13 Hulst van der RRWJ, Wildenberg van der FAJM, Vroemen JPAM, et al. Intramedullary nailing of pathologic fractures. J Trauma 1994; 36: 211-215.

14 Stapert JW, Geesing CL, Jacobs PB, de Wit RJ, et al. First experience and complications with the long Gamma nail. J Trauma 1993; 34: 394-397.

15 Habermann ET, Sachs R, Stern RE, et al. The pathology and treatment of metastatic disease of the femur. Clin Orthop 1982; 169: 70-82.

16 Fidler M. Incidence of fracture through metastases in long bones. Acta Orthop Scand 1981; 52: 623-627.

17 Lewallen RP, Pritchard DJ, Sim FH. Treatment of pathologic fractures or impending fractures of the humerus with Rush rods and methylmethacrylte. Experience with 55 cases in 54 patients: 1969-1977: Clin Orthop Rel Res 1982; 166: 193-197.

18 Hardman PDJ, Robb JE, Kerr GR, Rodger A, et al. The value of internal fixation and radiotherapy in the management of upper and lower limb bone metastases. Clinical Oncology 1992; 4: 244-248.

19 Nordin M, Frankel VH: Biomechanics of bone. In Nordin M, Frankel VH (ed). Basic biomechanics of skeletal system. Philadelphia, Lea & Febiger, 1989: 3-29.

20 Ward F, White J. Interlocked intramedullary nailing of the humerus. Orthopedics 1989; 12: 135-138.

21 Hoare JR. Pathological fractures. In: Proceedings of North-west Metropolitan Orthopaedic Club. J Bone Joint Surg 1968; 50B: 232.

22 Beals RK, Lawton GD, Snell WE. Prophylactic internal fixation in metastatic breast cancer. Cancer 1971; 28: 1350-1354.

23 Fidler M. Prophylactic internal fixation of secondary neoplastic deposits in long bones. Br

Med J 1973; 1: 341-343.

24 Schocker JD, Brady LW. Radiation therapy for bone metastasis. Clin Orthop 1982; 169: 38-43.

25 Harrington KD: Orthopaedic management of metastatic bone disease. St Louis, CV Mosby, 1988: 92.

26 Bonarigo BC, Rubin P. Nonunion of pathologic fracture after radiation therapy. Radiology 1967; 88: 889-898.

27 Howland WJ, Loeffler RK, Starchman DE, et al. Postirradiation atrophic changes of bone and related complications. Ther Radiol 1975; 117: 677-685.

28 Chan PYM, Norman A. Hyperthermia (HT) effects of methamethylacrylate (MM) in bone metastases. Proc Am Assoc Caner Res 1979; 20: 299.

29 Cameron HU, Jacob CBR, Macnab I, et al: Use of polymethylmethacrylate to enchance screw fixation in bone. J Bone Joint Surg 1975; 57A: 655-656.

# Chapter 4

# Prediction of pathological subtrochanteric fractures due to metastatic lesions

## A retrospective study of 54 lesions at risk to fracture

PDS Dijkstra[1], M Oudkerk[2], and T Wiggers[1]

Departments of Surgical Oncology, and Radiology[2], Daniel den Hoed Cancer Center,
Rotterdam, the Netherlands

*Arch Orthop Trau Surg 1997; 116: 221-224*

## Introduction

Malignant metastatic tumour is the most common bone tumour. The incidence of skeletal metastasis to the femur is high (30-50%)[1,2] and rising due to prolonged patient survival as a result of more effective treatment of visceral metastases.[3] About 10% of patients with disseminated breast cancer develop a pathological fracture of the proximal femur.[4] One third of impending and actual femoral fractures is located in the subtrochanteric region.[5-7]

Pathological fractures can greatly affect the quality of life. Prophylactic fixation of impending fractures is generally preferred over treatment of actual fractures. Quick relief of pain, earlier mobility, decreased hospital stay and reduction of operative complications are reported as significant advantages.[8-10] As a result, prophylactic fixation is being increasingly performed. There are three main accepted principles in assessing femoral fracture risk[9]: (1) a lytic lesion 25 mm or larger involving the femur, (2) lytic circumferential cortical destruction of 50% or more, (3) persistent pain with weight-bearing, despite local therapy. At present, these criteria pervade clinical practice, despite the fact that several authors have concluded that pain is not a reliable sign in diagnosing impending fractures. Furthermore, one half of the standard radiographs are not evaluable, i.e. measurements of radiographic appearance or pathology adequately cannot be evaluated.[6,11-13,14]

Therefore, there is a need for criteria for lesions at risk of fracturing. In an attempt to develop such criteria for a metastatic lesion, we retrospectively analysed patients with impending and actual fractures due to metastatic bone lesions in the subtrochanteric femoral region, paying special attention to size of the metastases, involvement of the cortex nd bone pain at the site of the lesion.

## Materials and methods

Data were collected by reviewing all of the files and radiographs of 54 consecutive patients with 30 impending and 24 actual pathological fractures in the subtrochanteric femoral region treated from 1978 to 1990. The criteria of an impending pathological fracture were: a lytic lesion of 25 mm or more, circumferential destruction of 50% or more and persistent pain. There were 43 women and 11 men, with a median age of 58 years (range 24-85 years). The primary tumours were breast in 35 patients, multiple myeloma in 5, bronchus in 4, kidney in 4, prostate in 2, sarcoma in 2, and other sites in 2. The median period between the diagnosis of the primary tumour and actual or impending pathological fracture was 31 months (range 0-193 months). In 28 patients the bone lesion was located only in the subtrochanteric region. The intertrochanteric region was also involved in 12 patients and the proximal diafyseal region in another 14 patients.

The anteroposterior (AP) and lateral radiographs were examined in the following manner by one observer. First, the bone lesions were classified as lytic, blastic or mixed (lytic and blastic). Then the appearance of the lesion as circumscript solitary, circumscript with multiple foci, or diffuse was recorded. Third, the following measurements of the metastasis were made (Figure 1)[6]: largest width of the metastasis (W), largest width of bone (B) at W, largest intramedullary length of the metastasis (H), longitudinal length of cortex involvement (A), the remaining cortex on the level of the largest involvement of the cortex ($D_{medial}$, $D_{lateral}$, $D_{anterior}$, $D_{posterior}$), and the uninvolved cortex below or above the bone lesion ($C_m$,$C_{ll}$,$C_a$,$C_p$). Calculations were made of percentage of cortex destruction $P=(1-(D_m+D_l+D_a+D_p)/(C_m+C_l+C_a+C_p))*100$, and largest ratio between width of the metastasis and width of the bone (W/B). The measurements of the radiographs were corrected for the magnification at the rate of 1.2.

The Spearman rho test was used for correlation analyses, the Mann-Whitney test for non-paired analyses of two groups, and the Fisher exact test for one case in different groups.

## Results

Nearly all lesions were radiographically classified as lytic. In two patients lytic and blastic (mixed) lesions were recorded. The radiographic aspect of the lesions was recorded in 16 patients as solitary, in 23 patients as multiple foci, and in 15 patients as diffuse. However, in 5 cases no measurements could be made of the AP radiograph and in 22 cases of the lateral radiograph, due to unidentifiable margins of

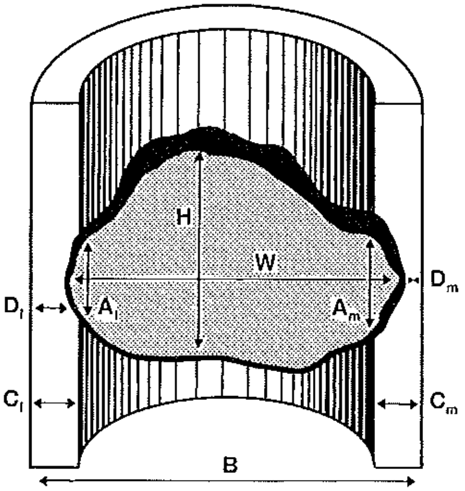


*Figure 1. Measurements of size of the metastases of actual and impending pathological subtrochanteric fractures. W; width of metastases, B; width of bone, H; length of metastases,* $C_m$ *and* $C_l$*; width of cortex,* $D_m$ *and* $D_l$*; width cortical destruction, and* $A_m$ *and* $A_l$*; axial cortical destruction.*

the bone involded. In 27 patients (50%) accurate measurements were made. In the anteroposterior view 8 metastases medial (30%) $[(1\text{-}D_m/C_m)\text{-}(1\text{-}D_l/C_l)>1/4]$ and 11 metastases were located centrally $[(1\text{-}D_m/C_m)\text{-}(1\text{-}D_l/C_l)<1/4]$. In the lateral view 11 metastases (40%) were located anterior and 7 metastases posterior. No relationship was found between the measurements of the metastases and the histology of the

*Table 1. Radiographic measurements in median values of 9 actual and 18 impending fractures. A,B,D,H,W are visualized in figure 1.* $^*$ *P<0.05*

| Measurements of bone lesion | Actual | Impending | Total |
|---|---|---|---|
| Width metastases (W) | 33 (21-48) | 28 (17-50) | 30 (17-50) |
| Ratio: W / width of bone | 0.88 (0.5-1) | 0.79 (0.2-1) | 0.83 (0.2-1) |
| Length metastases (H) | 100 (42-200) | 65 (25-150) | 75 (25-200) |
| Maximal height cortical destruction (A)$^*$ | 54 (38-100) | 38 (7-125) | 42 (7-105) |
| Transverse cortical destruction (D) | 0.37 (0-0.71) | 0.5 (0.07-0.94) | 0.44 (0-0.94) |
| Total | 9 | 18 | 27 |

lesion. There is a significant difference measurements of the maximal destruction of the longitudinal cortex (A) among patients with an actual or impending fracture ($P<0.05$). The other three assessments (W,B,H) showed no significant difference between the two groups (Table I). In the search for lesions at risk we found a 'cut-off-point' in several measurements between actual and impending treated patients: ratio of maximal longitudinal cortex destruction to the width of the bone was equal to or greater than 1.2 (A/B), maximal longitudinal cortex destruction (A) was equal to or greater than 38 mm, intramedullary bone lesion width (W) was equal to or greater than 35 mm, and the ratio of metastasis width to bone width exceeded 0.9 (W/B)(Table 2).

*Table 2. Prevalence of radiographic risk factors in actual and impending fractures. The 95% confidential limits are given in parentheses.* $^{@}$ *$P<0.005$,* $^{*}$ *$P<0.05$*

| Risk factors | Actual | Impending |
|---|---|---|
| Maximal longitudinal cortical destruction ≥ 38 mm$^{@}$ | 9 (0.58-0.83) | 9 (0.24-0.59) |
| Ratio: width metastases / width of bone ≥ 0.9$^{*}$ | 7 (0.45-0.94) | 5 (0.13-0.51) |
| Maximal width bare lesion >30 mm$^{*}$ | 8 (0.48-0.82) | 8 (0.21-0.55) |
| Total | 9 | 18 |

At first presentation local pain had occurred in 41 patients (78%) within 14 weeks (median) before fracturing, with a range of 1 to 220 weeks. In this study approximately one-third of patients with an impending (11/30) or actual (9/24) fracture complained of initial pain within 3 months before surgery. However, 6 patients complained of aggravating pain of which 5 developed an actual fracture within 2 months (95% confidencel limits= 57%-100%; $P<0.05$). Pain was not related to tumour histology nor to radiographic measurements.

## Discussion

In this selected series nearly all (99%) osseous lesions were lytic. In contrast, Keene et al[11] found in non-selected data no difference in fracture rate among lytic, blastic or mixed lesions. Most studies, however, report a higher fracture risk for lytic osseous lesions.[5,13,15] Several investigators have considered the difficulty of accurate measurements of these bone lesions.

These data show that 46-60% are evaluable.[7,11] In the remaining group the margins of bone involvement were not well enough defined or actual fracture had distorted the geometry of the bone lesions. In our study there was difficulty in identifying the involvement of the cortex in 50% (27 cases) due to unidentifiable margins of bone involvement. Controversially, Menck et al.[6] reported no problems in radiographic evaluation in 69 patients with pathological femoral fractures. Patient selection and differences in measurement methods probably explain these contradictory results. If the conventional AP or lateral radiograph is not evaluable, computed tomography has been suggested as a diagnostic option.[12,13]

The indications for prophylactic internal fixation, first described by Griesmann and Schüttemeyer[16], concern the size and extent of the cortical destruction by metastases and have been controversial since their proposal(Table 3).

*Table 3. Literature review of femoral bone lesions at risk of fracturing.*
*(a) Despite radiotherapy, (b) including pathological humerus, (c) occult lesion and ↑ for increasing pain.*

| Reference | Fractures (actual) | Pain | Radio-graphic lytic aspect | Transverse cortical bone destruction | Circum-ferential bone destruction (%) | Size of well-defined lesion (mm) | Longitudinal cortical destruction (mm) | Ratio: width metastases / bone |
|---|---|---|---|---|---|---|---|---|
| Parrish[17] | 109 (103) | ↑ | + | | + > 50 | | | |
| Beals[1] | 27 (22) | + | | + | | + ≥ 25 | | |
| Fidler[10] | 19 (19) | - | + c | | + > 50 | | | |
| Zickel[5] | 46 (35) | ↑ | | + | | | | |
| Fidler[19] | 87 (32) | | + | | + > 50 | + ≥ 25 | | |
| Harrington[9] | - (-) | + a | + | | + > 50 | + ≥ 20 | | |
| Miller[18] | 136 (15) | | - | + | + > 25 | - | | |
| Keene[11] | 516 (26) | - | | | - | | + > ? | |
| Menck[6] | 69 (69) | - | + | | + > 50 | | + ≥ 30 | + ≥ 0.6 |
| Mirels[13] | 78 (27) b | ↑ | | | + > 67 | | | |
| Yazawa[7] | 120 (71) | + | + | | + > 50 | | | |
| Dijkstra | 54 (19) | ↑ | | | | | + ≥ 38 | + > 0.9 |

Several combinations of criteria have been suggested: pain, lytic aspect, occult lesion, amount of cortical destruction, size of well-defined lesion, longitudinal cortical destruction and the ratio metastasis width to bone width. The assessment of the percentage of the circumferential cortical destruction to intact bone is generally regarded as essential. [6,7,9,10,17-19] However, there are some arguments to emphasize. Often it is difficult to radiograph these painful and dysfunctioning limbs and, without radiographic standardization in two directions, assessment of the circumferential cortical destruction seems rather questionable. Furthermore, for therapy purposes alone often only AP radiographs are taken.

In this study we used a modified formula $P=(1-((D_m+D_l+D_a+D_p) / (C_m+C_l+C_a+C_p) )*100$ suggested by Hipp et al.[12] to calculate the percentage of destroyed cortical wall thickness to intact cortical wall thickness from radiographs in two directions. Hipp et al[12] considered a 50% reduction in bone strength in an experimental study of endosteal shaft lesions in dog femora when 35% cortical destruction had occurred. Zickel and Mouradian[5] described in a clinical study of 46 impending and actual pathological subtrochanteric fractures the concept of a 'high risk femur' as a lesion with a pure lytic aspect, an occult lesion with increasing pain and (any) involvement of the cortex (Table 3). Keene et al.[11] and Bremner and Jelliffe[20], on the other hand, concluded in a clinical study that there is no relationship between the involvement of the cortex and bone fracture.

Metastatic lesions tend to follow a path of least resistance and therefore commonly occur along the endosteal surface of long bones without completely penetrating the cortical wall. Beals et al.[1] described in a small series of 27 cases that a size of more than 25 mm in a well defined metastatic lesion has a predictive value for bone fracture. Accurate measurements of 69 actual pathological femur fractures by Menck et al.[6] indicated that longitudinal cortical destruction of more than 30 mm has a reliable predictive value for bone fracture. This is compatible with our results (38 mm or more). Similarly, in an experimental study Frankel and Burstein[21] found that a single saw cut of one-fifth of the length of the tibia decreased torsional energy absorption by 70%, while increasing the width and maintaining the same length did not further weaken the torsional strength. This reduction is mainly due to a redistribution of shear stress in the cross-sectional bone. However, Clark et al.[22] and McBroom et al.[23] reported no significant strength reduction by longitudinal cortical destruction.

Although the bone width versus width of the metastases greatly varied in the peritrochanteric region, an intramedullary width of the lesion of 30 mm or more has a predictive value. According to the findings by Menck et al.[6] the relative width of the metastases (W/B) has a predictive value for bone fracture (0.9 or more: Table 3). Many authors mention (increasing) pain as a sign of impending fracture and as a criterion for prophylactic surgery (Table 3).[1,2,5,7,13,17] Pre-fracture pain is reported to occur in 11%-84% and it seems to be a questionable criterion for prophylactic surgery.[6,11,19] According to our results, pain at first presentation occurred in a very large time window prior to fracturing. Also, no differences were found between impending and actual fractures. No pain was observed in 11 patients (18%). Therefore, in this series, pain at onset prior to fracture was not considered a predictive sign. However, if increasing pain was recorded, an actual fracture followed within two months in 5 of the 6 cases. We regard increasing local pain as an indication for a lesion at risk.

The indications for prophylactic fixation of impending fractures in the long bones have not been defined clearly, and the available information comes from retrospective studies. Prospective studies should be performed but are unfeasible since there too few patients. This suggests a role for in *vitro* experiments.

The risk of pathological fractures is a constant concern in the management of metastatic disease in long bones. To prevent an actual pathological fracture, an aggressive approach to impending fractures is imperative. The high-risk criteria of impending fractures in metastatic bone lesions still have to be defined.

## References

1 Beals RK, Lawton GD, Snell WE. Prophylactic internal fixation of the femur in metastatic breast cancer. Cancer 1971; 28: 1350-1354.

2 Habermann ET, Sachs R, Stern RE, Kirsch DM, Anderson WG. The pathology and treatment of metastatic disease to the femur. Clin Orthop Rel Res 1982; 169: 70-82.

3 Albright JA, Gillspie TE, Butaud TR. Treatment of bone metastases. Semin Oncol 1980; 7: 418-434.

4 Malawer M, Delaney TF. Treatment of metastatic cancer of the bone. In: Devita VTJ (ed): Cancer: Principles and practices of Oncology. Lippincott, New York, 2298-2315.

5 Zickel RE, Mouradian WH. Intramedullary fixation of pathological fractures and lesions of the subtrochanteric region of the femur. J Bone J Surg 1976; 58(Am): 1061-1066.

6 Menck H, Schulze S, Larsen E. Metastasis size in pathologic femoral fractures. Acta Orthop Scand 1988; 59 : 151-154.

7 Yazawa Y, Frassica FJ, Chao EYS, Pritchard DJ, Sim FH, Shives TC. Metastatic bone disease. Clin Orthop Rel Res 1990; 251: 213-219.

8 Dijkstra PDS, Wiggers T,Geel AN van, Boxma H. Treatment of impending and actual pathological fractures in patients with bone metastases of the long bones. Eur J Surg 1994; 160: 535-542.

9 Harrington KD. New trends in the management of the lower extremity metastases. Clin Orthop Rel Res 1982; 169: 53-61.

10 Fidler M. Prophylactic internal fixation of secondary neoplastic deposits in long bones. B M J 1973; 1: 341-343.

11 Keene JS, Sellinger DS, McBeath AA, Engber WD. Metastatic breast cancer in the femur. Clin Orthop Rel Res 1986; 203: 282-288.

12 Hipp JA, McBroom RJ, Cheal EJ, Hayes WC. Structural consequences of endosteal metastatic lesions in long bones. J Orthop Res 1989; 7: 828-837.

13 Mirels H. Metastatic disease in long bones: a proposed scoring system for diagnosing impending pathologic fractures. Clin Orthop Rel Res 1989; 14: 513-525.

14 Cheal EJ, Hipp JA, Hayes WC. Evaluation of finite element analysis for prediction of the strength reduction due to metastatic lesions in the femoral neck. J Biomech 1993; 26: 251-264.

15 Bunting R, Lamont-Havers W, Schweon D, Kliman A. Pathologic fracture risk in rehabilitation of patients with bony metastases. Clin Orthop Rel Res 1985; 192: 222-227.

16 Griesmann H, Schüttemeyer, W. Weitere Erfahrungen mit der Marknagelung nach Küntscher an der Chirurgischen Universitätsklinik Kiel. Chirurg 1947; 17-18: 316-333.

17 Parrish FF, Murray JA. Surgical treatment for secondary neoplastic fractures. A retrospective study of ninety-six patients. J Bone Joint Surg 1970; 52 (Am): 665-686.

18 Miller F, Whitehill R. Carcinoma of the breast metastatic to the skeleton. Clin Ortop Rel Res 1984; 184: 121-127.

19 Fidler M. Incidence of fracture through metastases in long bones. Acta Orthop Scand 1981; 52: 623-627

20 Bremner RA, Jelliffe AM. The management of pathological fracture of the major long bones from metastatic cancer. J Bone Joint Surg 1958; 40(Br): 652-658

21 Frankel VH, Burstein AH. Load capacity of tubular bone. In: Kenedi RM (ed) Biomechanics and related Bio-Engineering Topics. Pergamonn Press, Oxford; pp 381-396

22 Clark CR, Morgan C, Sonstegard DA, Matthews LS. The effect of biopsy hole shape and size on bone strenght. J Bone Joint Surg 1977; 59 (Am): 213-217

23 McBroom RJ, Cheal EJ, and Hayes WC. Strength reductions from metastatic cortical defects in long bones. J Orthop Res. 1988; 6: 369-378.

# Chapter 5

# Torsional strength reduction by cortical defects: in vitro experiments on human femora

PDS Dijkstra[1], M ten Have[2], CJ Snijders[3], and T Wiggers[4]

Department of Orthopaedic Surgery, Westeinde Hospital[1], Den Haag, Laboratory for Engineering Mechanics[2], Delft University of Technology, Delft, Department of Biomedical Physics and Technology[3], Erasmus University, Rotterdam, Departement of Surgical Oncology, Daniel den Hoed Cancer Center[4], Rotterdam, The Netherlands

*Submitted*

## Introduction

The most common bone tumour is of metastatic origin. The incidence increases due to prolonged survival as a result of more effective treatment of visceral metastases.[1] In three-quarters of the patients the primary tumour was breast, bronchus, prostate or kidney carcinoma.[2-4] About 10% of patients with disseminated breast cancer develop a pathologic fracture of the proximal femur.[5] The incidence of skeletal metastases to the femur are high (30-50%).[2,6] One third of the impending and actual femoral fractures are in the subtrochanteric region.[3,7,8]

These pathologic fractures can highly influence the quality of life. Prophylactic fixation of impending fractures is generally preferred instead of treatment of actual fractures. Quick relief of pain, earlier mobility, decreased hospital stay and reduction of operative complications are reported as important advantages.[4,9,10] As a result, prophylactic fixation is increasingly performed. There are three mainly accepted methods in assessing femoral fracture risk [3,4,6-10,12-15]: (1) a lytic lesion 25 mm or larger, (2) lytic circumferential cortical destruction of 50% or more, (3) persistent pain with weight-bearing, despite radiotherapy. At present, these criteria pervade clinical practice. However, several authors have concluded that pain is not a reliable sign and that one half of the standard radiographs are not evaluable.[8,12,14,16-18] It is also questionable if these criteria can be based on small retrospective clinical studies and primary tumours of different origins. The variable effects of the different sizes, sites of the lesions and degree of osteoporosis are not adequately taken into account.[7,12,17,19,20] Therefore, there is a need for more objective criteria to asses fracture risk.[7,17,21,22]

In this specific patient group, with often bedridden patients, a pathological fracture can occur spontaneously or after a minor trauma [4,21]. We expect that in the daily life of these compromised patients the axial loading of the femur is less significant than torsion loading. According to Burke et al. who measured micromotion of stems of cemented femoral components in the femoral shaft there is more than five times increase of torsional micromotion during stair climbing in comparison to single limb stance.[23] Data from studies using hip protheses show that some of the highest hip contact forces and joint reaction forces occur when climbing stairs or getting out of a chair.[24,25] Furthermore, torsional loading is stated as an optimal testing modality for a satisfactory strength analysis of bone.[26]

Little is known about the influence of cortical defects on strength reduction in human femora in torsional loading, especially in cases of defects larger than a bone diameter. Investigations of the effects on strength reduction due to cortical lesions are imperfect because of material (embalmed bone, plastic), form (tube, length), side (tibia, fibula) and species (dog, sheep, canine) of the specimens and the little variety in length size of the lesions used in these experiments.[27-35] In an experimental study Frankel et al. described up to 70% torsional strength reduction after a solitary incision of one fifth of the length of the embalmed tibial bone.[30] They later suggested that in cortical defects smaller than the outer bone diameter this reduction be probably due to a stress riser effect. In larger defects an open section effect occurred.[36,37] These different types of defects have also been described in engineering literature. A stress riser, a small size defect or irregularity surface, in a tube under a torsional load resulted in an increase in local stress concentration. In an open section a dramatic weaking under a torsional load in a large longitudinal defect occurred.[38,39] So, axial loading is of minor importance in the research of strength reduction in cortical defects in the long bones when compared to torsional loading.

The foregoing shows that knowledge on the effect of torsional loading is restricted, both with respect to the size of cortical defects as well as the location in the clinically relevant subtrochanteric region. Therefore, the aim of this study was further to investigate the geometry effect of cortical defects on torsional strength reduction in the subtrochanteric region of human femora.

## Materials and methods

Paired femora were collected from 15 fresh human cadavers and in a sealed bag stored at - 30°C. A period of four hours at a room temperature of 21C° was taken before testing. Throughout the experimental procedures the bones were kept moist with NaCl 0.9% fluid at a room temperature of 21°C. In experiment A 14 femora came from 4 female donors and 10 male donors, ranging in age from 48 to 97 years (median=77 years )(Table 1). Bone samples were excluded from the experiment if local alterations in bone architecture that could affect its mechanical properties, like Paget disease, bone metastasis and old fractures, could be detected. For a carefully screening standard antero-posterior and lateral radiographs of the bone were taken. The proximal and distal ends of each bone were embedded in aluminium molds filled with acrylate (2012 AB Araldite, Ciba, Swiss) at a distance of one bone diameter below the greater trochanter and two bone diameters above the condyle, respectively (Figure 1). For better fixation the head of the femur was removed, and eight screws were used at both molds. Selected at random, one bone of each pair contained the defect (9 right and 5 left femora) while the contralateral bone was left intact, and served as a control.

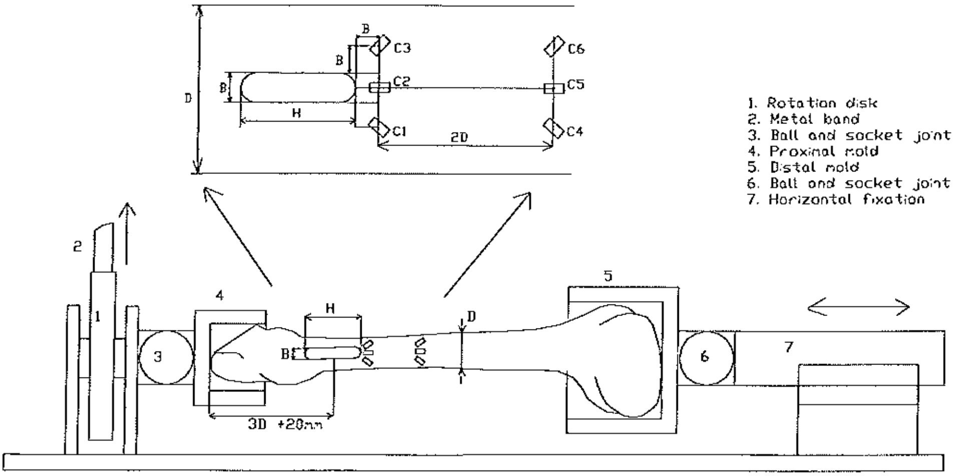


*Figure 1. The test equipment for torsional loading experiments with fresh frozen human femora. Both ends of the femur were 80mm potted in acrylate. The torsion axis was in the middle at the end of both molds. All defects were transcortical and elongated at the medial line with the center of the defect 3D+20mm from the trochanter major top. The torsional loading was in all specimens in respect to exorotation of the femur. The three proximal strain gauges were positioned at a distance equal to width (W), and the three distal strain gauges were found at W+2D adjacent to the defect.*

*Table 1. Description and results of the paired human femora on torsional loading in experiment A. * At the defect site the fracture line was initially* $90^0$.

| No. | Sex | Age | Site of lesion | Ratio: height defect / bone diameter | Moment of failure (Nm) | Deformation angle at failure (deg) | Energy (J) | Rigidity (Nm$^2$) | Fracture angle (deg ) | Fracture location |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | ♂ | 50 | right | 0.5 | 190.8 | 18.6 | 35.4 | 223.6 | 30 | distal |
| | | | | control | 193.2 | 26.7 | 55.8 | 211.8 | 36 | distal |
| 2 | ♂ | 48 | right | 0.5 | 145.9 | 20.1 | 25 | 158.5 | 45 | defect |
| | | | | control | 219.4 | 29.2 | 61.8 | 238.6 | 35 | proximal |
| 3 | ♂ | 97 | right | 0.5 | 179.1 | 17.8 | 29.1 | 258.1 | 46 | proximal |
| | | | | control | 195.2 | 28.1 | 47.8 | 210 | 39 | distal |
| 4 | ♂ | 73 | right | 1 | 64.5 | 11.7 | 6.6 | 115.8 | 38 | defect |
| | | | | control | 159.5 | 45.3 | 73.4 | 112.3 | 39 | proximal |
| 5 | ♂ | 62 | right | 1 | 96.2 | 14.9 | 11.9 | 141.3 | 30 | defect |
| | | | | control | 104.4 | 17.4 | 14.9 | 141.6 | 36 | proximal |
| 6 | ♂ | 78 | left | 1 | 128.7 | 17.8 | 17.7 | 172.4 | 45 | defect |
| | | | | control | 136 | 17.2 | 17.8 | 177.8 | 28 | distal |
| 7 | ♀ | 80 | left | 1 | 149.8 | 20.6 | 26.2 | 147.8 | 37 | defect |
| | | | | control | 145.2 | 17.8 | 24 | 152.2 | 37 | distal |
| 8 | ♀ | 76 | left | 1.5 | 92.1 | 13.2 | 11.6 | 147.4 | 32 | distal |
| | | | | control | 72.1 | 16 | 10.6 | 92.3 | 30 | distal |
| 9 | ♂ | 88 | left | 1.5 | 122.3 | 17.2 | 18.1 | 157.7 | 42 | defect |
| | | | | control | 166.8 | 33.1 | 58.4 | 162.4 | 45 | proximal |
| 10 | ♂ | 61 | right | 1.5 | 125.2 | 14.9 | 16 | 159 | 45 | defect |
| | | | | control | 185.9 | 20.6 | 34.7 | 191.6 | 38 | middle |
| 11 | ♂ | 78 | right | 1.5 | 66.3 | 14.3 | 7.5 | 79.1 | 36* | defect |
| | | | | control | 110.6 | 19.5 | 19.3 | 125.2 | 37 | distal |
| 12 | ♀ | 87 | right | 2 | 46.1 | 7.4 | 3 | 123.8 | 34* | defect |
| | | | | control | 92.3 | 13.9 | 11.7 | 129 | 31 | distal |
| 13 | ♂ | 84 | left | 2 | 106.7 | 18.4 | 18.1 | 116.2 | 30* | defect |
| | | | | control | 159.5 | 35.8 | 62.2 | 127.9 | 35 | distal |
| 14 | ♀ | 53 | right | 2 | 46.3 | 8.6 | 3.1 | 96.3 | 36* | defect |
| | | | | control | 152.5 | 29.2 | 35.5 | 99.7 | 35 | middle |

Bone defects were introduced to simulate metastatic defects. The center of all defects was positioned at the medial line and 3 bone diameters with 20 mm below the top of the greater trochanter (Figure 1). These extramedullary oblong holes with rounded ends were penetrating the entire cortex and were drilled in different heights (*d*). The ratio defect height divided by the mediolateral outer bone diameter (*D*; at the center of the defect) was performed in four categories *(d/D)*: 0.5, 1, 1.5 and 2. The width of the defect was 0.25 times the bone diameter (median 8 mm). Each defect was achieved by extramedullary drilling with progressively larger drill bits at 800 rpm to avoid splintering at the edges of the defect.

Anteroposterior and lateral radiographs were made of the femora pairs to measure inner and outer bone diameter, the thickness of each cortex, and the sizes of the cortical defect. Identical radiographic projection of all specimens were assurred. A magnification ratio of 1.05 was estimated, so no measurement correction was done. Computed Tomography scans (Siemens type Somaton 4 Plus; 140KeV; pixel size; 0.59 mm; 512 ×512 matrix) were made with slices thickness of 2 mm over the proximal femoral region. At the shaft 20 mm slices were made. This results in a median of 72 slices ( range: 68 to 86) over the length of the femora. The CT scan data were linearly calibrated in terms of apparent density of the calibration phantoms using a formula for conversion to physical density (Appendix A).

After cleaning the sites with dry sand paper and ethylmetanchloride, a single component cyanoacrylate (CC-33A, Kyowa, Japan) was used as an adhesive to attach strain gauges (KFG-5-120-C1-11-L1-M2R, Kyowa, Japan) to the femur at six standardized locations (Figure 1). The strain gauge profile is as follows: gage length 5mm, grid 1.4 mm, gage factor 2.1 and resistance 120 Ohm. The strain gauges of the contralateral femur were used as dummies, and were in a half bridge circuit connected with a strain amplifier (KWS 3073 TF-mess, Germany). Silicone coating (M coating, M&M, Japan) was used to protect the strain gauges. Linear regression was used to correlate with those of the measured principal strains with the magnitudes of the predicted principal strains that were at approximately $45^0$ to the longitudinal axis of the shaft.

Based on the observation of fracturing at proximal, middle and distal part of the femora in both groups in experiment A, an additional experiment was performed. So, the possible influence of maximal stress concentration at different sites of the femora cloud be reduced. In 6 of the 14 femora pairs used in experiment A, a large intact part of the shaft to the condyle remained after fracturing, and were used again in experiment B. One additional intact femur pair was obtained (no. 15: Table 2). The preparation of the specimens was similar to experiment A exception for: the femur pairs used in experiment A were cut to the same size, the center of the defect was positioned at the medial line and in the middle between proximal and distal fixation following a procedure described above, and no strain gauges were used. The created defect never involved the segment of one outer bone diameter, measured medio-lateral in the middle, adjacent to the molds.

In experiment A and B each femur was loaded to failure in torsion using a Zwick 1484 (Munich, Germany) computed-controlled electrohydraulic material testing machine. A torsion load was applied to the proximal mold. The distal end had a rigid fixation except axial translation.

*Table 2. Description and results of the specimen on torsional loading in experiment B.* At the defect site the fracture line was initially* $90^0$.

| No. | Sex | Age | Site of lesion | Ratio: height defect / bone diameter | Moment of failure (Nm) | Deformation angle at failure (deg) | Energy (J) | Rigidity (Nm$^2$) | Fracture angle ($^0$) | Fracture location |
|---|---|---|---|---|---|---|---|---|---|---|
| **15** | ♀ | 69 | left | 0.5 | 97.8 | 13.2 | 12.1 | 48.5 | 34 | defect |
| | | | | control | 72 | 23.5 | 14.9 | 14.8 | 36 | middle |
| 1 | ♂ | 50 | right | 0.5 | 171.8 | 14.4 | 18 | 79.4 | 38 | defect |
| | | | | control | 209.4 | 20.7 | 37.2 | 66.2 | 36 | middle |
| 4 | ♂ | 73 | right | 1 | 83.5 | 11.5 | 7.7 | 95.8 | 30 | defect |
| | | | | control | 160.8 | 33.2 | 47.8 | 64.2 | 34 | middle |
| 5 | ♂ | 62 | right | 1 | 54 | 8.6 | 3.9 | 80.1 | 30 | defect |
| | | | | control | 135.6 | 13.2 | 13.5 | 130.9 | 32 | middle |
| 8 | ♀ | 76 | left | 1.5 | 91.6 | 10.8 | 8.9 | 71 | 28 | defect |
| | | | | control | 115.6 | 20.5 | 27.8 | 32.2 | 36 | middle |
| 9 | ♂ | 88 | left | 1.5 | 38.8 | 12.9 | 2.7 | 45.7 | 30 | defect |
| | | | | control | 165.6 | 29.8 | 39 | 64.7 | 33 | middle |
| 3 | ♂ | 97 | right | 1.5 | 85.9 | 1.22 | 7.5 | 293.1 | 30* | defect |
| | | | | control | 253.7 | 2.33 | 73.9 | 85.9 | 38 | middle |

All specimens were tested on torsion to failure at a rate of $5^0$ per second and without axial loading.[40] The results of loading versus angular displacement were plotted, while the energy absorption to failure and initial bone stiffness were calculated. To correct for the deformation angle at failure of the testing device the ultimate deformation angle for each femur was subtracted by $\rho_{\text{correction factor}}$, $\rho_{cf}=-0.00122$ * *moment of torque*, based on experiments with a rigid steel rod in the same loading conditions as described. The torsional rigidity of bone is the torque divided by the angle of deformation per unit length of bone, and refers to the initial slope of the force to displacement curve of each bone at its initial linear phase prior to the occurrence of plastic deformation.

The results were statistically analyzed using rank correlation the Spearman and Kruskal-Wallis both corrected for ties, and Fischer exact test for one case in different groups.

## Results

In this study, all of the failures in the defect group, three with twice a ratio *d/D* 0.5 and one 1.5, appeared to have a spiral fracture through the defect, as expected. Two of the femora fractured distally. One, with ratio *d/D* 0.5, the fracture was close to the defect (Figure 2). In the control group in 4 specimen the fractures occurred in the proximal part of the femur, while in the remaining specimen this was observed more distally (Table 1). The results in experiment A are shown in Table 1 and regard torque at failure, deformation angle at failure, calculated energy, and rigidity. In the control group the median torque at failure, deformation angle at failure, and energy were 156 Nm, $23.7^0$ and 35.1 J, respectively. The values for each biomechanical parameter in the defect group were expressed as a ratio of these parameters in the control group. For the strength reduction, there was very little change apparent in the range of ratio 0.5 and 1 defects (Figure 3). A gradual decline in strength occurred, 0.7 to 0.5, for defects from ratio 1.5 and 2. A small height defect with a ratio less or equal to one of the outer diameter had a strength reduction of less than one-quarter, while a larger defect had more strength reduction ($P < 0.05$). No significant rank correlation was found between the ratio of defect height and strength reduction, deformation angle at failure and energy. However, because the fracture sites in the control group were different, and so the location of the maximal stress at the bone was not just in the subtrochanteric region, we found a significant rank correlation between strength reduction and the ratio *d/D* when the group with a proximal fracture was left out ($R = -0.71$; $P < 0.05$). For the ratio of ultimate energy and angle of torque an increase was found of the ratio of defect

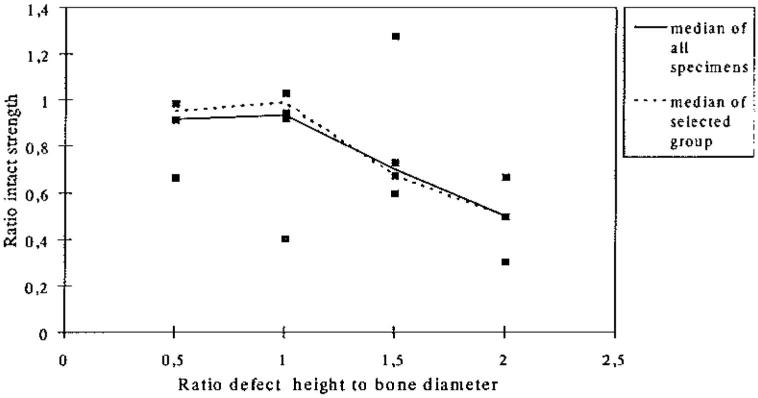


*Figure 3. Ratio intact strength versus ratio defect height to bone diameter. The plotted line describes the median values in experiment A of all tests and those with a proximal fracture in the control group were dotted printed and left out.*

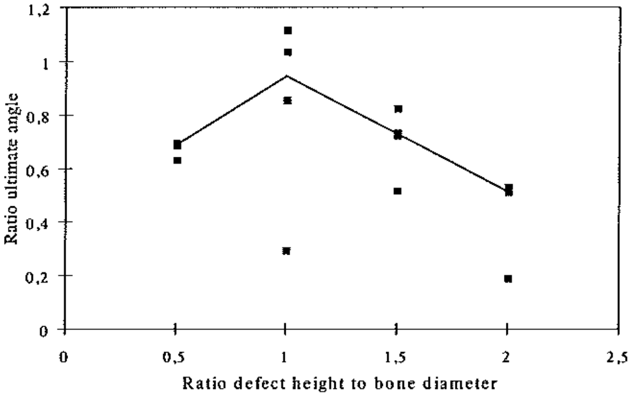


*Figure 4. Ratio ultimate deformation angle at failure versus ratio defect height to bone diameter. The line shows the median data.*

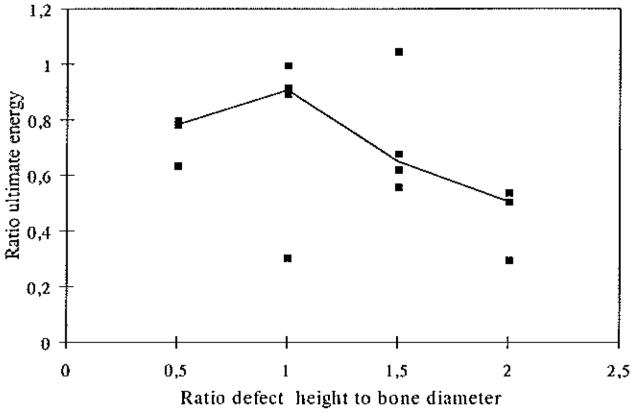


*Figure 5. Ratio ultimate energy versus ratio defect height to bone diameter. The line represents median data.*

height to outer bone diameter from 0.5 to 1, followed by a gradual decline of strength reduction to eventually 0.5 for a defect ratio 2 (Figure 4 and 5). There was no change in rigidity between the intact bones and those with a defect of any height, the median are 131.6 $Nm^2$ and 133.6 $Nm^2$, respectively.

The location of the maximum local stress point was strongly influenced by the defect height, depending on the helix angle at the initial fracture site to the neutral bone axis. For the smallest height defect the median angle of the helix remained $45^0$. At a ratio *d/D* of 2 and, in one case 1.5, the initial fracture median angle at the defect site changed cardinal, in the first part $90^0$ and shifting abruptly to 34 $^0$ (Figure 6). An insignificant rank-correlation was estimated between ratio *d/D* and the fracture angle ($R$=-0.35).

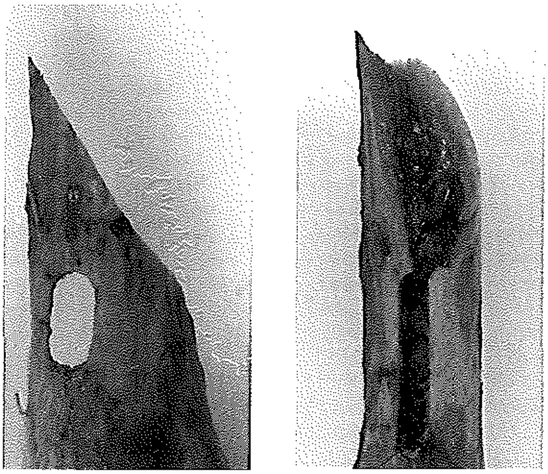


*Figure 2. At the left site, in this specimen with a ratio d/D 0.5 the fracture line was close to but not through the defect. In a specimen with a ratio d/D 2 the initial fracture angle at the defect site changed in the first part to 90 $^0$ and shifting abruptly to 34 $^0$,this is shown at the right site.*

The obtained strain measurements in experiment A are shown in appendix B. Because the helix angle could differ, the strain data is given of the strain gauge (C) value at the site of the defect divided by the value at the intact part of the shaft, printed as a ratio C3/C6 and C1/C4 (Figure 6 and 7). The median strain ratio's of C3/C6 and C1/C4 in the control measurements of the intact bone stayed 0.89 and 0.93, respectively. The increment of reduction of ratio between control and defect group of 3 times occurred from ratio *d/D* 0.5 to 2 ($P$<0.01). There was a

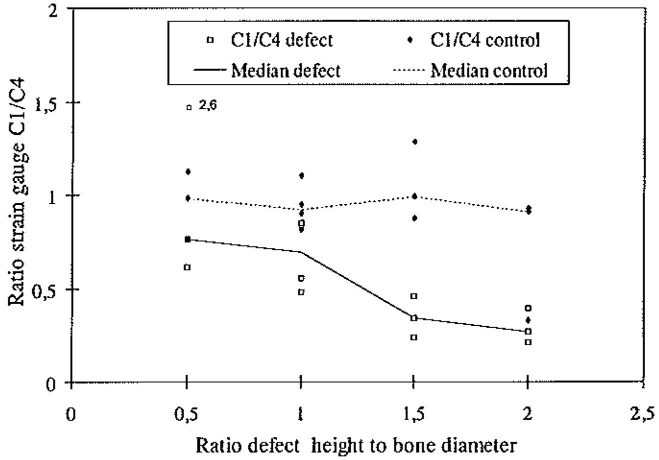


*Figure 6. The ratio strain versus ratio defect height to bone diameter of C 1/ 4 in the defect and control group.*

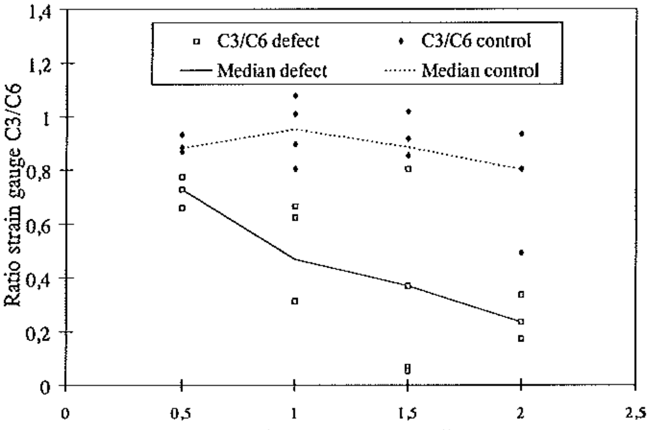


*Figure 7. The ratio strain versus ratio defect height to bone diamter for gauges C 3/6 for the defect and control group.*

correlation between the defect height and the increasing reduction in both ratio's C3/C6 ($P<0.02$, $R=-0.58$) and C1/C4 ($P<0.01$, $R=-0.84$).

The bone mineral density (BMD) values ranged from 1.75 to 1.92, with a median of 1.85. The association between gender and age on one hand and BMD on the other was not significant. A difference for the values of BMD concerning the region of the femur was estimated ($P<0.005$). The lowest BMD value was found at the proximal side of the femur (median 1.83) followed by the distal side (median 1.85), and the highest BMD value at middle part of the femur (median 1.86). The relation torque at failure versus bone mineral density was significant for the proximal region of the femur in the control group ($P<0.01$, $R=0.49$)(Figure 8), this was in contrast to the outcome of the middle and distal region ($P=0.3$ and $P=0.7$, respectively).

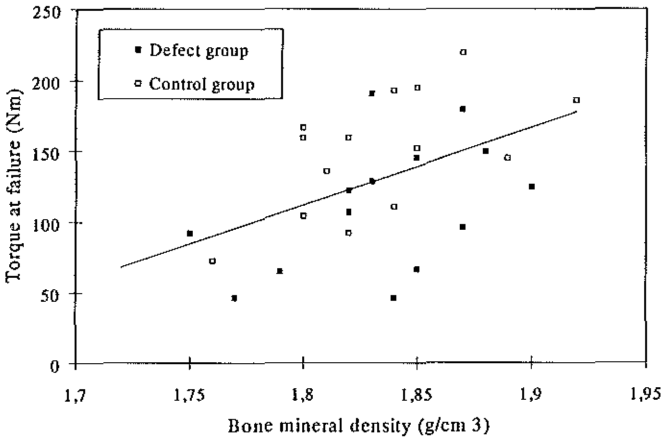


*Figure 8. Moment of torque versus bone mineral density. The plotted linear regression line presented the significant relation between moment of torque versus BMD ($P<0.01$, $R=0.49$).*

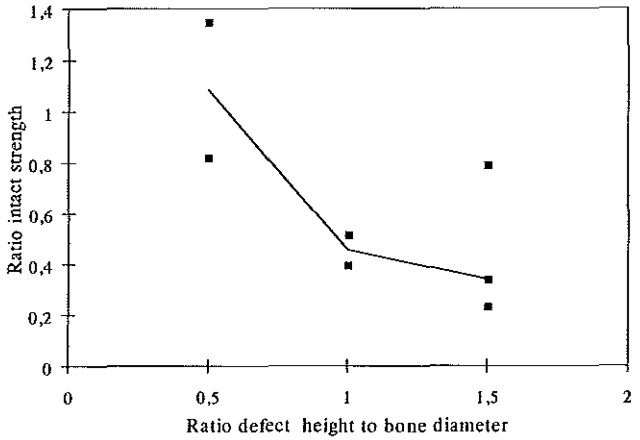


*Figure 9. Ratio intact strength versus ratio defect height to bone diameter in experiment B. Plotted line represented the median data.*

Neither a correlation occurred for cross-sectional area, estimated by computed tomography, versus moment of torque and strength reduction in the control and defect group, nor predicted the site of fracturing. The results of the one-third to two-third shortened paired femora in experiment B are shown in Table 2. All fractures in the control group were in the middle, and in the defect group at the lesion. In this shortened specimen (n=7) a significant ($P<0.05$) rank-correlation between ratio $d/D$ and strength reduction was found ($R=0.76$)(Figure 9).

## Discussion

In literature a few studies have utilized torsion for evaluating cortical defects, and no study has assessed the weakening of a range of longitudinal cortical defects in fresh frozen human femora under torsional loading. In mechanical testing of bone, varieties in specimen and storage have an important influence on the outcome of biomechanical properties. Freezing at -30°C is a method of preservation which affects the mechanical properties of bone less than 5%.[41-44]

*Table 3. Mean and standard deviation (parentheses) in experiment A of the control group compared to the results in literature*

| Reference | Number of specimen | Sex F:M | Age | Torque at failure (Nm) | Deformation angle at failure (Deg) | Energy (J) | Rigidity ($Nm^2$) |
|---|---|---|---|---|---|---|---|
| Mensch | 35 | 1.2:1 | 58.5 (14.1) | 134.9 (45.2) | 13.4 (7) | 17.3 (12.9) | - |
| Martens | 46 | 1:2.5 | 58 (13.3) | 183 (54) | 20 (4.5) | 35 (14) | 192 (62) |
| This study | 15 | 1:4.3 | 72.5 (15.3) | 149.5 (42.7) | 25.1 (9.4) | 37.7 (21.8) | 150.5 (47.5) |

In Table 3 our biomechanical parameters for human femora related to gender and age are shown. This data is inconsistent to previous reports. A mean of 149.5 Nm with a range of 72.1 Nm to 219.4 Nm for the torque at failure was found for this control group. In 1876, when Rauber tested torsional strength in small samples of fresh human bone, he estimated a shearing strength of 79 Nm.[45] One century later, Hubbard tested twenty fresh cadaver femora at an unspecified loading rate and recorded an average torque at failure of 87.8 Nm (range 41.9 to 317.9), which is 59% of our results.[46] According to our study the findings in literature contained a high variability of sites of fracture of the control bone, torque at failure, deformation angle at failure of torque, absorbed energy and rigidity.[47-49] The influence of increasing age on the ultimate stress is low. Nevertheless, the strain is strongly reduced.[50] In contrast to our findings, Martens et al. and Mensch et al. showed higher values of deformation angle at failure and the energy in intact bone.[48-49] These differences in the outcome were due to a higher rate of torsional loading, younger age of specimen, a higher ratio male to female included and an error in the measurement of angular deflection. [47]

The range of variation in most mechanical properties seen between the control bones is very large.[51,52] In this study the difference in torque at failure was up to 38%, considering the twice tested control specimen (median 159.5 and 160.8, respectively). This intra-specimen variety is due to drying and re-wetting, difference of temperature of the site of bone, difference of hardening of the acrylate in the molds, the measurements of deformation angle of torque and the difference between dominant side and non-dominant side of bones.[47,48,53,54] According to literature, torsional loading of intact long bones had shown that the bone length had no significant effect of strength reduction on the torsional loading.[55] The differences produced by drying and re-wetting are small, in bending 5% and in torsional loading 20%, and in comparison with the various types of differences it could be ignored in case of compact bone.[41,56] Although no difference in strength between bones taken from left or right side of the body is found, we randomly used the left or right side as a control subject to eliminate this effect.[48,53,54]

In literature, much confusion exists about the interpretation of the results in experiments where no torsional loading in single-cortex defects was performed. For instance the four point bending loading experiments by McBroom et al., and Hipp et al., and axial forces by Cheal et al.[16,17,57] Caution should be made to compare the results of these different loading experiments. Furthermore, our study considered single cycle failures. In daily life most bones will be subject to repetitive, variable loads. Although each type of loading may be below the ultimate strength of bone, loads of different directions can be cumulative, sufficient to cause microfractures, and other manifestations of fatigue.[58-60]

The effect of torsional loading of a long bone with a cortical defect was first described by Frankel and Burstein.[30] A single saw cut one-fifth of the length of embalmed tibiae decreased the maximal 70% energy absorption of in the twelve pairs tested. Increasing the width of these saw cuts to one-half and full bone diameter did not cause further weakening. In close agreement with this study, we found a variation in strength reduction between the paired bones with similar defects of up to 60%. Frankel et al. claimed to have found 'open section' defect. Unfortunately, the transformation zone from 'stress riser' to this 'open section' was not studied. In contrast, Brooks et al. found that the energy absorption reduction in twenty paired femora of dogs with small cortical holes of 2.8 or 3.6 mm in lateral to medial direction was 55%, with no significant effect of the ratio *d/D*.[27] Furthermore, Burchardt et al. suggested that there is a critical size of a cortical defect below which no significant stress concentration occurs, based on the observations of no torsional strength reduction by six small holes in canine fibulae.[29] Clark et al. found that oblong holes withstand more torque than rectangular holes with square corners.[31] They also studied in thirty-six embalmed human femora the effect of a lateral single-cortex defect with variable width and length on torsional loading. They concluded that the variation of the hole width produces greater strength reduction than variations of length. This result is questionable because embalmed femora cannot be used in torsional strength tests in a non paired order. DeSouza et al. investigated the strength reduction of a rectangular cortical defect in paired bones subjected to torsional loading.[32] They concluded that stress reduction was dependent on both length and width of the defect. The influence of open section effect by posteriorly located circular single-cortex defects in fresh frozen paired sheep femora was investigated by Edgerton et al.[33] The defect ratio *d/D* ranged from 0.1 - 0.6; less than 0.1 the torsional strength reduction was insignificant, beyond 0.1 this reduction highly increased, and above 0.2 this was followed by a linear reduction with the diameter of the defect. Since the engineering literature and the data of Frankel and Burstein indicate that the open section effect occurred in relation to a longitudinal increase of the defect in torsional loading, the open section defect cannot be studied with a symmetrical increase of length and width, as in circular defects.[37] A ratio *d/D* of less than three-quarter may be a stress riser area and not an open section region. Kuo et al reported that varying transverse circular defects in an acrylatic tubular structure, with a range of the ratio *d/D* 0.1-0.6, resulted in a torsional strength reduction inversely proportional to defect size.[34] The influence of anisotropy, heterogeneity, and transverse geometric irregularities on torsional loading response seems to be important. Using such data in practice is questionable, considering the nonlinear anisotropic properties of cortical bone. [48,55,61]

The stress concentration factor as a local parameter at the defect, first described by Okubo and Sato, consisted of the stress region around a transverse hole of a shaft subjected to torsional loading.[62] Jessop et al. used a photo elastic frozen stress technique to study the stress concentration factor of a circular defect penetrating both walls in a hollow cylinder made of hot setting resin.[38] The results were expressed in terms of ratio: diameter defect to diameter outer tube (*d/D*). The point of maximum stress was found at the bore of the hole beneath the outer surface of the tube. Another local effect was described by Kuo et al., they measured the shift angle associated with each defect ratio, 0.1-0.4, the angle remained at $45^0$, from 0.5-0.6 a smaller angle occurred.[34] In our study the fracture angle (median value) declined in relation to increasing the ratio *d/D* (Table 1,2), but not significantly. Because in a non cylindrical anisotrop solid, as in bone, less energy is required for fracturing in longitudinal than in transversal direction.[28,63] In both experiments at ratio *d/D* 1.5 and 2 in some specimen a fracture angle of $90^0$ occurred, probably due to a sudden large change in a stress pattern around the defect that could be a sign of an open section effect. It has been shown by Behiri and Bonfield that the fracture characteristics of bone depend on the velocity of the propagating crack and in particular, which below a certain critical velocity fracture becomes more dependent on the bone microstructure.[28,63] The effect of osteoporosis to fracture risk prediction is particularly seen in studies concerning the trabecular bone of femora. Change in bone mineral density of the cortical part of the femoral shaft in relation to strength is not well documented.[64,65] The prevailing notion in the literature is that the strength of the proximal shaft of the femur is primarily dependent on cortical bone.[66-68] However, the effects of menopause and age in this cortex may be less dramatic than those on the femoral neck and the vertebrae.[69] Equal to the results of Sakkers et al. the bone mineral density in our study did not significantly correlate with gender and age.[70] The moderate correlation between the values of torque at failure and bone mineral density at the proximal region is interesting, but is probably due to the influences to quantitative computed tomography of the fat containing medullary content and disappeared tissue around the femur, the differences of cross-sectional area and geometry at the region of the femur (see further appendix A).[71] The condition of the trabecular bone next to the defect may be an important factor in predicting the risk to fracture.[19] However, no literature is available about the influence of cortical bone density changes in human femora on mechanical properties. In torsional loading this could be a relevant fracture risk predictor.

The clinical relevance of our study is found in the identification of a solid criterion for prophylactic surgery in patients with a cortical defect of the long bone. In experiment A, a gradual decline in strength reduction occurred up to 50% at ratio defect height to bone diameter of 2, shifting in experiment B to 64% strength reduction at a ratio defect of size 1. This shift is mainly due to different energy absorption at different bone locations.[47,50] There are just a few studies known providing guidelines on when prophylactic fixation should be employed. Fidler is frequently quoted for stating that the lesion is at risk to fracture when the cortical destruction exceeds 50% of the circumferention.[15] He also reported that a well-defined lesion with a size equal or larger than 25 millimeters should be prophylactic operated. This critical defect size (≥ 25 mm in width or height) was earlier found by Beals et al.[6] Considering the ratio of defect *d/D*, as mentioned above, and a patient population with a mean maximal outer bone diameter of the proximal femoral human shaft of 30 mm, the result will be 0.8.[8,18] This study confirms the clinical results reported by Menck et al. and Dijkstra et al. They found that a lesion at risk to fracture occurred as the ratio defect height to an outer bone diameter is equal to or exceeds 1 and 1.2, respectively.[8,18]

The results of this study showed in relation to the mechanical properties not only the existence of a stress-riser but also of an open-section effect, although the measured strength reductions were less dramatic than those described in engineering literature.[72] The influence of bone mineral density to the torsional strength reduction of bone is low, except the proximal side.

In conclusion, we believe that a transcortical defect with a ratio height lesion to an outer diameter of the long bone exceeds one, prophylactic surgery should be employed.

## References

1 Albright JA, Gillspie TE, Butaud TR. Treatment of bone metastases. Semin Oncol 1980; 7: 418-434.

2 Habermann ET, Sachs R, Stern RE, Kirsch DM, Anderson WG. The pathology and treatment of metastatic disease to the femur. Clin Orthop Rel Res 1982; 169: 70-82.

3 Yazawa Y, Frassica FJ, Chao EYS, Pritchard DJ, Sim FH, Shives TC. Metastatic bone disease. Clin Orthop Rel Res 1990; 251: 213-219.

4 Dijkstra PDS, Wiggers T, van Geel AN, Boxma H. Treatment of impending and actual pathological fractures in patients with bone metastases of the long bones. Eur J Surg 1994; 160: 535-542.

5 Malawer M, Delaney TF. Treatment of metastatic cancer of the bone. In: Devita VTJ (ed): Cancer: Principles and practices of Oncology. Lippincott, New York, 2298-2315.

6 Beals RK, Lawton GD, Snell WE. Prophylactic internal fixation of the femur in metastatic breast cancer. Cancer 1971; 28: 1350-1354.

7 Zickel RE, Mouradian WH. Intramedullary fixation of pathological fractures and lesions of the subtrochanteric region of the femur. J Bone Jt Surg 1976; 58 (Br): 1061-1066.

8 Menck H, Schulze S, Larsen E. Metastasis size in pathologic femoral fractures. Acta Orthop Scand 1988; 59 (2): 151-154.

9 Harrington KD. New trends in the management of the lower extremity metastases. Clin Ortop Rel Res 1982; 169: 53-61.

10 Fidler M. Prophylactic internal fixation of secondary neoplastic deposits in long bones. Brit Med J 1973; 1: 341-343.

11 Francis KC. Prophylactic internal fixation of metastatic osseous lesions. Cancer 1960; 13:75-76.

12 Mirels H. Metastatic disease in long bones: a proposed scoring system for diagnosing impending pathologic fractures. Clin Orthop Rel Res 1989; 14: 513-525.

13 Parrish FF, Murray JA. Surgical treatment for secondary neoplastic fractures. A retrospective study of ninety-six patients. J Bone Joint Surg (Am) 1970; 52(4): 665-686.

14 Keene JS, Sellinger DS, McBeath AA, Engber WD. Metastatic breast cancer in the femur. Clin Orthop Rel Res 1986; 203: 282-288.

15 Fidler M. Incidence of fracture through metastases in long bones. Acta Orthop Scand 1981; 52: 623-627.

16 Cheal EJ, Hipp JA, Hayes WC. Evaluation of finite element analysis for prediction of the strength reduction due to metastatic lesions in the femoral neck. J Biomechanics 1993; 26: 251-264.

17 Hipp JA, McBroom RJ, Cheal EJ, Hayes WC. Structural consequences of endosteal

metastatic lesions in long bones. J Orthop Res 1989; 7: 828-837.

18 Dijkstra PDS, Oudkerk M, Wiggers T. Prediction of pathological subtrochanteric fractures due to metastatic lesions. Arch Orthop Trau Surg published in 1997 (chapter 4).

19 Hipp JA, Katz G, Hayes WC. Local demineralization as a model for bone strength reductions in lytic transcortical metastatic defects. Invest Radiol 1991; 26: 934-938.

20 Hipp JA, Rosenberg AE, Hayes WC. Mechanical properties of trabecular bone within and adjacent to osseous metastases. J Bone Mineral Res 1992; 7: 1165-1171.

21 Springfield D, Jennings C. Pathologic fractures. In: Rockwood CA and Green DP (ed): Fractures in Adults, Volume 1. Lippencott - Raven, New York. 1996. 513-519.

22 Bunting R, Lamont-Havers W, Schweon D, Kliman A. Pathologic fracture risk in rehabilitation of patients with bony metastases. Clin Orthop Rel Res 1985; 192: 222-227.

23 Burke DW, O'Conner DO, Zalenski EB, Jasty M, Harris WH. Micromotion of cemented and uncemented femoral components. J Bone Joint Surg (Br) 1991; 73: 33-37.

24 Hodge WA, Fijan RS, Carlson KL, Burgess RG, Harris WH, Mann RW. Contact pressores in the human hip joint measured in vivo. Proc Natl Acad Sci USA 1986; 83: 2879-83.

25 Davy DT, Kotzar GM, Brown RH, et al. Telemetric force measurements across the hip after total hip arthroplasty. J Bone Joint Surg (Am) 1988; 70-A: 45-50.

26 Burstein AH, Frankel VH. Technical note: a standard test for labarotory animal bone. J Biomech 1971; 4: 155-158.

27 Brooks DB, Burstein AH, Frankel VH. The biomechanics of torsion fractures: The stress concentration effect of a drill hole. J Bone Joint Surg 1970; 3 (Am): 507-514.

28 Bonfield W, Grynpas MD. Spiral fracture of cortical bone. J Biomechanics 1982; 15: 555-559.

29 Burchardt H, Busbee GA III, Enneking WF. Repair of experimental autologous grafts cortical bone. J Bone Joint Surg 1975; 57 (Am): 814-819.

30 Frankel VH, Burstein AH. Load capacity of tubular bone. In: Kenedi RM (ed): Biomechanics and related Bio-Engineering Topics. Pergamonn Press, Oxford 1965: pp 381-396.

31 Clark CR, Morgan C, Sonstegard DA, Matthews LS. The effect of biopsy hole shape and size on bone strenght. J Bone Joint Surg (Am) 1977; 59(2): 213-217.

32 DeSouza ML, An KN, Morrey BF, Chao EYS. Strenght reduction of rectangular cortical defects in diaphyseal bone. Trans Orthop Res Soc 1989; 14: 113.

33 Edgerton BC, An K, Morrey BF. Torsional strength reduction due to cortical defects in bone. J Orthopaedic Research 1990; 8: 851-855.

34 Kuo RF, Chao EYS, Rim K, Park JB. The effect of defect size on the stress concentration and frature characteristics for tubular torsional model with transverse hole. J Biomechanics 1991; 24: 147-155.

35 Hipp JA, Edgerton BC, An KN, Hayes. Structural consequences of transcortical holes in long bones loaded in torsion. J Biomechanics 1990; 12: 1261-1268.

36 Frankel VH, Nordin M. Basic biomechanics of the musculoskeletal system. 2th ed.

Philadelphia: Lea & Febiger , 1989:19 -23.

37 Frankel VH, Burstein AH. Orthopaedic biomechanics. Philadelphia, Lea & Febiger 1970.

38 Jessop HT, Snell J, Allison JM. The stress concentration factors in cylindrical tubes with transverse circular holes. Aeronaut Q 1959; 10: 326-344.

39 Peterson RE. Stress concentration factors. New York. John Wiley & Sons 1974.

40 Lacroix H, Arwert H, Snijders CJ, Fontijne WPJ. Prevention of fracture at the distal locking site of the gamma nail. J Bone Joint Surg (Br) 1995; 77: 274-276.

41 Pelker RR, Friedlander GE, Markham TC, Panjabi MM, Moen CJ. Effects of freezing and freeze-drying on the biomechanical properties of rat bone. J Orthop Res 1984; 1: 405-411.

42 Sedlin E. A rheological model for cortical bone. Acta Orthop Scand 1965; 36(suppl 83): 1-77.

43 Bright R, Burstein A. Material properties of preserved cortical bone. Trans Orthop Res Soc 1978; 3: 210-215 .

44 Stromberg L, Dalen N. The influence of freezing on the maximum torque capacity of long bones. Acta Orthop Scand 1976; 47: 254-256.

45 Rauber AA. Elasticitat un Festigkeit der Knochen. Englemann, Leipzig, 1876, pp7

46 Hubbard, MJS. The fixation of experimental femoral shaft torque fractures. Acta Orthop Scand 1973; 22: 55-61.

47 Sammarco J, Burstein A, Davis W, Frankel V. The biomechanics of torsional fractures: the effect of loading on ultimate properties. J Biomechanics 1971; 4: 113-121.

48 Martens M, van Audekercke R, de Meester P, Mulier JC. The mechanical characteristics of the long bones of the lower extremity in torsion loading. J Biomechanics 1980; 13: 667-676.

49 Mensch JS, Markolf KL, Roberts SB, Finerman GM. Experimental stabilization of segmental defects in the human femur. J Bone Joint Surg 1978; 58 (Am): 185-190.

50 Burstein AH, Reilly DT, Martens M. Aging of bone tissue: mechanical properties. J Bone Joint Surg 1976; 58 (Am): 369-378.

51 Panjabi MM, White AA, Southwik WO. Mechanical properties of bone as a function of rate deformation. J Bone Joint Surg 1973; 55(Am): 322-330.

52 Currey JD. The evolution of the mechanical properties of amniote bone. J Biomechanics 1987; 20: 1035-1044 .

53 Bechtol CO. Metals and Engineering and joint surgery. Baltimore, Williams & Wilkins, 1959, 127-142.

54 Mather BS. The symmetry of the mechanical properties of the human femur. J Surg Res 1967; 7: 222-225.

55 Kennedy JG, Carter DR. Long bone torsion: I effects of heterogeneity, anisotropy and irregularity. J Biomech Engin. 1985; 107: 183-188.

56 Currey JD. The effects of drying and re-wetting on some mechanical properties of cortical bone. J Biomechanics 1988; 21: 439-441.

57 McBroom RJ, Cheal EJ, and Hayes WC. Strength reductions from metastatic cortical defects

in long bones. J Orthop Res. 1988; 6: 369-378.

58 Netz P, Eriksson K, Stromberg L. Ultimate failure of diaphuseal bone. An experimental study on dogs. Acta Orthop Scand 1980; 51: 583-588.

59 Jonsson U, Eriksson K. Microcracking in dog bone under load. Acta Orthop Scand 1984; 55: 441-445.

60 Carter DR, Hayes WC. Compact bone fatigue damage. Clin Orthop Rel Res 1977; 127: 265-274.

61 Cezayilioglu H, Bahniuk E, Davy DT, Heiple KG. Anistropic yield behaviour of bone under combined axial force and torque. J Biomechanics 1985; 1: 61-69.

62 Okubo H, Sato S. Stress concentration factor in shafts with transversal holes as found by electroplating method. J Appl Mech Trans ASME 1955; 77: 193-196.

63 Behiri JC, Bonfield W. Crack velocity and the longitudinal fracture in bone. J Mater Science 1980; 15: 1841-1849.

64 Hayes WC, Wright TM. An emperical strenght theory for compact bone. Fracture 1977; 3: 1173-1179.

65 Ross PD, Davis JW, Epstein RS, Wasnich RD. Pre-existing fractures and bone mass predict vertebral fracture incidence in women. Ann Intern Med 1991; 114: 919-925.

66 Esses SI, Lotz JC, Hayes WC. Biomechanical properties of the proximal femur determined in vitro by single-energy quantitative computed tomography. J Bone Mineral Res 1989; 4: 715-722.

67 Horsman A, Nordin C, Simpson M, Speed R. Cortical and trabecular bone status in elderly women with femoral neck fractures. Clin Orthop 1982; 166: 143-151.

68 Melton LJ III, Riggs BL. Epidemiology of age-related fractures. In: Avioli LV (ed) The osteoporotic Syndrome: detection, prevention, and treatment. Grune & Stratton, New York, pp 45-72.

69 Alho A, Hoiseth A, Husby T. Bone-mass distribution in the femur. A cadaver study on the relations of structure and strength. Acta Ortop Scand 1989; 60: 101-106.

70 Sakkers RJB, Valkema R, de Wijn JR, Lentjes EGWM, van Blitterswijk CA, Rozing PM. The intramedullary hydraulic pressure tolerance of the femur. Clin Orthop Rel Res 1995; 311: 183-189.

71 Mazess RB, Vetter J. The influence of marrow on measurement of trabecular bone usingcomputed tomography. Bone 1985; 6: 349-351.

72 Pugh J, Sherry HS, Futterman B, Frankel VH. Biomechnics of pathologic fractures. Clin Orthop Rel Res 1982; 169: 109-114.

# Chapter 6

# Comparison of torsional strength reduction of cortical defects in femora estimated by surgeons using radiographs and computed tomography and measured by in vitro experiments

PDS Dijkstra[1], HMJ van der Zwaag[2], PGH Mulder[3], CJ Snijder[4], M Oudkerk[5], and T Wiggers[6]

Department of Orthopaedic Surgery[1], Westeinde Hospital, Den Haag, Medical student[2], University Hospital Leiden, Leiden, Departments of Epidemiology and Biostatistics[3], Biomedical Physics and Technology[4], Erasmus University, Rotterdam, Departement of Radiology[5] and Surgical Oncology[6], Daniel den Hoed Cancer Center, Rotterdam, The Netherlands

*Submitted*

## Introduction

The incidence of an impending or actual pathologic fracture of the long bones in patients with metastatic disease is increasing, mainly due to prolonged survival resulted from more effective treatment of visceral metastases.[1] One-half of these impending and actual femoral fractures are found in the proximal femur, and in two-third the primary tumour is breast carcinoma.[2-9]

Quick relief of pain, earlier mobility, decreased hospital stay and reduction of operative complications are reported as important advantages of prophylactic fixation of impending fractures.[7,12,13] Although there is in literature much contradiction in the guidelines to prophylactic treatment of the long bones, three main criteria are pervaded in clinical practice: a lytic lesion of 25 mm or larger, a lytic circumferential cortical destruction of 50% or more, and persistent pain.[7-16]

All of the available studies that use measurements of cortical destruction to predict the risk of fracture due to metastatic lesions used conventional radiographic images. However, these radiographs are limited in several ways; no exact comparison with conventional radiographs can be made because no standard radiographs or no mutual perpendicular projection are made, variable effects of the geometry and destruction of the lesion to bone occur, margins of the lesion are poorly defined and cause error in the accurate measurement of the involved cortical bone, the location of the lesions in the long bones is different and the osteoporosis is variable. [16-18 Chapter 4,5]

Furthermore, it is noted that the inter observer variation in radiographic measurements of metastatic lesions has not been evaluated in clinical studies, and so the application of widely accepted clinical guidelines for predicting pathologic fracture risk should be done with caution.[16, 18]

In literature, the computed tomographic scan examination of cortical defects due to bone metastases is frequently advocated as an additional value to the use of conventional radiographs.[19, 20] Based on in vitro experiments CT scan examinations are considered even more accurate than radiographs in the measurements of cortical destruction.[21] In practice, CT scans are often preferred in predicting strength reduction for long bones with metastatic defects.[22]

The aim of this study is to determine which criteria are used in practice by (orthopaedic) surgeons for prophylactic treatment of cortical defects in the proximal femur due to metastasis, and to assess the inter observer variability in the measurement of these lesions and the predicted torsional strength reduction. Therefore, measurements of such lesions in the subtrochanteric region of the femur on radiographs and CT scans by surgeons were compared with the real strength reduction measured with a load test.

## Material and methods

From December 1996 to February 1997 thirty (orthopaedic) surgeons from 12 different hospitals were invited to participate in this study. They were asked to measure sizes of three different cortical defects created at the subtrochanteric region of the human femur and to predict torsional strength reduction, using radiographs and CT scans. They were first asked about the criteria used for prophylactic surgery for cortical defects by bone metastases in the femur, whether the standard radiographs are made in two directions, if additional radiographs are routinely used, and whether computed tomography is additionally used. Then, they were asked to describe the different surgical treatments for this location, and when radiotherapy should be applied. General information about the observers degree of profession, sort of hospital, and number of patients with pathological fractures of the long bones treated surgically were recorded. After this basic information the surgeons had to review the radiographs and computed tomography scans of three fresh human femora with different created subtrochanteric cortical defects, named femur nr one to three (Figure 1 to 3). Measurements of the cortical lesions on an antero-posterior and lateral radiograph and on CT scan were made of the following parameters (Figure 4): maximal outer bone diameter (W), maximal width of cortical destruction (B), maximal height of cortical destruction (H), minimal cortex remaining at the site of the defect (D) and of the intact bone (C). All measurements were done in millimetres. After these measurements the surgeons had to indicate if these radiographs should be followed by a CT scan, and they had to predict the torsional strength reduction based on the radiograph and CT scan findings, separately. Finally, they were asked whether they would do an operation and if so what type of surgical treatment should be performed.

The radiographs and computed tomography scans of the three defected femora were presented to each observer in the same sequence, starting with the radiograph in two directions. The computed tomography scans (Siemens type Somaton plus 4; 140 KeV; pixel size 0.59 mm; 512 × 512 matrix) were made using 2 mm slices at 2 mm intervals over the proximal region. For the radiography a magnification ratio of 1.05 was estimated, and for the computed tomography this ratio varied between 0.75 and 1.3. In the radiographic group this magnification ratio was small and constant while in the CT group there were large ratio variations. Therefore, calculations for corrections were done for both groups. The procedure of creating these cortical defects at the proximal part of femora and torsional loading tests are extensively described in a previous study.[Chapter 5] In summary, paired femora were collected from 3 fresh human cadavers, stripped to the bone and stored at -30$^0$C. Bone samples were discarded of the experiment if local alterations in bone architecture could be detected by radiography. The proximal and distal ends were embedded in aluminium moulds filled with acrylate. Selected at random, one femur contained the defect while the contra lateral was left intact, and served as a control. These intra- and extra medullary defects were positioned at the medial line, two were transcortical and one was almost penetrating the cortex. Each femur was loaded in torsion (rate 5$^0$/sec) using a Zwick 1484 (Munich, Germany) computed controlled electro hydraulic material testing machine, and applied to the proximal mould while the distal mould had a rigid fixation except for axial translation. The description of the patients femur like age, gender, and lesion site are printed in Table 1.

The results were statistically analysed using the Friedman test for rank-correlation corrected for ties, and the student-t test for one case in different groups. For assessing the agreement between two methods of clinical measurement the statistical methods of Bland and Altman were used. [23]

## Results

One-half of the thirty observers was from a university hospital, and 12 observers treated surgically four or more patients with a pathologic fracture of the long bones in one year. The population of observers consisted of three residents in orthopaedic surgery, 25 orthopaedic surgeons of which 3 professors, and 2 general surgeons. The used criteria for prophylactic surgery for impending pathologic fractures in the femur are plotted in Figure 5. Seven observers did not use guidelines for prophylactic surgery. The amount of cortical destruction was most frequently mentioned as a criterium, and less frequently the use of previous radiotherapy.

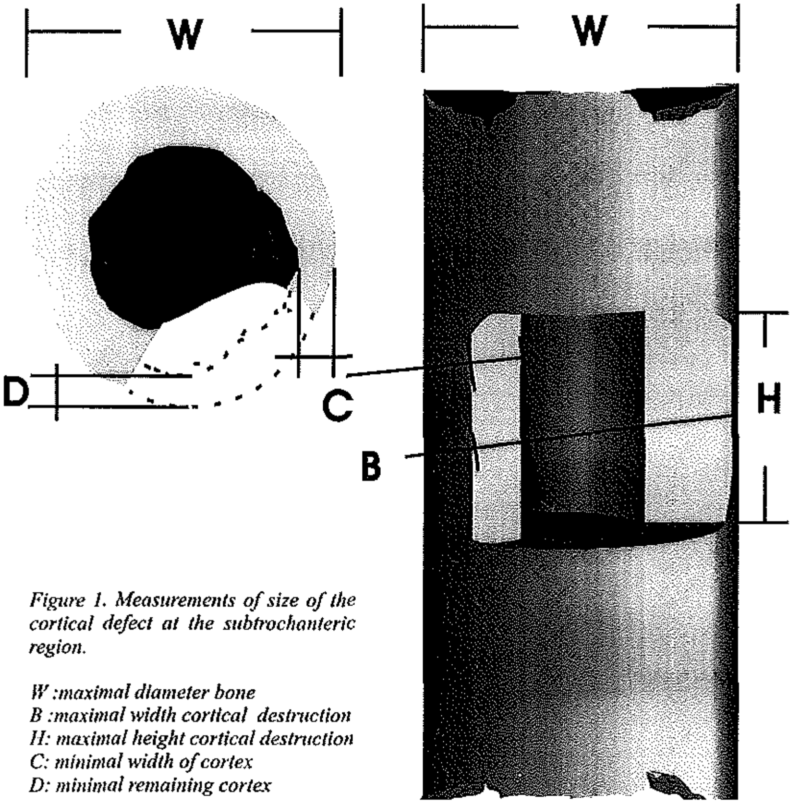


*Figure 1. Measurements of size of the cortical defect at the subtrochanteric region.*

*W :maximal diameter bone*
*B :maximal width cortical destruction*
*H: maximal height cortical destruction*
*C: minimal width of cortex*
*D: minimal remaining cortex*

*Table 2. Mean and standard deviation of the mean (SD) of measurements of the cortical defect in femur nr 1. In vitro measurements were: W=32, B=26, H=16.*

| Measurements of bone defect | Radiographic | | | | CT scan | |
|---|---|---|---|---|---|---|
| | Antero-posterior | | Lateral | | | |
| | mean | SD | mean | SD | mean | SD |
| Maximal outer bone diameter (W) | 29.5 | 1.6 | 29.7 | 1.4 | 33 | 2.7 |
| Maximal width cortex destruction (B) | 15.3 | 3.7 | 28.9 | 2.4 | 31.7 | 3.5 |
| Maximal height cortex destruction (H) | 17.6 | 2 | 16.9 | 1.1 | 18.9 | 5.9 |
| Minimal cortex adjacent to defect (C) | 5.6 | 1.4 | 3.8 | 0.8 | 4.8 | 1.4 |

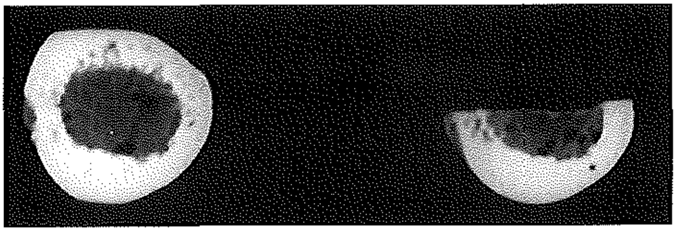


*Table 3. Mean and standard deviation of the mean (SD) of measurements of the cortical defect in femur nr 2. In vitro measurements were: W=28, B=7, H=30.*

| Measurements of bone defect | Radiographic | | | | CT scan | |
|---|---|---|---|---|---|---|
| | Antero-posterior | | Lateral | | | |
| | mean | SD | mean | SD | mean | SD |
| Maximal outer bone diameter (W) | 27.7 | 2.2 | 26.1 | 3.3 | 31.1 | 2.1 |
| Maximal width cortex destruction (B) | 6.5 | 1.2 | 8.4 | 1.4 | 7.7 | 1 |
| Maximal height cortex destruction (H) | 33.8 | 0.6 | 34.3 | 0.6 | 30.1 | 5.9 |
| Minimal cortex adjacent to defect (C) | 5.1 | 0.9 | 2.8 | 1.32 | 4.9 | 1.2 |

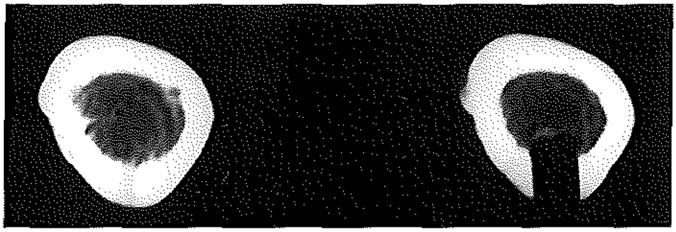
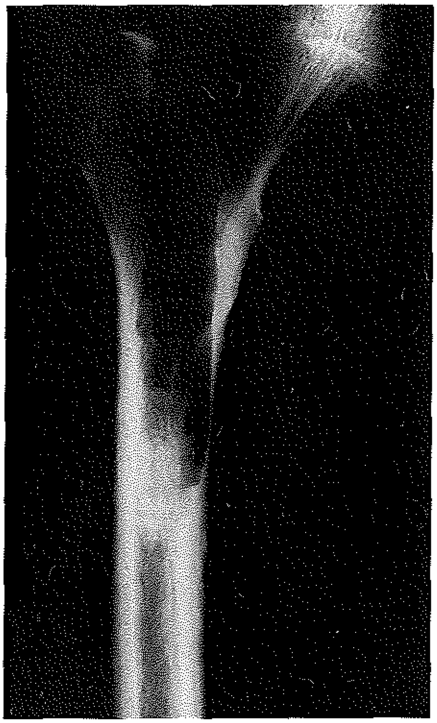
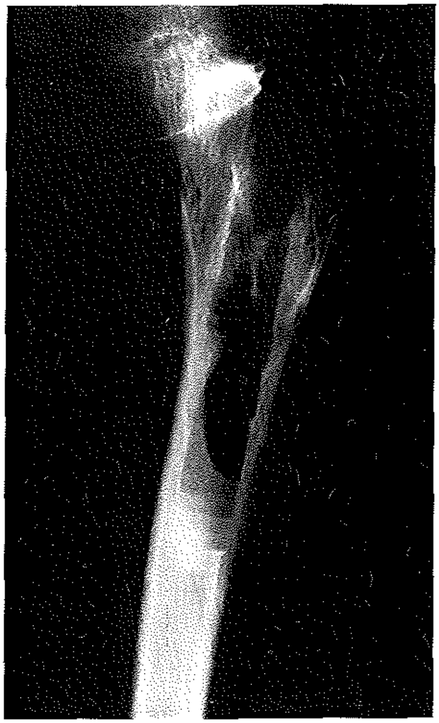
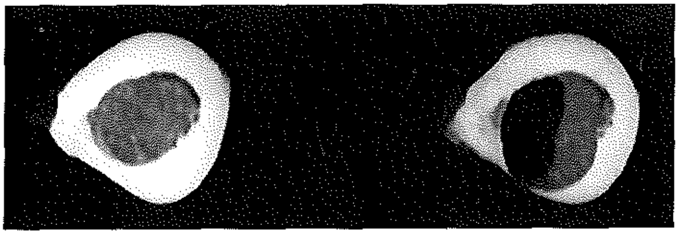


*Table 4. Mean and standard deviation of the mean (SD) measurements of cortical defects in femur nr 3. In vitro measurements were: W=30, H=61, B=15.*

| Measurements of bone lesions | Radiographic |  |  |  | CT scan |  |
|---|---|---|---|---|---|---|
|  | Antero-posterior |  | Lateral |  |  |  |
|  | mean | SD | mean | SD | mean | SD |
| Maximal outer bone diameter (W) | 32.1 | 4.6 | 31.1 | 4.4 | 33.2 | 2.7 |
| Maximal width cortex destruction (B) | 20.4 | 2.7 | 18.4 | 3.7 | 13.6 | 5.8 |
| Maximal height cortex destruction (H) | 63.5 | 8.3 | 64.1 | 10 | 44.9 | 9.2 |
| Minimal cortex adjacent to defect (C) | 4.6 | 1.2 | 3.5 | 1.2 | 4.6 | 1.2 |
| Minimal remaining cortex (D) | 0.9 | 0.3 | 1.7 | 1.1 | 0.8 | 0.3 |







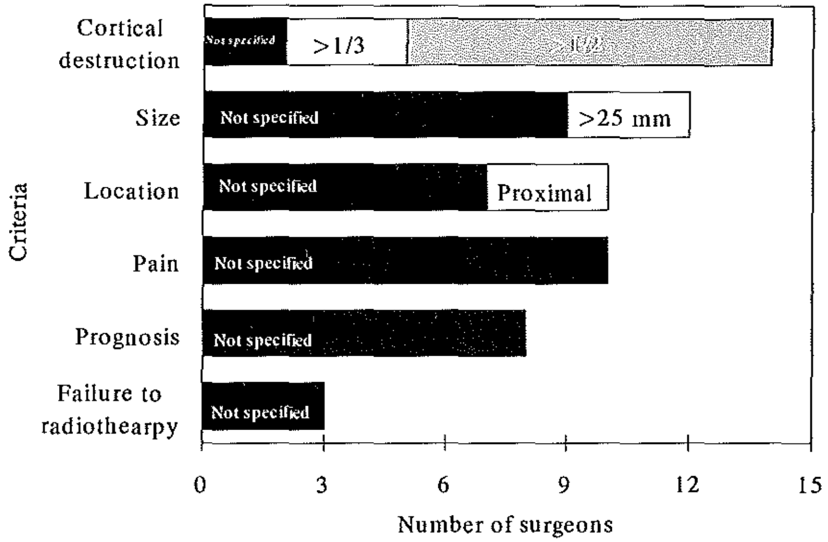
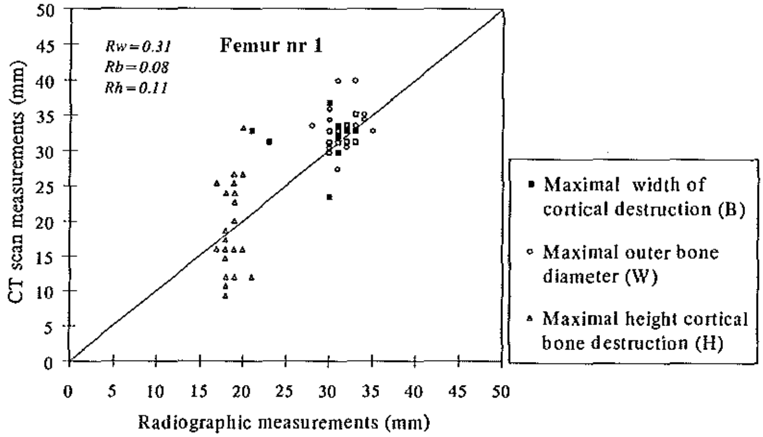


*Figure 5. Criteria for prophylactic surgery of cortical defects due to bone metastasis in the femur.*

All participants routinely made a radiograph in antero-posterior and lateral direction, and 50% of them asked for an additional radiograph. In practice, two-third of the observers advocated a computed tomography scan if necessary, apart from radiographs. In general, intra medullary nailing (n=27) was more often the treatment of first choice, plate osteosynthesis (n=18) and adjunctive bone cement was used in 11 and 18 participants, respectively. Radiotherapy was used by seven observers preoperative, by 13 postoperative, by 6 on indication, and by 3 no radiotherapy was used at all.

The radiographic and CT scan measurements of the cortical lesions of femora nr 1 to 3 are shown in Figure 2 to 4 and Table 2 to 4. In comparison to the in vitro sizes of defects the mean value of measurements W, B, H showed differences in outcome on radiographs in a range from 1% (W) to 26% (B) with median of 7% and on CT scan from 1% (H) to 25% (H) and median of 10%.



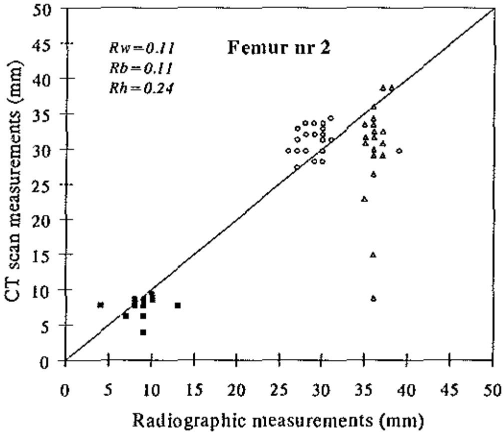
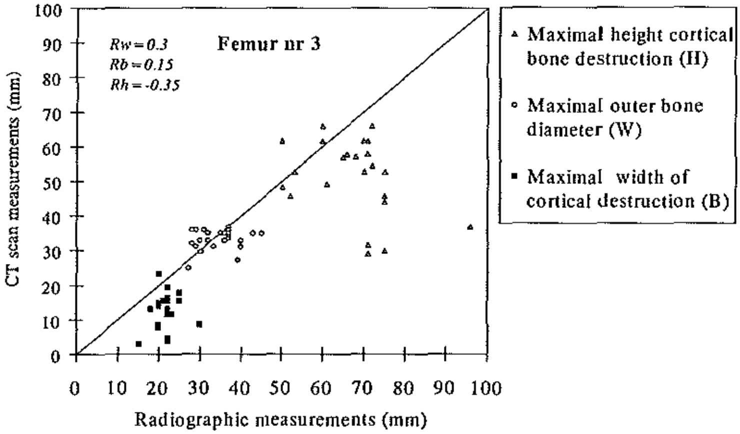


*Figure 6-8. Assessing agreement for the measurements of the defect in femur nr 1 to 3 between radiographic and CT scan examination. The measurement of outer bone diameter had the closest agreement between the two methods, the maximal height a poor agreement. The plotted line represents equality between radiograph and CT scan measurements. The correlation coefficient (R) for W, B, and H is printed.*



Furthermore, the lowest (femur nr 2) and highest (femur nr 3) standard deviation of mean (SD) for all cortical defects, using radiographs, was found for the maximal height of cortical destruction (H). In the CT scan group the SD of mean of the maximal height of the cortical destruction was always the highest in comparison to the other measurements, which was for femur nr 1 to 3 at least 5.9 (Table 1 to 3). To assess the agreement of the measurements W, B, and H of femur 1 to 3 between radiographic and CT scan examination the results were plotted against each other in Figure 6 to 8. According to these figures there was for the maximal outer bone diameter (W) a close agreement and for the maximal height of cortical bone destruction (H) a poor agreement. Compared with nr 1 and 2 the largest range of all parameters was in case of the measurements of femur nr 3, except measurement C in the CT scan group. If the ratio's maximal width defect to maximal width outer bone diameter (B/W) and maximal height defect to maximal outer bone diameter (H/B) were calculated for radiographic values, the SD of H/B measurements was compared with B/W measurements increasing by the height of the cortical defect, up to 3 times higher in femur nr 3.

*Table 1. Description and results of the paired human femora on torsional loading.*

| No. | Sex | Age | Site of lesion | Ratio: height defect to bone diameter | Strength reduction (%) | Torque at failure (Nm) | Deformation angle at failure (deg) | Energy (J) | Rigidity (Nm$^2$) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | ♂ | 85 | left | intact | | 35.3 | 16.3 | 5 | 42.6 |
| | | | | 0.5 | 30 | 24.8 | 11.4 | 3.5 | 94.2 |
| 2 | ♂ | 73 | right | intact | | 159.5 | 45.3 | 73.4 | 112.3 |
| | | | | 1 | 60 | 64.5 | 11.7 | 6.6 | 115.8 |
| 3 | ♀ | 87 | right | intact | | 140.8 | 22.6 | 31.4 | 140.8 |
| | | | | 2 | 52 | 67 | 9.4 | 5.3 | 140.9 |

The results of the experiment in which these femora were torsional loaded to failure are shown in Table 1. According to the findings of a previous study in which the intact bones served as a control group the median of torque at failure, deformation

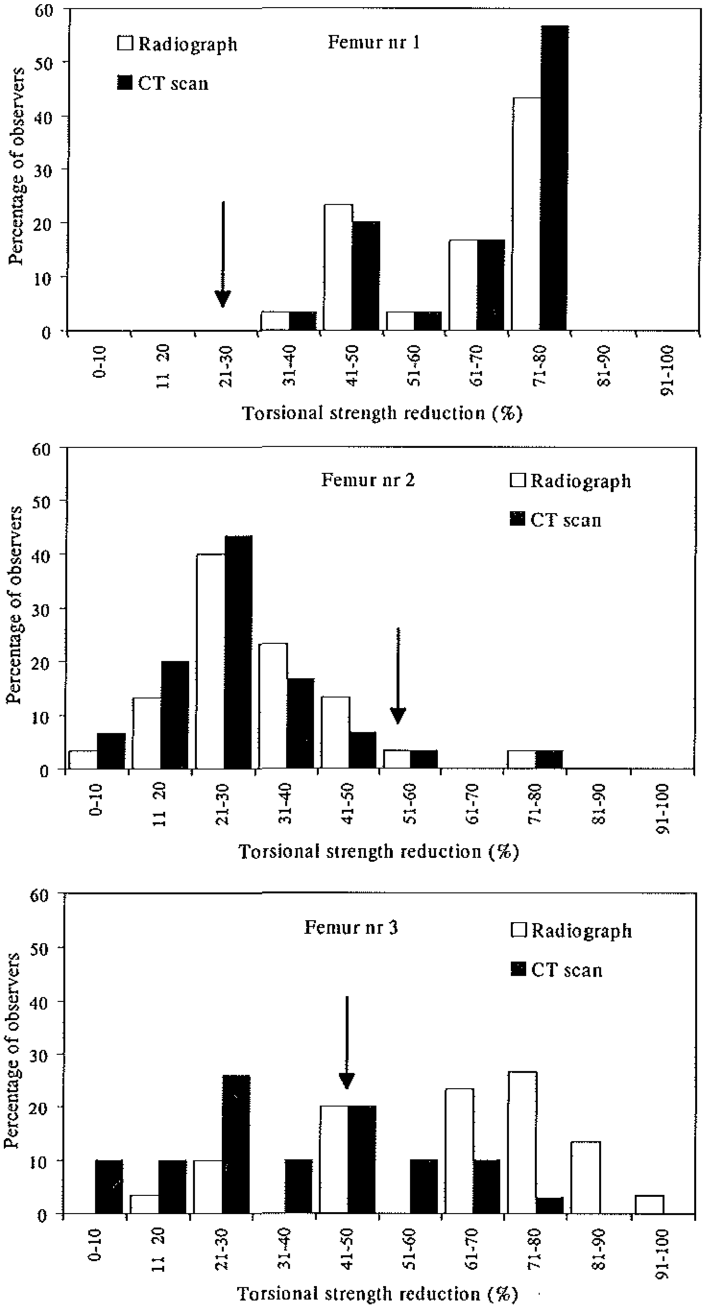


*Figure 9 to 11. Torsional strength reduction predicted by surgeons for femur nr 1 to 3, using radiographic and CT scan examinations. The results of strength reduction in these femora tested in torsional loading were 30% (upper figure), 60% (middle figure), and 52%, respectively (→).*

angle at failure, and calculated energy and rigidity were 140.8 Nm, 22.6$^0$, 31.4 J, and 112.3 Nm$^2$, respectively. [Chapter 5] The low values in case of femur nr 1 for torque of failure, energy, and rigidity, were due to osteoporosis The torsional strength reduction was 30% in femur nr 1, 60% in femur nr 2, and 52% in femur nr 3.
The mean torsional strength reduction for femora nr 1 to 3 predicted by observers in the radiographic group and CT scan group were, 67.3 and 68.3, 33.9 and 29.9 ($P<$ 0.05), 64.7 and 39.3 ($P<0.0001$), respectively. There was a significant correlation ($P<$ 0.005) between the mean strength reduction in the radiographic group and CT scan group for femur nr 1 to 3 (R=0.8, 0.86, and 0.53, respectively). Furthermore, there was no correlation between the degree of profession of the surgeon and accuracy in predicting torsional strength reduction. Within a range of 20% accuracy, the percentage of observers who correctly predicted the strength reduction was very low (≤20%), except the outcome based on CT scan measurements in femur nr 3 (40%)(Figure 9 to 11). Thus, the use of an additional performed CT scan gives no improvement of the prediction of strength reduction in case of femur nr 1 and 2, while there was a nearly significant improvement of outcome in case nr 3 ($P=0.06$).

## Discussion

In literature, no studies are available about the accuracy and intra- and interobserver variability in radiographic and CT scan measurements of cortical defects in the long bones due to bone metastasis. Several retrospective clinical studies have been done to find the specific size of the defect on radiographs that predicts fracture risk of a metastatic lesion. [10-16] Hipp et al.[17] tried to set whether the axial strength reduction caused by defects in the intertrochanteric region of the femur can be estimated using both radiographs and CT scan measurements. He asked 3 orthopaedic oncologic surgeons to review radiographs of femurs with simulated metastatic defects, to measure the defects and to estimate the axial strength reduction. The strength reduction was tested and it was demonstrated that experienced orthopaedic surgeons cannot predict the strength reduction or load-bearing capacity from radiographs or CT examinations. It should be noted that the quality of radiographs from a human specimen is better than from normal clinical origin because of the absence of soft tissue, as in this study. Together with the fact that the projection of the transcortical defects was optimal because of sharp cuts and of complete visualisation due to coaxial direction of the radiographic beam, it may be expected that in clinical practice a good judgement will be more difficult than in the simulated situation. The cortical defects due to metastatic lesions may present as lytic, blastic or both. However, qualitative radiographic analysis of bone lesions can be misleading, since 50% of the bone mineral content of the cancellous bone must be resorbed before changes are visually evident. In the cortical bone this necessary destruction is much smaller for detection. [6, 24]

The defects can also have an irregular geometry, and often appear as multiple lesions. In contrast, the simulated defects in our study were presenting solitary lytic defects, which penetrated the cortical wall partially or complete. On plane radiographs, McBroom et al.[21], demonstrated variations in the ratio defect size to bone diameters up to 10%, while in this study this was 13%. In addition, errors of as much as 100% can occur when measuring simple solitary cortical defects from plane radiographs.[25] Furthermore, with the use of clinical plane radiographs there were difficulties in identifying the size of the cortex, i.e. up to 50% due to unidentifiable margins of the bone, as shown by Keene et al. and in our previous study.[26, Chapter 4] In this study there was a large interobserver variability using the radiographic measurements. Thus, there are limitations in the predictive capabilities of these radiographic methods.

Nevertheless, the use of CT scan examinations is suggested to be helpful in detection of cortical involvement of a metastatic bone lesion, in determining the local extend of these lesions and to support the decision for prophylactic surgery.[17-20, 21,22,27] The introduction of the magnetic resonance imaging did not alter these findings, while CT scan examination is more accurate than MRI in showing cortical destruction, mineralisation, and imaging normal bone.[28] Although the visualization of a cross-section of bone with a cortical defect with CT scan examination may be more accurate than using radiographs, we were not able to find such an improvement in our study. Errors of as much as 25% can occur in CT scan measurements and even the median value is higher than with radiographic measurements (10% vs. 7%, respectively). This is mainly because of the large inter observer variability. According the very large range measured of the height of the cortical defect, CT scan examination should not be used for this measurement.

There are several limitations in this study which should be considered before the result of strength reduction due to cortical defects are applied to practice. First, we have only tested torsional loads, whereas multi axial loads are involved in patients with a metastatic lesion. Only three pairs of specimens were used in the in vitro experiment. Large ranges of variation are found in the results of mechanical testing of human femora. [29-31, Chapter 5] Third, we studied geometric changes with rounded edges and clear boundaries in rectangular cortical defects in two of the three different specimens. In practice these defects are considered more complex in geometric patterns. Finally, no demineralized border of these defects was obtained, while clinically bone density around metastatic lesions varied widely and have an increased strength reduction in comparison to nondemineralized defects.[25] It should be noted that the torsional strength reduction was 60% for the ratio defect height to bone diameter is equal to one. This was in contrast to our previousness finding when a median reduction of 7% occurred.[Chapter 5] However, after correction to this median torsional strength reduction of the results in this study no changes occurred in statistical outcomes. The use of an additional performed CT scan gives no improvement of the prediction of strength reduction when rectangular transcortical defect was measured, while there is a trend to improvement of the outcome when, the boundaries of the cortical defect are less clear on conventional radiographs.

These findings show that for cortical defects in the subtrochanteric region, surgeons cannot accurately measure the sizes of a cortical defect, they cannot estimate the torsional strength reduction from radiographs, and the supplementary use of CT scan does not improve these findings.

In conclusion, the application of the pervaded clinical guidelines to predict the fracture risk of a metastatic lesion in the long bones, using radiographic and CT scan measurements, should be done with caution.

## References

1 Albright JA, Gillspie TE, Butaud TR. Treatment of bone metastases. Semin Oncol 1980; 7: 418-434.

2 Holzheimer RGE. Kunze KG. Die paliative operative therapie pathologischer frakturen. Unfallchirurgie 1988; 14: 283-290.

3 Ryan JR, Rowe DE, Salciccioli GG. Prophylactic internal fixation of the femur for neoplastic lesions. J Bone Joint Surg 1976; 58(Am): 1071-1074.

4 Karachalios T, Atkins RM, Sarangi PP, Crichlow TPKR, Solomon L. Reconstruction nailing for pathological subtrochanteric fractures with coexisting femoral shaft metastases. J Bone Joint Surg 1993; 75 (Br): 119-122.

5 Yazawa Y, Frassica FJ et al. Metastatic bone disease: a study of surgical treatment of 166 pathological humeral and femoral fractures. Clin Orthop 1990; 251: 213-219.

6 Galasko CSB. The management of skeletal metastases. Royal Coll Surg Edin 1980; 25: 143-161.

7 Dijkstra PDS, Wiggers T, van Geel AN, Boxma H. Treatment of impending and actual pathological fractures in patients with bone metastases of the long bones. Eur J Surg 1994; 160: 535-542.

8 Zickel RE, Mouradian WH. Intramedullary fixation of pathological fractures and lesions of the subtrochanteric region of the femur. J Bone Joint Surg 1976; 58(Am): 1061-1066.

9 Menck H, Schulze S, Larsen E. Metastasis size in pathologic femoral fractures. Acta Orthop Scand 1988; 59: 151-154.

10 Francis KC. Prophylactic internal fixation of metastatic osseous lesions. Cancer 1960; 13: 75-76.

11 Parrish FF, Murray JA. Surgical treatment for secondary neoplastic fractures. J Bone Joint Surg 1970; 52(Am): 665-686.

12 Fidler M. Profylactic internal fixation of secondary neoplastic deposits in long bones. Brith Med J 1973; 1: 341-343.

13 Harrington KD. New trends in the management of the lower extremity metastases. Clin Orthop 1982; 169: 53-61.

14 Fidler M. Incidence of fracture through metastases in long bones. Acta Orthop Scand 1981; 52: 623-627.

15 Beals RK, Lawton GD, Snell WE. Profylactic internal fixation in metastatic breast cancer. Cancer 1971; 28: 1350-1354.

16 Mirels H. Metastatic disease in long bones: a proposed scoring system for diagnosing impending pathologic fractures. Clin Orthop 1989; 14: 513-525.

17 Hipp JA, Springfield DS, Hayes WC. Predicting Pathologic Fracture Risk in the Management of Metastatic Bone Defects. Clin Orthop Rel Res 1995; 312: 120-135.

18 Springfield D, Jennings C. Pathologic fractures. In: Rockwood CA and Green DP (ed):

Fractures in Adults, Volume 1. Lippencott - Raven, New York. 1996. 519-521.

19 Gold RI, Seeger LL, Bassett LW, Steckel RJ. An integrated approach to the evaluation of metastatic bone disease. Radiol Clin North 1990; 28: 471-483.

20 Rafii M, Firooznia H, Kramer E, Golimbu C, Sanger J. The role of computed tomography in evaluation of skeletal metastases. J Computed Tomogr 1988; 12: 19-24.

21 McBroom RJ, Cheal EJ, and Hayes WC. Strength reductions from metastatic cortical defects in long bones. J Orthop Res. 1988; 6: 369-378.

22 Habermann ET, Rafael AL. Metastatic disease of bone and treatment of pathological fractures. Orthop Clinics North America 1989; 20: 469-486.

23 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. The Lancet 1986; i: 307-310.

24 Edelstyn GA, Gillespie PJ, Grebbel FS. The radiological demonstration of osseous metastases. Experimental observations. Clin Radiol 1967; 18: 158-162.

25 Hipp JA, Katz K, Hayes WC. Local demineralization as a model for bone strength reductions in lytic transcortical metastatic lesions. Investig Radiol 1991; 26: 934-937.

26 Keene JS, Sellinger DS, McBeath AA, Engber WD. Metastatic breast cancer in the femur. Clin Orthop Rel Res 1986; 203: 282-288.

27 Muindi J. Coombes RC, Golding S, Powles TJ, Khan O, Husband J. The role of computed tomography in the detection of bone metastases in breast cancer patients. Br J Radiol 1983: 56; 233-236.

28 Zimmer WD, Berquist TH, McLeod RA, et al. Bone tumours: magnetic imaging versus computed tomography. Radiol 1985: 155; 709-718.

29 Currey JD. The effects of drying and re-wetting on some mechanical properties of cortical bone. J Biomechanics 1988; 21: 439-441.

30 Panjabi MM, White AA, Southwik WO. Mechanical properties of bone as a function of rate deformation. J Bone Joint Surg 1973; 55(Am): 322-330.

31 Sammarco J, Burstein A, Davis W, Frankel V. The biomechanics of torsional fractures: the effect of loading on ultimate properties. J Biomechanics 1971; 4: 113-117.

# Chapter 7

## Risk assessment of femoral fractures due to metastatic lesions of different sizes based on finite element analysis

M.F. ten Have[1,3], P.D.S Dijkstra[2], F. van Keulen[1]

Laboratory for Engineering Mechanics [1], Delft University of Technology, Delft, The Netherlands. Department of Orthopaedic Surgery [2], Westeinde hospital, Den Haag, The Netherlands. Department of Biomedical Physics and Technology [3], Faculty of medicine, Erasmus University Rotterdam, The Netherlands.

*Submitted*

## Introduction

The main clinical consequence of skeletal involvement in metastatic cancer is the pathological fracture. These fractures commonly occur spontaneously or after a minor trauma which influences the quality of live to a large extent.[1] Prophylactic fixation of impending fractures is generally preferred instead of treatment of actual fractures.[1, 2, 3] As a result, prophylactic fixation is increasingly applied. Three main accepted principles in assessing femoral fracture risk are performed: a lytic lesion of 25 mm or larger involving the femur, lytic circumferential cortical destruction of 50% or more, and persistent pain with weight-bearing.[2-7] At present these criteria are based on clinical practice.[8] Although these guidelines arise from several retrospective clinical studies, neither guideline has been confirmed through in vitro experiments.[8]
Previous studies applied finite element methods to investigate the biomechanics of regular cortical defects in long bones subject to bending, axial loading and torsion.[9-13] All this research, however, have been restricted to small defects like screw holes in cylindrical models representing the femoral shaft and femoral neck.[9-13]
Because of the limited knowledge on fracture risk of larger defects, experiments on fresh frozen femora with artificial holes were acted. All defects were in the subtrochanteric region because the proximal femur is the most common place for bone metastasis of the long bones.[1] The aim of this study is to analyse fracture risk predicted with a finite element model of the femora in relation to experimentally observed fracture risk to different heights of transcortical defects.

## Method and materials

The geometry of all fresh frozen femora (n=28) used in the experimental study was defined by using CT-scans. These specimens were used in experiment and described in Chapter 5. Eighty transverse CT-scan slices were obtained from the entire bone. The slice thickness was 2.0 mm; pixel size 0.59 mm; and a matrix size of 512x512 mm. These scans were digitized with a semiautomatic contouring algorithm (Scilimage 1.0, University of Amsterdam, Amsterdam, The Netherlands) so the inside and outside cortical bone geometry was obtained. The geometry of the basic finite element model was determined by using the inside and outside contours of one bone specimen. An 87-year-old female was the donor of the femur used for the finite element modelling (FEM), representative for the in vitro experiments. Created by stacking of all these contours was filled. The volume was modeled using four node tetraeder elements (Figure 1). These elements had linear interpolation functions, three degrees of freedom per node and isotropic material properties. The elastic modulus was 18.4 GPa and Poisson's ratio 0.32, which corresponds with cortical bone values.[14] The eventual model had approximately 25.000 nodes, 90.000 elements and 75.000 degrees of freedom and two elements along the thickness. The length of the model was 328 mm, representative for the experiments, and started from just above the trochanter minor until the condyle.

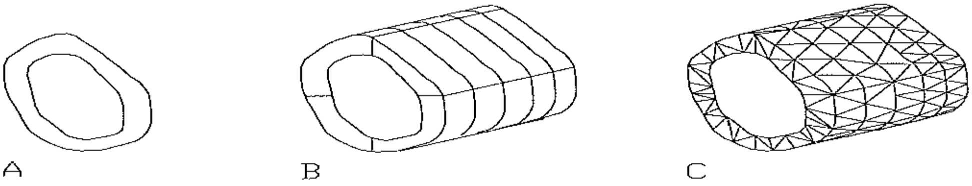


*Figure 1. The inside and outside cortical bone contour after digitising a CT scan slice (A). A volume was created after stacking all contours (B). Eventually, meshing with four-noded tetraeder solid elements (C).*

The torsion load in the FEM model was applied by fixing the proximal end and applying rotation of the longitudinal axis of the femur, representative for the situation that occurred in the experiments. The effect of defect size was investigated. The defects ranged from a length of 0.5 times the bone diameter (L/D=0.5) to twice the bone diameter. The width was held constant at 0.25 times the bone diameter (W/D=0.25). All defects were in the subtrochanteric region (Figure 2).

The calculations were done by using linear analysis. The finite element models were evaluated by determining the magnitude and the location of the maximum Von Mises stress in a FEM model containing a defect and the maximum Von Mises stress predicted by a model of an intact bone.

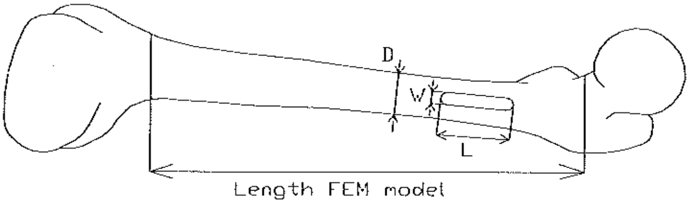


*Figure 2. The region of the femur where the cortical defect of the bone specimen and the finite element model are found. The length ratio L/D varied from 0.5 to 2. The width was constant 0.25 ratio W/D.*

## Results

The results from the finite element model and experiments are compared with handbook solutions and with a finite element model of a cylinder.[15] The cylinder had an inner diameter of 20 mm, outer diameter 30 mm and a length of 328 mm. The defects in the cylinder, boundary conditions, loading conditions and material properties were the same as defined in the FEM model of the femur. The handbook calculationswere obtained for an ovaloid in an infinite wide plate subjected to shear stress. [15]

All values presented are on a relative scale. The experimentally determined fracture load of the femur with a defect is related to the fracture load of the intact contralateral femur. For the finite element models, the stress of a model containing a defect is related to the stress of an intact model.

The linear model of the cylinder predicts a rapid drop in strength when the defect length is 50% of the bone diameter (Figure 3). Elongated, the defect results in a gradually decreasing strength. This is in close agreement with the handbook solutions of Peterson what suggests that the mesh refinement of this finite element model was sufficient.[15] No strength reduction was found in the finite element model of the femur with a ratio of 0.5 defect to the bone diameter. The peak stress of this FEM model was not located near the defect but distal to the corresponding location for the intact bone (no defect). However, when the defect is elongated a gradually rapid drop in strength is predicted (Figure 4). This finite element model was based on a single femur included in the in

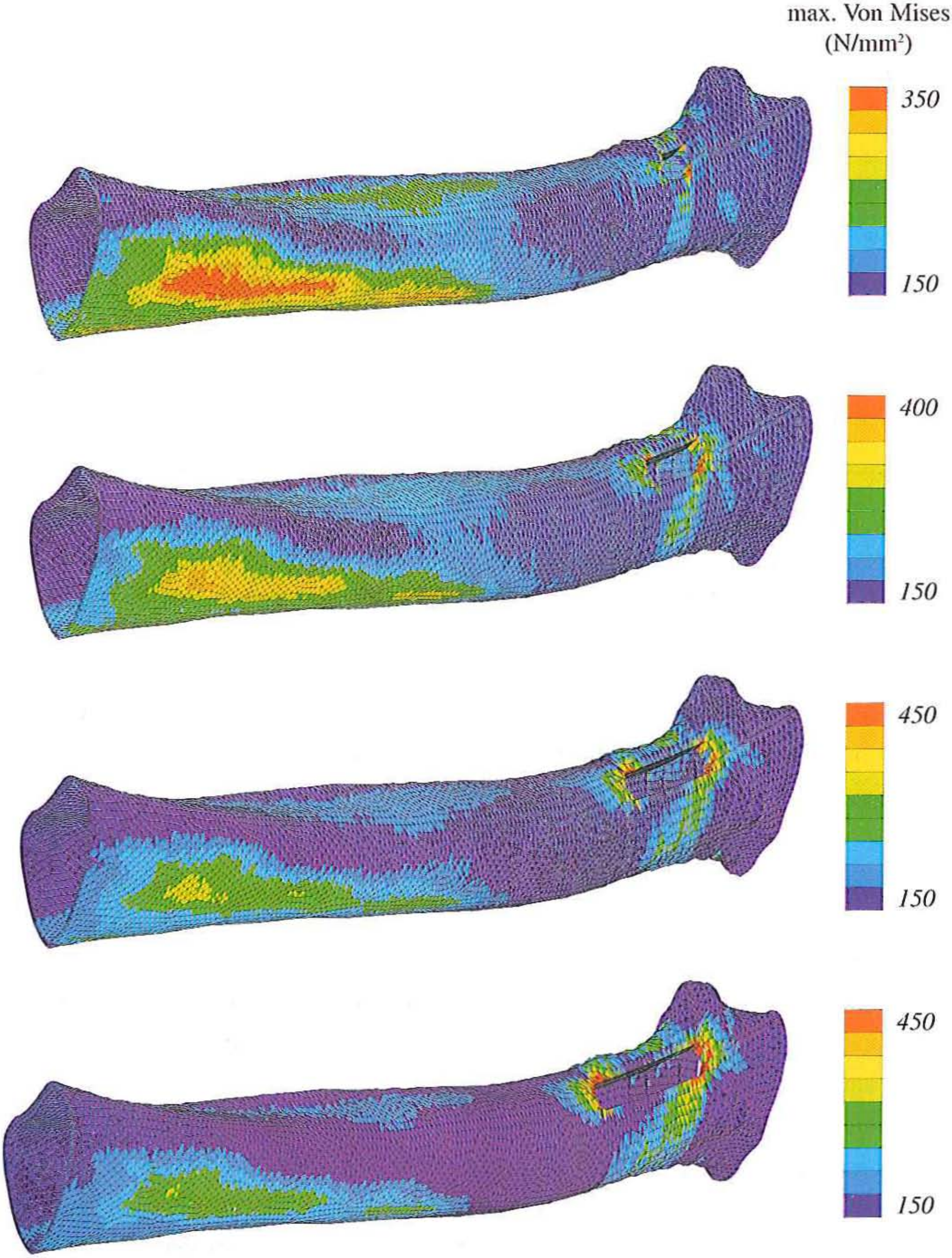


*Figure 4. The maximum Von Mises stress in the different finite element models of the femur with transcortical defect length is 0.5 to 2 of the bone diameter (L/D).*

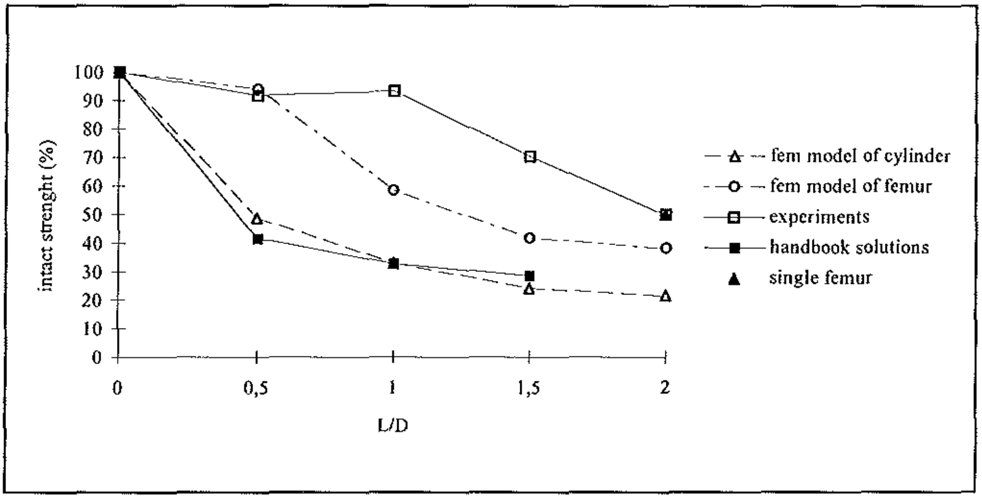


*Figure 3. The relative intact strength versus defect length divided by bone diameter ( in %). Cylinder model data obtained from* FEM *corresponding well with stress concentration handbook values. The strength reduction pattern of fresh frozen human femora in the experiments agree with the* FEM *analysis of a femur model with the same dimensions.*

vitro experiments. Comparing the result of the finite element model to the experiment of the bone specimen, an error of 10 percent was found in the torsion strength reduction.

## Discussion

### *Modelling*

In this study we could theoretically support our earlier findings on fracture risk related to the size of cortical defects in femora with metastatic cancer. We restricted ourselves to the study of torsion because, in practice, subtrochanteric femoral fractures occur "spontaneously" during daily live activities with low energy impact. For instance, rising from a seat or turning in bed. The appearance of these fractures is often spiral, which suggests involvement of a torsion load. Reported by Burke, who measured micro motion of cemented femoral shaft components, there were larger strains due to torsion load as compared to bending in these daily life activities found. [16]

A linear analysis was applied in the calculations because the experiments showed a linear relation between the total torque at failure and deformation angles at failure (Chapter 5). Furthermore, if finite element results are expressed in a stress ratio to the normal bone, linear finite element models can provide a good estimate of bone strength.[5] Our finite element model predictions were evaluated based upon Von Mises stress criterion. This stress criterion may not be the ultimate failure criterion for torsion loaded bone. An advanced failure criterion seemed not to be justified due to the uncertainty in material properties of the different femora used in the experimental study.[12] The experimental results were related to the intact contralateral femur. So equal material constants were assumed for left and right leg and therefore the influence of different stadia of osteoporosis was expected to be small. Kuo et al. found that a simple isotropic modelling approach can be used to approximate the stress concentration factor in long bones.[7] Therefore, we used isotropic material assumptions in our finite element model.

*FEM of a cylindrical tube*

The linear finite element models of the cylindrical tube and the handbook solutions do not give a good prediction of the strength reduction compared with the experiments. These solutions underestimate the intact bone strength. This is in comparison with the results of Hipp et al.[13] They found that the finite element model represented by a cylindrical tube underestimated the torsion strength compared with the experiments of Edgerton et al. for small holes.[18] Edgerton et al. predicted no strength reduction for small circular holes (smaller than ratio 0.1).[18] For larger circular holes, 0.2 and 0.3 of the bone diameter, a reduction in torsion strength of respectively 30 and 40% was observed. In contrast, Brooks et al. found that small circular holes significantly decreased the torsion strength of canine femora.[19] The defects were 0.14 to 0.18 of the bone diameter and reduced the energy absorbing capacity to 55% of an intact bone. No extra strength reduction was observed when the defect diameter was increased. The experiments performed in our study predicted no strength reduction when the defects have a width of 0.25 and a length of 0.5 of the bone diameter.[Chapter 5]

*FEM of a human femur*

The finite element analysis based on the data of a fresh frozen human femur shows the same strength reduction pattern as the experiments (Figure 3). Only a strength reduction of 40% is found by the finite element model when the defect length is one times the bone diameter while the experiments show this reduction when the defect length is between 1.5 and 2 times the bone diameter. The most likely explanations for disagreement are either that the modeled femur was not a representative of the all the experimens or the FEM model prediction were less accuratefor all the different defects used in the experiments. A large variety is found in torsion strength reduction in long bones with a cortical defect. More FEM models specific to the bones used in the experiments are necessary to evaluated this disagreement. However, the results are in close agreement with the observations of Frankel et al.[20] They concluded that an open section effect occurs when a discontinuity in a bone is longer than the bone diameter.[20] The torsion strength of our FEM model shows a reduction of approximately 60% by a length/diameter lesion ratio of two. Frankel and Burstein predicted 70% reduction for a half width cut with a length of one fifth of the tibia.[21]

The maximum Von Mises stress of the intact FEM model was found at the same spot where the single intact femur included in the in vitro experiments fractured. Furthermore, the FEM model with a ratio (L/D) length of the defect to the diameter intact bone of two was based on a single bone specimen also used in the experiments. Comparing the result of the FEM model with this bone specimen, an error of 10% was found in the torsion strength reduction.

*Model restrictions*

A limitation of the finite element model was that only the macroscopic behaviour of the bone was represented. However, fracture initiation is a localised event dominated by the properties of the microstructure architecture of the bone tissue.[22,23] The accuracy of FEM model may depend to the underlying variability of bone microstructure that cannot be taken into account using uniform strength criteria over the entire bone.

The material properties of bone strongly influence the structural properties. Several assumptions must be made in finite element models of bone with respect to anisotropy, linearity and homogeneity. Inclusion of these material yielding in the model formulation can result in higher strength estimates due to the lower postyield modulus of bone and the resulting redistribution of the stresses. McBroom et al. found that finite element model which represent inelastic behaviour in bone provide a more accurate estimate of the absolute bending strength of long bones with transcortical holes.[9] However, they did not normalise the strength data to model predictions for an intact bone. Hipp et al. found that linear finite element models agreed with experimental data when the linear models were normalised to models of intact bone.[10] Our linear FEM model of the mur overestimate the torsion strength reduction while Hipp et al. described an underestimation of torsional strength reduction in a nonlinear FEM model, applying torsional load.[10,13]

None of the previous published studies concerning transcortical destruction analysed by FEM models takes into account the geometrical factors of the subtrochanteric region of the femur. Using a linear FEM model it seems important that the data are normalized to the strength of each intact femur.

While our experiments and FEM model of the femur show that defect length influences torsion strength reduction of long bone, which was also predicted by Hipp et al. and Frankel et al., Clark et al. found that defect width weakens bone more than defect length.[13,20,21,24] However, Clark et al. did not normalise their experimental results to the contralateral intact femur.[24]

Several other material properties and geometric considerations were not investigated in this study. This is due to the number of parameters that should be included in a rigorous analysis. However, these considerations could be of clinical significance. For instance, a decrease in the elastic modulus at the border of endosteal metastatic defects reduces the bending strength of long bones.[10] Finally, the cortical and trabecular bone density changes characteristic bordering the defect of metastatic lesions are likely to effect the torsional strength reduction of long bones.[13,25,26] Keyak et al. reported, a promising technique providing improved predictions of patient specific fracture risk by using quantitative computed tomography to generated the bone anatomy and density in a three-dimensional FEM model.[27,28] In the further, this points of localised stress concentration which initiates crack should be analysed.

In conclusion, linear FEM analysis gives a good prediction of torsion strength reduction by a transcortical hole in a fresh frozen specimen of a human. The FEM model compared with our experiments shows that the height of a transcortical destruction in relation to the bone diameter is an important fracture risk.

## References

1 Dijkstra PDS, Wiggers T, van Geel AN, Boxma H. Treatment of impending and actual pathological fractures in patients with bone matastases of the long bones. Eur J Surg 1994; 160: 535-542.

2 Fidler M. Prophylactic internal fixation of secondary neoplastic deposits in long bones. Brit Med J 1973; 1: 341-343.

3 Harrington KD. New trends in the management of the lower extremity metastases. Clin Orthop Rel Res 1982; 169: 53-61.

4 Beals RK, Lawton GD, Snell WE. Prophylactic internal fixation of the femur in metastatic breast cancer. Cancer 1971; 28: 1350-1354.

5 Behr JT, Doboz WR, Badrinath K. The treatment of pathologic and impending pathologic fractures of proximal femur in the eldery. Clin Orthop Rel Res 1985; 198: 173-178.

6 Krebs H. Management of pathologic fractures of long bones in malignant disease. Arch Ortop Trauma Surg 1978; 92: 133-137.

7 Yazawa Y, Frassica FJ, Chao EY, Pritchard DJ, Sim FH, Shives TC. Metastatic bone disease: a study of surgical treatment of 166 pathological humeral and femoral fractures. Clin Orthop Rel Res 1990; 251: 213-219.

8 Hipp JA, Springfield DS, Hayes WC. Predicting pathologic fracture risk in the management of metastatic bone defects. Clin Orthop Rel Res 1995; 312: 120-135.

9 McBroom RJ, Cheal EJ, Hayes WC. Strength reductions from metastatic cortical defects in long bones. J Orthop Res 1988; 6: 369-378.

10 Hipp JA, McBroom RJ, Cheal EJ, Hayes WC. Structural consequences of endosteal metastatic lesions in long bones. J Orthop Rel Res 1989; 7: 828-837.

11 Cheal EJ, Hipp JA, Hayes WC. Evaluation of finite element analysis for prediction of the strength reduction due to metastatic lesions in the femoral neck. J Biomechanics 1993; 3: 251-264.

12 Kuo RF, Chao EYS, Rim K, Park, JB. The effect of defect size on the stress concentration and fracture characteristics for tubular torsion model with transverse hole. J Biomechanics 1991; 24: 147-155.

13 Hipp JA, Edgerton BC, An KN, Hayes WC. Structural consequences of transcortical holes in long bones loaded in torsion. J Biomechanics 1990; 12: 1261-1268.

14 Currey JD. The mechanical adaptations of bones. Princeton University Press 1984.

15 Peterson RE. Stress concentration factors. John Wiley & Sons, New York 1974.

16 Burke DB, O'Conner DO, Zalenski EB, Jasty M, Harris WH. Mircomotion of cemented and uncemented femoral components. J Bone Joint Surg (Br) 1991, 73: 33-37.

17 Cezayilioglu H, Bahniuk E, Davy DT, Heiple KG. Anisotropic yield behaviour of bone under combined axial force and torque. J Biomechanics 1985; 1: 61-69.

18 Edgerton BC, An KN, Morrey BF. Torsion strength due to cortical defects in bone. J Orthop Res

1990; 8: 851-855.

19 Brooks DB, Burstein AH, Frankel VH. The biomechanics of torsion fractures: The stress concentration effect of a drill hole. J Bone and Joint Surg 1970; 3: 507-514.

20 Frankel VH, Nordin M. Basic biomechanics of the musculoskeletal system. Lea & Febiger Philadelphia, London 1989 second edition.

21 Frankel VH, Burstein AH. Load capacity of tubular bone. In Biomechanics and related Bioengineering Topics. (Edited by Kenedi RM) 1965; 381-396.

22 Behiri JC, Bonfield W. Crack velocity dependence of longitudinal fracture in bone. J of Mat Science 1980; 15: 1841-1849.

23 Choi K, Kuhn JL, Ciarelli J, Goldstein SA. The elastic moduli of human subchondral, trabecular, and cortical bone tissue and the size-dependency of cortical bone modulus. J Biomechanics 1990; 23: 1103-1113.

24 Clark CR, Morgan C, Sonstegard DA, Matthews LS. The effect of biopsy hole shape and size on bone strength. J Bone Joint Surg (Am) 1977; 59(2): 213-217.

25 Hipp JA, Katz G, Hayes WC. Local demineralizationas a model for bone strength reductions in lytic transcortical metastatic lesions. Invest Radiol 1991; 26: 934-938.

26 Hipp JA, Rosenberg AE, Hayes WC. Mechanical properties of trabecular bone wthin and adjacent to osseous metastases. J Bone Mineral Res 1992; 7: 513-519.

27 Keyak JH, Meagher JM, Skinner HB, CD Mote. Automated three-dimensional finite element modelling of bone: a new method. J Biomed Eng 1990; 12: 389-397.

28 Keyak JH, Fourkas MG, Meagher JM, Skinner HB. Validation of an automated method of three -dimensional finite element modelling of bone. J Biomed Eng 1993; 15: 505-509.

# Chapter 8

# General discussion

## General discussion

The significance of this thesis has to be found in establishing criteria for prophylactic surgery and evaluating treatment of pathological fractures of the long bones. We were convinced that an experimental approach with the application of advanced computing techniques like finite element modelling, after evaluation of the clinical aspects, could satisfy our aim. The experiments have resulted in the assessment of a reliable discrimination point with respect to geometry of the lytic metastatic defect of the subtrochanteric region of the femur (Table 1). In fact these findings correspond well with an old clinical 'rule of thumb' that a defect size exceeding 2.5 cm is an indication for surgery.[1,2] The maximal bone width at the proximal region of the femoral shaft is approximately 30 mm.[Chapter4,5] So, a ratio for the height of the defect to outer bone diameter of more than 0.8 is often used in practice. Based on our clinical and experimental studies a torsional strength reduction in the subtrochanteric region of the femur occurs when the ratio of maximal longitudinal cortex destruction to the width of the bone is more than 1.[Chapter 4,5,7] In contrast, two studies handling about this region of the proximal femur reported no consistent relationship between the size of measurable lesions and their risk to fracture.[3,4] Although the available information comes from retrospective studies, the accepted criteria for prophylactic internal fixation for all metastatic lesion sites of the lower extremity are the presence of a painful lesion despite irradiation, size of a destructive cortical lesion of 2.5 cm, and circumferential cortex destruction of 50% or more. [1,5-9, Chapter2,4] In case of an impending pathological fracture of the humerus surgical fixation is necessary when there is persistent pain after irradiation, and circumferential cortex destruction of 50% or more.[6,8] In doubt of diagnosing an impending pathologic fracture in the long bones an alternative

*Table 1. Criteria for prophylactic surgery of lytic metastatic lesions of the subtrochanteric region of the femur.*

| |
|---|
| Increasing local pain despite analgesics and/or radiotherapy |
| The ratio maximal longitudinal cortex destruction to bone width exceeding one |

scoring system can be used. This method of prediction analyses each risk factor contributing to an actual pathological fracture.[10,11] However, the criteria for prophylactic surgical fixation of a pathological lesion in the long bones are still not well established. "Surgical overtreating" of metastatic bone lesions that will never progress to fractures is a true risk. Clinically, the advantages of prophylactic fixation of an impending fracture of the long bones are imperative: easier and faster to achieve a good function of the extremity, and less local and systemic complications.[12,Chapter2] Experiments with rats have shown that prophylactic fixation of bone metastases compared to actual treated bone lesions resulted in a decrease in the incidence of actual fractures and in dissemination.[13] Prophylactic fixation could raise the issue of possible dissemination of metastases of the involved bone during operation.[14] However, although tumour cells can be detected in the bloodstream during surgical treatment, in these patients with already disseminated disease, this appears not to influence disease course and outcome.[1,15-19] This may be due to the relative short survival time of these patients and possibilities of systemic treatment.[20-22,Chapter2] In an attempt to find clearly defined high risk criteria of impending fracture in metastatic bone lesions more studies are necessary in different regions of the long bones, with special emphasis on the integration of the results of clinical studies, in vitro experiments, and finite element modelling.

Considerable forces and moments act, in a large variation, on the long bones and the adjacent joints during a variety of physical activities.[23] In these physical compromised patients with bone metastases in the long bones a pathological fracture can occur spontaneously or after a minor trauma.[2,Chapter2] We expect that during physical activities in this specific patient group the axial and bending loading of the femur are less significant than torsion loading.[Chapter5,7] However, reports concerning these different loadings on the entire femur in healthy humans during daily living activities are still lacking.[24] Knowledge on torsion loading may be derived from studies of the hip joint forces. Torsion loads were found to vary over a large range, from zero to 20 Nm.[23,25] Furthermore, data from *in vivo* studies using hip protheses show that some of the highest hip reaction forces and torsional femur load occur when climbing stairs or getting out of a chair.[26-29] The loading conditions of the proximal femur can be altered because of changes in the gait pattern in disabled patients.[30] Concerning a cortical defect in the long bone the influence of torsion loads increases compared to axial and bending loads, especially when the velocity of torque is reduced.[31-33,Chapter5] Thus, it is difficult to determine the amount of torsional loading, especially for these patients with bone metastases in the femora. In addition, torsional loading is stated as an optimal testing modality for a satisfactory analysis of bone.[34] Beside the applied forces of the femoral bone, changes in structure and mechanical properties are also of particular importance. In intact long bones these properties changes are due to trabecular and cortical osteoporosis and different sizes and geometry of the bone.[35-39] Experimental studies reported a reduction of the torsion strength for a long period after irradiation of intact or fractured long bones.[40-43] This could cause a significant effect in clinical practice. Bone metastases of the long bones occur in a large variety of appearances.[44] In this experimental study we used an oblong transcortical defect with rounded corners.[Chapter5] In controversy, the clinical appearances of these bone lesions have with sharp and/or rough boundaries, partial destruction of the cortex, defect geometries of all kinds and local bone density changes. Although these appearances seem important in predicting the risk to fracture, there are just a few studies considering the mechanical properties within and around osseous metastatic bone defects.[45-48] In daily life the femur will be subject to repetitive loads of various magnitudes in multiple directions.[49-51] In addition, fracture initiation is caused by gradual formation and/or growth of microcracks.[52,53] This progressive accumulation of diffuse structural damage developed before final fracturing.[54,55] In contrast, our experimental study considered a single cycle to failure by applying a torsion load.[Chapter5] As shown in clinical and experimental studies the location of a cortical defect in the femur is an important factor in predicting fracture risk.[10, 56,Chapter 5]

For clinical evaluation of a metastatic lesion in a long bone an anteroposterior and lateral radiograph of the entire affected bone should be made (Table 2). These radiographs are limited in several ways; no standard radiograph or mutual perpendicular projection is performed, variable effects of geometry and destruction of the bone lesion on radiographical detection occur, margins of the lesion are poorly defined and cause error in the accurate measurement of the involved cortical bone, the different locations of the lesions and the degree of bone density are variable.[2,10,57,58,Chapter4-6] If the geometry of the cortical defect cannot adequately be determined, a computed tomography scan examination can be additionally performed.[59,60,Chapter6] Radiographic and CT scan examinations have a large interobserver variability, so they should be interpreted with caution.[2,10,58,Chapter6] Magnetic resonance imaging examination should not be used to predict such a lesion at risk to fracture.[61] Radionuclide scanning with technetium-99m is a very sensitive modality for identification of associated bone lesions, and should be used to determine whether the metastatic lesion is single or whether multiple sites are involved.[62-64]

Preoperative a stereotactic biopsy should be carried out when a carcinoma of an unknown origin, sarcoma or multiple myeloma, is suspected.[65] Peroperative tissue sampling of pathologic lesions is necessary to confirm the bone metastasis of the known primary tumour.[65] Prior to intramedullary stabilization a closed intramedullary biopsy should be performed. [66,67] In case of plate osteosynthesis or hemiarthoplasty with curettage of the lesion tissue sampling is easily performed.[18,Chapter2]

The treatment of bone metastases should be managed by a multi-disciplinary team. If so, the (orthopedic) surgeon, together with medical oncologist and radiation oncologist, should take in account the extend of the metastatic disease, previous treatment and possibilities still available, and coordinate treatment both systemic and local. Depending on the primary tumour, systemic treatment of the primary tumour can be chemotherapy, hormonal therapy, administration of radionuclides, or bisphosphonate therapy.[68] Local modalities include radiation therapy or surgery, or both.[68] A survival expectancy of a predefined period, i.e. six weeks, is no contraindication for surgical treatment because in terminally ill patients with a short life expectancy, the precise surviving period is unknown, while they could have benefit from rigid internal fixation.[Chapter2]

There are many different surgical techniques for the treatment of metastatic lesions of the long bones.[11,69,70,Chapter2] In the present studies generally no preference for nail or plate osteosynthesis was found. However, we believe that nearly all patients with a pathological fracture of the long bones are likely to benefit from rigid internal fixation with an appropriately selected device.[Chapter2,3] The complication rate after surgical treatment depends mainly on the loading capacity of the implant and the cortex. This is greatly influenced by size, location, progression of the metastatic defect and actual or impending fracture. It is important that in each case the (surgical) treatment should be individualized. For the optimal surgical treatment the following items should be taken into account; [1] improvement of quality of life due to surgery, [2] local tumour progression in spite of radiotherapy, humoral and chemotherapy, [3] life expectancy based on histology and systemic spread of the primary tumour in combination with the possibility of systemic treatment, [4] experience of the surgeon. In case of highly vascular tumours, like a renal carcinoma, preoperative arterial embolisation should be considered.[71]

Based on these considerations we provide a protocol for evaluation and treatment as follows (Table 2). The different types of operation techniques used for the treatment of pathological fractures should all allow direct loading of the affected limb.[Chapter2] Lesions within the femoral head are adequately treated with replacement of a hemi-arthroplasty.[62,72,73,Chapter2] Routine total hip replacement is not necessary, and is only indicated when the acetabulum has lost its strength.[2,74] Adjuvant bone cement (polymethylmethacrylate) after curretage of the bone lesion is necessary in case of total and hemi hiparthroplasty and plate osteosynthesis,.[8,62,Chapter2,4] The use of screw techniques of the femoral neck should be avoided.[76] A high incidence of failure of fixation complications is reported, approximately one-fifth, after treatment with plate and screws in the proximal femur. In these cases an endoprothesis with adjuvant bone cement should be placed when possible (Figure 1).[8,68,Chapter2] A megaprothesis or modular endoprothesis, used when the entire proximal femur is destroyed, are rarely necessary.[2,8,68,Chapter2] Furthermore, this surgical treatment also has a high incidence of complications.[77] In case of an impending or actual fracture in the intertrochanteric or subtrochanteric region, an interlocking nail with fixation of femoral neck and head or an angled plate fixation can be used. [11,69,78,Chapter2] One-third of the patients treated with Enders nails in this region developed a complication of fixation.[5] In contrast, recent studies reported no complications of fixation after using a reconstruction nail without bone cement, but the follow up period was short.[79-81] Although AO plates provide in experimental and clinical studies an excellent rigid fixation, we recommended an interlocking nail, with or without bone cement, as most effective surgical treatment in the femoral shaft lesions.[82,83,Chapter2] In general, multiple metastases in a shaft of a long bone are treated with an interlocking nail, with rigid proximal and distal fixation.[78] In an impending fracture with widely diffuse metastases of the femur or humerus a closed reamed nailing technique with

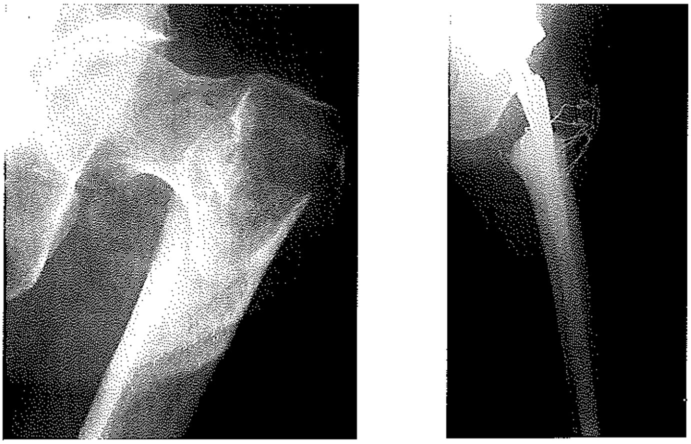


*Figure 1. Actual pathologic femur fracture of the intertrochanteric region due to bone metastases of carcinoma of the bladder. A long stem endoprothesis with bone cement was used because of the large involvement of the proximal femur.*

supplementary low viscosity bone cement can be used.[70,84,85,86] Supracondylar fractures are treated with angled blade plates or retrograde intramedullary nailing both with augmentation of bone cement to improve the screw fixation.[2, Chapter2] It is still not clear which fixation method, plating or nailing, should be advocated in the surgical treatment of pathologic fractures of the humeral shaft. The best advise is to use the device that is most familiar to the surgeon.[Chapter2,3] In case of multiple bone metastases of the humeral shaft an interlocking nail is performed.[87,Chapter3] Metastases distal to elbow or knee are unusual and we recommended plate osteosynthesis with supplementary bone cement after excising of the lesion.[88] It should be noted that postoperative complications of all the devices used in treatment of pathological fractures at long-term period can resulted in fatigue fracture and loosening.[8,18,Chapter2] In these cases a replacement of the device should be done. Additional use of bone cement after curretage of the bone lesion improved the bone strength.[89,90] To prevent additional local tumour growth, recent studies indicated that methotrexate loaded bone cement may have an important role as part of this management. [91]

It should be stressed that irradiation therapy of a lytic metastatic defect gives consolidation after a long period of time.[5,20,92] One-third of the patients with different sizes of metastatic lesions in the long bones who are irradiated subsequently ractured within a period of six months. The risk to fracture is related to the dose of irradiation.[10,93] Irradiation after surgical fixation of impending or actual pathological fractures is generally considered standard therapy, but the suggested benefit is not based on clinical evidence.[62,64,94,95] Reviewing literature, there is only one retrospective study available to support this combination of treatment.[95] Furthermore, recommendation of an optimal postoperative irradiation schedule is still not possible.[96,97] If irradiation therapy is indicated it should be performed postoperatively, starting one week after surgery. Irradiation therapy should be given after intramedullary interlocking nailing.[Chapter2] It should be given after plate osteosynthesis with adjunctive bone cement when there is evidence of persistent tumour adjacent to the device or local progression.[Chapter2]

Another prophylactic treatment of pathological lesions due to bone metastasis could be the use of bisphosphonates which inhibits bone resorption. Long-term administration of this drug showed impairment in the occurrence of fractures and reduction of bone pain.[64,98,99,100]

During the course of the studies included in this thesis, new questions have emerged, a number of questions have been answered and others remain elusive. Prospective randomized studies dealing with different kinds of surgical treatment are possible, but difficult to do due to heterogeneous population. However, the use of protocols and uniform registration are the only way to provide more knowledge about the population, the indications of surgery, the indication of irradiation, and the outcome of the different surgical treatments of metastatic lesions of the long bones.[101] Recommendation for further research could be; investigation of the rigid torsional stability of the system composed by bone, implant and screws, with special attention to the distal intramedullary nail locking; to expand the experiments described in this thesis to axial loading and to other long bones; application of the developed loading tests and finite element modelling to more sizes of partial or transcortical defects; and optimalization of the rigid fixation of the different devices using finite element modelling.

Table 2. Evaluation and surgical treatment of a patient with an impending or actual pathological fracture of the long bone probably due to bone metastasis.[Chapter 2-7, 2, 68, 83]

| | | | |
|---|---|---|---|
| **History** | age of patient | | mean 60 years |
| | previous malignancy | | 80% carcinoma of breast, prostate, bronchus, kidney |
| | systemic disease | | deteriation general condition, paraneoplastic symptoms |
| | pain | local | 75% of the patients: at night, at load bearing |
| | | systemic | other sites of the skeleton involved |
| | severity injury | | spontaneous fracture, minor trauma |
| | fracture at first sign 10% | | unknown primary tumours : only screening for carcinoma of breast, lung, renal, prostate, thyroid. |
| **Laboratory studies** | serum calcium, albumin | | hypercalcemia |
| | tumourmarkers | | depending on the primary tumour |
| **Radiograph** | method | | perpendicular in two directions |
| | location | usually | metaphyseal-diaphyseal junctions: femur, humerus |
| | lesions | | one-third solitary, one-third multiple, one-third diffuse |
| | appearances | common | lytic, cortical destruction, local osteoporosis |
| | | | large variety possible: mixed (lytic and blastic), blastic |
| | | | permeative,"moth eaten", no sharp border of transition |
| | additional screening | | pelvis, both femora, bone with local pain |
| | measurement sizes lesion | | width of the bone, height of the cortical destruction |
| | | | circumferential cortical destruction |
| **CT scan** | indication | | when sizes lesion on radiograph are not measurable |
| **MRI scan** | indication | | rarely |
| **Technetium 99m body scan** | indication | | screening for other sites of bone metastases |
| **Biopsy** | indication | preoperative | in doubt of primary malignant bone tumour |
| | | peroperative | always confirm malignancy |
| | pitfalls | | reach the site unaffected by fracture, risk to fracture |
| **Differential diagnosis** | primary malignant bone | | myeloma, sarcoma |
| | systemic skeletal disease | | osteoporosis, osteomalacia |
| | primary benign disease | | nonossifying fibroma, aneurysmal bone cyst, giant cell |
| **Consulting** | multi-disciplinary | | medical oncologist, radiation oncologist |
| **Surgical treatment** | impending fracture | | criterion prophylactic fixation; *page 114* |
| | type of fixation | | individualized surgical treatment |
| | no contraindication | | life expectancy and quality of the bone |
| | carcinoma of kidney | | preoperative angiographic embolization |
| | rigid osteosynthesis | | plate: adjuvant bone cement after curettage of the lesion |
| | | | nail: rigid proximal and distal fixation |
| | | | nail: extended lesion: adjuvant bone cement |
| | femur proximal | | endoprothesis, total hip arthroplasty |
| | | subtrochanteric | intramedullary, angled plate |
| | | shaft | intramedullary |
| | | condyle | intramedullary, angled plate |
| | other sites | solitary | intramedullary, plate |
| | | multiple | intramedullary |
| **Irradiation** | timing postoperative | | starting one week after surgical fixation |
| | indication | | *page 120* |

## References

1 Beals RK, Lawton GD, Snell WE. Prophylactic internal fixation in metastatic breast cancer. Cancer 1971; 28: 1350-1354.

2 Springfield D, Jennings C. Pathologic fractures. In: Rockwood CA and Green DP (ed): Fractures in Adults, Volume 1. Lippencott - Raven, New York. 1996. 513-519.

3 Zickel RE, Mouradian WH. Intramedullary fixation of pathological fractures and lesions of the subtrochanteric region of the femur. J Bone Joint Surg 1976; 58(Am): 1061-1066.

4 Keene JS, Sellinger DS, McBeath AA, Engber WD. Metastatic breast cancer in the femur: a search for the lesion at risk of fracture. Clin Orthop 1986; 203:282-288.

5 Behr JT, Dobozi WR, Badrinath K. The treatment of pathologic and impending pathologic fractures of the proximal femur in the elderly. Clin Orthop 1985; 198:173-178.

6 Fidler M. Incidence of fracture through metastases in long bones. Acta Orthop Scand 1981; 52: 623-627.

7 Krebs, H. Management of pathologic fractures of long bones in malignant disease. Arch Orthop Trauma Surg 1978; 92: 133-137.

8 Yazawa Y, Frassica FJ, Chao EYS et al. Metastatic bone disease: a study of surgical treatment of 166 pathologic humeral and femoral fractures. Clin Orthop 1990; 251: 213-219.

9 Menck H, Schulze S, Larsen E. Metastasis size in pathologic femoral fractures. Acta Orthop Scand 1988; 59: 151-154.

10 Mirels H. Metastatic disease in long bones: a proposed scoring system for diagnosing impending pathologic fractures. Clin Orthop 1989; 14: 513-525.

11 Friedl W. Pathologische frakturen des proximalen femurendes. Zentr Chirurgie 1995; 120: 873-880.

12 Bunting R, Lamont-Havers W, Schweon D, Kliman A. Pathologic fracture risk in rehabilitation of patients with bony metastases. Clin Orthop Rel Res 1985; 192: 222-227.

13 Bouma WH, Mulder JH, Hop WC. The influence of intramedullary nailing upon the development of metastases in the treatment of an impending pathological fracture: an experimental study. Clin Exp Metastasis 1983; 1:205-212.

14 Peltier JF. Theoretical hazards in the treatment of pathologic fractures by Kuntscher intramedullary nail. Surgery 1951; 29: 466-467.

15 Hoare JR. Pathological fractures. In: Proceedings of North-west Metropolitan Orthopaedic Club. J Bone Joint Surg 1968; 50B: 232.

16 Fidler M. Prophylactic internal fixation of secondary neoplastic deposits in long bones. Brith Med J 1973; 1: 341-343.

17 Parrish FF and Murray JA. Surgical treatment for secondary neoplastic fractures. J Bone Joint Surg 1970; 52(Am): 665-686.

18 Harrington KD, Sim FH, Enis JE, Johnston JO, Dick LM, Gristina AG. Methylcrylate as an

adjunct in internal fixation of pathological fractures. J Bone Joint Surg 1976; 58(Am): 1047-1054.

19 Springfield DS. Mechanisms of metastasis. Clin Orthop 1982; 169: 15-19.

20 Schocker JD, Brady LW. Radiation therapy for bone metastasis. Clin Orthop 1982: 169:38-43.

21 Bhardwaj S, Holand JF. Chemotherapy of metastatic cancer in bone. Clin Orthop Rel Res 1982; 169: 28-33.

22 Nielsen OS, Munro AJ, and Tannock IF. Bone metastases: Pathophysiology and management policy. J Clin Oncology 1991; 9:509-524.

23 Simon SR, Alaranta H, An K, et al. Kinesiology. In: Simon SR (ed): Orthopaedic basic science. American Academy of Orthopedic Surgeons, Rosemont, IL, 1994. pp 582-584.

24 Gdoutos EE, Raftopoulos DD, Baril JD. A crtical review of the biomechanical stress analysis of the human femur. Biomaterials 1982; 3: 2-8.

25 Crowninshield RD, Johnston RC, Anrews JG, Brand RA. A biomechanical investigation of the human hip. J Biomechanics 1978; 11: 75-85.

26 Hodge WA, Fijan RS, Carlson KL, Burgess RG, Harris WH, Mann RW. Contact pressores in the human hip joint measured in vivo. Proc Natl Acad Sci USA 1986; 83: 2879-83.

27 Davy DT, Kotzar GM, Brown RH, et al. Telemetric force measurements across the hip after total hip arthroplasty. J Bone Joint Surg (Am) 1988; 70-A: 45-50.

28 Bergmann G, Graichen F, Rohlmann A. Hip joint forces during walking and running, measured in two patients. J Biomech 1993; 26: 969-990.

29 Kotzar GM, Davy DT, Berilla J, Goldberg VM. Torsional loads in the early postoperative period following total hip replacement. J Orthop Res 1995; 13: 945-955.

30 Paul JP, McGrouther DA. Forces transmitted at the hip and knee joint of normal and disabled persons during a range of activities. Acta Orthopaedica Belgica 1975; 41 Suppl : S78-88.

31 Litsky AS, Spector M. Biomaterials. In: Simon SR (ed): Orthopaedic basic science. American Academy of Orthopedic Surgeons, Rosemont, IL, 1994. pp 458-459.

32 Behiri JC, Bonfield W. Crack velocity and the longitudinal fracture in bone. J Mater Science 1980; 15: 1841-1849.

33 Bonfield W, Grynpas MD. Spiral fracture of cortical bone. J Biomechanics 1982; 15: 555-559.

34 Burstein AH, Frankel VH. Technical note: a standard test for labarotory animal bone. J Biomechanics 1971; 4: 155- 158.

35 Esses SI, Lotz JC, Hayes WC. Biomechanical properties of the proximal femur dtermined in vitro by single-energy quantitative computed tomography. J Bone Mineral Res 1989; 4: 715-722.

36 Horsman A, Nordin C, Simpson M, Speed R. Cortical and trabecular bone status in elderly women with femoral neck fractures. Clin Orthop 1982; 166: 143-151.

37 Melton LJ III, Riggs BL. Epidemiology of age-related fractures. In: Avioli LV (ed) The osteoporotic Syndrome: detection, prevention, and treatment. Grune & Stratton, New York, pp 45-72.

38 Alho A, Hoiseth A, Husby T. Bone-mass distribution in the femur. A cadaver study on the relations of structure and strength. Acta Ortop Scand 1989; 60: 101-106.

39 Kennedy JG, Carter DR. Long bone torsion: I effects of heterogeneity, anisotropy and irregularity. J Biomech Engin. 1985; 107: 183-188.

40 Komender A. Influence of preservation on some properties of human haversian bone. Mater Med Pol 1976; 8: 13-15.

41 Pelker RR, Friedlaender GE, Markham TC. Biomechanical properties of bone allografts. Clin Orthop Rel Res 1983; 174: 54-57.

42 Brown RK, Pelker RR, Friedlaender GE, Peschel RE, Panjabi MM. Postfracture irradiation effects on biomechanical and histologic parameters of fracture healing. J Orthop Res 1991; 9:876-882.

43 Widman RF, Pelker RR, Friedlaender GE, Panjabi MM, Peschel RE. Effects of prefracture irradiation on biomechanical parameters of fracture healing. J Orthop Res 1993; 11: 422-428.

44 Wilner D. Cancer metastases to bone. In: Wilner D (ed). Radiology of bone tumours and allied disorders.. WB Saunders, Philadelphia. pp 3641-3711.

45 Clark CR, Morgan C, Sonstegard DA, Matthews LS. The effect of biopsy hole shape and size on bone strenght. J Bone Joint Surg (Am) 1977; 59(2): 213-217.

46 Hipp JA, McBroom RJ, Cheal EJ, Hayes WC. Structural consequences of endosteal metastatic lesions in long bones. J Orthop Res 1989; 7: 828-837.

47 Hipp JA, Katz G, Hayes WC. Local demineralization as a model for bone strength reductions in lytic transcortical metastatic defects. Invest Radiol 1991; 26: 934-938.

48 Hipp JA, Rosenberg AE, Hayes WC. Mechanical properties of trabecular bone within and adjacent to osseous metastases. J Bone Mineral Res 1992; 7: 1165-1171.

49 Williams JF. A force analysis of the hip joint. Biomed Eng 1968; 3: 365-373.

50 Ghista DN, Toridis TG, Srinivasan TM. Human gait analysis: determination of instataneous joint reactive forces, muscle forces and the stress distribution in bone segments. Biomedinizinische Technik 1976; 21: 3-12.

51 Toridis TG. Stress analysis of the femur. J Biomechanics 1969; 2: 163-171.

52 Netz P. The diaphyseal bone under torque. Thesis. Stockholm. Sweden 1979.

53 Netz P, Eriksson K, Stromberg L. Ultimate failure of diaphuseal bone. An experimental study on dogs. Acta Orthop Scand 1980; 51: 583-588.

54 Jonsson U, Eriksson K. Microcracking in dog bone under load. Acta Orthop Scand 1984; 55: 441-445.

55 Carter DR, Hayes WC. Compact bone fatigue damage. Clin Orthop Rel Res 1977; 127: 265-274.

56 Cheal EJ, Hipp JA, Hayes WC. Evaluation of finite element analysis for prediction of the strength reduction due to metastatic lesions in the femoral neck. J Biomechanics 1993; 26: 251-264.

57 Edelstyn GA, Gillespie PJ, Grabbell FS. The radiological demonstration of osseous metastases. Experimental observations. Clin Radiol 1967; 18: 158-162.

58 Hipp JA, Springfield DS, Hayes WC. Predicting Pathologic Fracture Risk in the Management of Metastatic Bone Defects. Clin Orthop Rel Res 1995; 312: 120-135.

59 Habermann ET, Rafael AL. Metastatic disease of bone and treatment of pathological fractures. Orthop Clinics North America 1989; 20: 469-486.

60 Rafii M, Firooznia H, Kramer E, Golimbu C, Sanger J. The role of computed tomography in evaluation of skeletal metastases. J Computed Tomogr 1988; 12: 19-24.

61 Zimmer WD, Berquist TH, McLeod RA, et al. Bone tumours: magnetic imaging versus computed tomography. Radiol 1985: 155; 709-718.

62 Galasko CSB. The management of skeletal metastases. Royal Coll Surg Edin 1980; 25:143-161.

63 Goris ML, Bretille J. Skeletal scintigraphy for the diagnosis of malignant metastatic disease to the bone. Radiotherapy Oncology 1985; 3: 319-329.

64 Body JJ. Metastatic bone disease: clinical and therapeutic aspects. Bone 1992; 12 Suppl 1: S52-S62.

65 Simon MA. Biopsy of musculoskeletal tumors. J Bone Joint Surg 1982; 64 A: 1253-1255.

66 Smith DG, Behr JT, Hall RF, Dobozi WR. Closed flexible intramedullary biopsy of metastatic carcinoma. Clin Orthop Rel Res 1988; 229:162-165.

67 Herbert J, Couser J, Seligson D. Closed medullary biopsy of dissemenated malignancy. Clin Orthop Rel Res 1982; 163: 214-217.

68 Aaron AD, Treatment of metastatic adenocarcinoma of the pelvis and the extremities. Review. J Bone Joint Surg 1997; 79A: 917-932.

69 Graupe F. Heitmann C, Becker M, et al. Palliative chirurgische behandelung von kochenmetastasen. Dtsch med Wschr 1996; 121: 393-397.

70 Vandeweyer E, Gebhart M. Treatment of humeral pathological fractures by internal fixation and methylmethacrylate injection. Eur J Surg Oncol 1997; 23:238-242.

71 Roscoe MW, McBroom RJ, St. Louis E, et al. Preoperative embolization in the treatment of osseous metastases from renal cell carcinoma. Clin Orthop Rel Res 1989; 238: 302-307.

72 Borel Rinkes IHM, Wiggers T, Bouma WH, van Geel AN, Boxma H. Treatment of manifest and impending pathological fractures of the femoral neck by cemented hemiarthroplasty. Clin Orthop 1990; 260: 220-223.

73 Lane JM, Sculco TP, Zolan S. Treatment of pathological fracture of the hip by endoprosthetic replacement. J Bone Joint Surg 1980; 62A:954-959.

74 Harrington KD. Orthopaedic management of extremity and pelvic lesions. Clin Orthop 1995;

312: 136-147.

75 Harrington KD. New Trends in the management of lower extremity metastasis. Clin Orthop Rel Res 1982; 169; 53-61.

76 Miller F, Whitehill R. Carcinoma of the breast metastatic to skeleton. Clin Orthop Rel Res 1984; 184: 121-127.

77 Sim FH, Chao EYS. Bone loss in the proximal femur: proximal femoral replacement. In: Morrey B. Joint Replacement Arthroplasty 1991. Churchill Livingstone, NewYork. pp 820-833.

78 Hulst van der RRWJ, Wildenberg van der FAJM, Vroemen JPAM, et al. Intramedullary nailing of pathologic fractures. J Trauma 1994; 36: 211-215.

79 Weikert DR, Scwartz HS. Intramedullary nailing for impending pathological subtrochanteric fractures. J Bone Joint Surg 1991; 73B: 668-670.

80 Karachalios T, Atkins RM, Sarangi PP, Crichlow TPKR, Solomon L. Reconstruction nailing for pathological subtrochanteric fractures with coexisting femoral shaft metastases. J Bone Joint Surg 1993; 75 (B): 119-122.

81 Nargol AVF, Port A, Seif-Assaad SS. Pathological fractures of the proximal femur treated with the Variwell reconstruction nail. Injury 1996; 27: 307-309.

82 Anderson JT, Erickson, Thompson RC, Chao EY. Pathologic femoral shaft fractures comparing fixation techniques using cement. Clin Orthop Rel Res 1978; 131: 273-277.

83 Harrington, KD. Orthopaedic reconstruction. In: Harrington KD (ed): Orthopaedic management of metastatic bone disease 1988. pp 140-308.

84 Lewallen PR, Pritchard DJ, Sim FH. Treatment of pathological fractures or impending fractures of the humerus with Rush rods and methylmatecrylate. Clin Orthop Rel Res 1982; 166: 193-198.

85 Kunec JR, Lewis RJ. Closed intramedullary rodding of pathologic fractures with supplemental cement. Clin Ortop Rel Res 1984; 188: 183-186.

86 Miller GJ, van der Griend RA, Blake WP, Springfield DS. Performance evaluation of a cement-augmented intramedullary fixation system for pathologic lesions of the femoral shaft. Clin Orthop Rel Res 1987; 221: 246-254.

87 Redmond BJ. Bierman JS, Blasier RB. Interlocking intramedullary nailing in pathological fractures of the shaft of the humerus. J Bone Joint Surg 1996; 78 (Am): 891-896.

88 Leeson MC, Makley JT, Carter JR. Metastatic skeletal disease: distal to elbow and knee. Clin Orthop Rel Res 1986; 206: 94-99.

89 Ryan JR, Begeman PC. The effects of filling experimental large cortical defects with methylmethacrylate. Clin Orthop 1984; 185:306-310.

90 Leggon RE, Lindsey RW, Panjabi MM. Strength reduction and the effects of treatment of long bones with diaphyseal defects involving 50% of the cortex. J Orthop Res 1988; 6:540-

546.

91 Wang HM, Galasko CS, Crank S, Oliver G, Ward CA. Methotrexate loaded acrylic cement in the management of skeletal metastases. Biomechanical, biological, and systemic effect. Clin Othop Rel Res 1995; 312:173-186.

92 Gainor BJ, Buchert P. Fracture healing in metastatic bone disease. Clin Orthop 1983; 178:297-302.

93 Tong D, Gillick L, Hendrickson FR. The palliation of symptomatic osseous metastases: final results of the study by RTOG. Cancer 1982; 50: 893-899.

94 Perez CA, Bradfield JS, Morgan HC. Management of pathologic fractures. Cancer 1972; 29: 684-693.

95 Townsend PW, Smalley SR, Cozad SC, Rosenthal HG, Hassanein RES. Role of postoperative radiation therapy after stabilization of fractures caused by metastatic disease. Int J Radiation Oncology Biol Phys 1995; 31: 43-49.

96 Poulsen HS, Nielsen OS, Klee M, Rorth M. Palliative irradiation of bone metastases. Cancer Treat Rev 1989; 16; 41-48.

97 Blitzer PH. Reanalysis of the RTOG study of palliation of symptomatic osseous metastasis. Cancer 1985; 55: 1468-1478.

98 Kanis JA. Bone and cancer: pathophysiology and treatment of metastases. Bone 1995; 17 2 (suppl): 101S-105S.

99 Body JJ, Margritte A, Dumon JC, Tueni E, Piccart M, Ford J. ADP for metastatic osteolysis: how much ? how often ? J Cancer Res Clin Oncol 1990; 116: 347.

100 van Holten Verzantvoort AT, Bijvoet OL, Cleton FJ, Hermans J. Kroon HM, Harinck HI, Vermey P, Elte JW, Neijt JP, Beex LV, Blijham G. Reduced morbidity from skeletal metastases in brreast cancer patients during long-term biphosphonate (APD) treatment. Lancet 1987; 2: 983-985.

101 Enneking WF, Dunham W, Gebhart MC, Malawar M, Pritchaerd DJ. A system for evaluation of reconstructive procedures after surgical treatment ot tumors of the musculoskeletal system. Clin Orthop Rel Res 1993; 286: 241-246.

# Appendix A

The estimation of the degree of osteoporosis depends on reliable methods for assessment of skeletal mineralization. The assessment that is required cannot be achieved by standard radiographic or related semiquantitative methods, like the Singh Index, because their sensitivity for detection of bone loss is low.[1,2] The ability of dual-photon absorptiometry to measure the cortical and trabecular bone is advanced in small long bones and the axial skeleton.[3,4] With the introduction of quantitative computed tomography (QCT) scanners a number of investigators attempted to use these instruments for bone mineral measurements in a specified region of the bone.[5-8]

The application in this study was to measure the cortical bone loss by QCT in all subjects used. Either the influence of osteoporosis on the control femora, or on the femora with the variety of defects was estimated. Normal bone mineral shows by QCT considerable variation at different sites of the skeleton.[9] The biologic variation among individuals is rather large.[10] Therefore, seperate measurements of both the defect site and the adjacent bone are necessary for accurately prediction of fracture risk.[11]

Transverse QCT measures the computed tomography (CT) number by the distribution of attenuation coefficient within the cross-section of an object, expressed in Hounsfield Units (HU). The total CT number (pixel intensity) in a circumscript cross-section of known thickness is computed for each point from a set of rontgengraphic transmission measurements. The absorption values are displayed as an image, on a gray-scale matrix. In our study 140 keV was used, as in practice. [10] Arial density is the preferred measurement, and is expressed as g/cm $^3$.[12] Because of the known variability in CT numbers among different types of CT scanners, among CT scanners of the same model, within the individual CT scanners, and within time, phantoms that contain known concentrations of calcium hydroxyapatite have been used to provide reference data for calibration of CT numbers.[13-16] In studies that use such calibration phantoms, single energy conventional CT has been useful for accurate measurement of calcium hydroxyapatite concentration with a precision of 1%-3%.[17-19] However, accurate quantitation of calcium hydroxyapatite concentration is limited by partial volume effects, X-ray beam hardening and scatter, scan width,

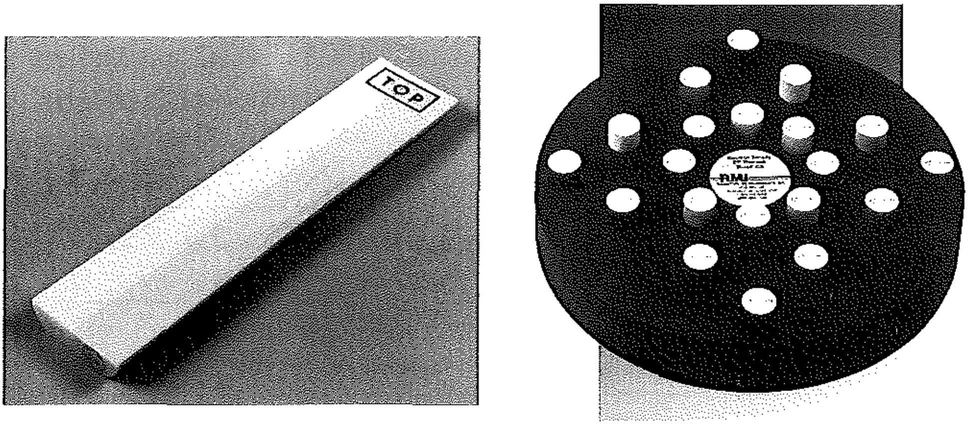


*Figure 1. At the right site the calibration phantom of Siemens medical systems, and the left site the calibration phantom of Gammex MRI.*

field of view and position in the field, and variations in object thickness.[15,20]

A calibration phantom ( Siemens medical Systems, Erlangen, Germany) was used to serve to control the QCT system stability and to provide a calibration standard for conversion of HU in density values (Figure 1).[16,18] This calibration phantom consisted two equal-sized regions (9 cm wide × 2,5 cm thickness × 40 cm length) and contained either 0 or 200 mg/cm$^3$ of calcium hydroxy-apatite (Table 1).

*Table 1. CT numbers (HU) measured by Siemens Somaton Plus 4 and physical density values of rod materials of Siemens CT phantom*

| Elemental composition rod | Fysical density (g/cm$^3$) | HU 1cm$^2$ | |
|---|---|---|---|
| | | mean in air | mean in tissue |
| water equivalent plastic | 0.98 | -6 | -32 |
| bone equivalent plastic | 1.113 | 245 | 105 |

The phantom was placed at the table mat adjacent to the sepecimen. Because cortical bone has a high density (from 1.4 to 2) we used an additional calibration phantom, RMI 465-1187 (Gammex RMI, Middtelon, United States), for conversion of the higher HU in density values. The RMI Electron Density Phantom consisted of a 33 cm diameter solid water disk (5 cm hight) with a matrix of twenty 2,8 cm diameter holes (7 cm length), hold in our study thirteen rods of various tissue and water substitutes (Figure 1). The physical density (g/cm$^3$) and CT numbers of rod materials measured by a Somaton Plus 4 scanner (Siemens, Erlangen, Germany) are listed in Table 2.

*Table 2. CT numbers (HU) measured by Siemens Somaton Plus 4 and physical density values of rod materials of Gammex RMI 465-1187 CT phantom*

| Elemental composition rod | Fysical density (g/cm$^3$) | HU in 1 cm$^2$ mean in air | HU in 1 cm$^2$ mean in tissue |
|---|---|---|---|
| CT solid water | 1.015 | -7 | 4 |
| CT solid water | 1.015 | -5 | -1 |
| CB3 resin mix | 1.02 | -4 | 22 |
| BRN-SR2 brain | 1.045 | 22 | 46 |
| LV1 liver | 1.08 | 84 | 92 |
| IB inner bone | 1.12 | 221 | 194 |
| B200 bone mineral | 1.145 | 244 | 215 |
| CB4 resin mix | 1.15 | 102 | 137 |
| CB2-10% CaCO3 | 1.17 | 175 | 191 |
| acrylic | 1.18 | 124 | 147 |
| CB2-30% CaCO3 | 1.34 | 488 | 456 |
| CB2-50% CaCO3 | 1.56 | 890 | 829 |
| SB3 cortical bone | 1.84 | 1330 | 1234 |

CT data obtained from each femur at the three locations described in chapter 5 were measured for cross-sectional area in cortical bone and calibration phantom (Figure 2, Table 3). The locations of measurements were; 3 times the diameter of the outer bone added 20mm for the proximal side, this same formule for the distal part and half of the bone length for the middle. At each side two measurements were performed. The results are shown in chapter 5. Even in a given phantom rod containing cortical bone, a variation in the CT number of 200 HU has been observed (Table 2)[8]

To convert the CT number data to bone mineral density, and to correct the fysical density estimated in air to a value in tissue conditions which makes comparison to clinical density data possible. The following corrections should taken in account.

Because fysical density is a three dimension value, according g/cm$^3$, analysis of one pair specimen (specimen number 10, chapter 5) at proximal, middle and distal part of the femur with varying the slice thickness from 1-10 millimeter was performed. In a Spearson rank-correlation test a high correlation coefficient for proximal (R=0.89), middle (R=0.95) and distal (R=0.99) occurred (Figure 5). No change

*Table 3. Conversion of CT numbers to fysical density of the paired human femora on torsional loading in experiment A.*

| *No.* | *Ratio: height defect to bone diameter* | *CT number* | | | *Fysical density (g/cm$^3$)* | | |
|---|---|---|---|---|---|---|---|
| | | *proximal* | *middle* | *distal* | *proximal* | *middle* | *distal* |
| 1 | 0.5 | 1480 | 1509 | 1444 | 1.83 | 1.85 | 1.81 |
| | control | 1492 | 1515 | 1445 | 1.84 | 1.85 | 1.81 |
| 2 | 0.5 | 1512 | 1539 | 1546 | 1.85 | 1.87 | 1.87 |
| | control | 1536 | 1566 | 1578 | 1.87 | 1.88 | 1.89 |
| 3 | 0.5 | 1548 | 1519 | 1501 | 1.87 | 1.86 | 1.85 |
| | control | 1512 | 1531 | 1503 | 1.85 | 1.86 | 1.85 |
| 4 | 1 | 1412 | 1410 | 1435 | 1.79 | 1.79 | 1.81 |
| | control | 1427 | 1430 | 1428 | 1.8 | 1.8 | 1.8 |
| 5 | 1 | 1533 | 1556 | 1471 | 1.87 | 1.88 | 1.83 |
| | control | 1424 | 1466 | 1500 | 1.8 | 1.83 | 1.85 |
| 6 | 1 | 1472 | 1500 | 1458 | 1.83 | 1.85 | 1.82 |
| | control | 1446 | 1479 | 1420 | 1.81 | 1.83 | 1.8 |
| 7 | 1 | 1557 | 1594 | 1545 | 1.88 | 1.9 | 1.87 |
| | control | 1577 | 1576 | 1519 | 1.89 | 1.89 | 1.86 |
| 8 | 1.5 | 1344 | 1395 | 1366 | 1.75 | 1.78 | 1.77 |
| | control | 1362 | 1394 | 1377 | 1.76 | 1.78 | 1.77 |
| 9 | 1.5 | 1449 | 1494 | 1481 | 1.82 | 1.84 | 1.83 |
| | control | 1431 | 1482 | 1462 | 1.8 | 1.84 | 1.82 |
| 10 | 1.5 | 1589 | 1565 | 1562 | 1.9 | 1.88 | 1.88 |
| | control | 1619 | 1587 | 1560 | 1.92 | 1.9 | 1.88 |
| 11 | 1.5 | 1503 | 1567 | 1561 | 1.85 | 1.89 | 1.88 |
| | control | 1496 | 1565 | 1578 | 1.84 | 1.88 | 1.89 |
| 12 | 2 | 1372 | 1433 | 1451 | 1.77 | 1.81 | 1.82 |
| | control | 1464 | 1511 | 1420 | 1.82 | 1.85 | 1.8 |
| 13 | 2 | 1456 | 1488 | 1497 | 1.82 | 1.84 | 1.84 |
| | control | 1456 | 1495 | 1463 | 1.82 | 1.84 | 1.82 |
| 14 | 2 | 1498 | 1549 | 1592 | 1.84 | 1.87 | 1.9 |
| | control | 1503 | 1560 | 1579 | 1.85 | 1.88 | 1.89 |

was estimated for the Siemens calibration phantom (mean=235). The difference between measurements of the three femur parts for one and two millimeter slices was less than 1%, and no correction to volume measurements was obtained. In

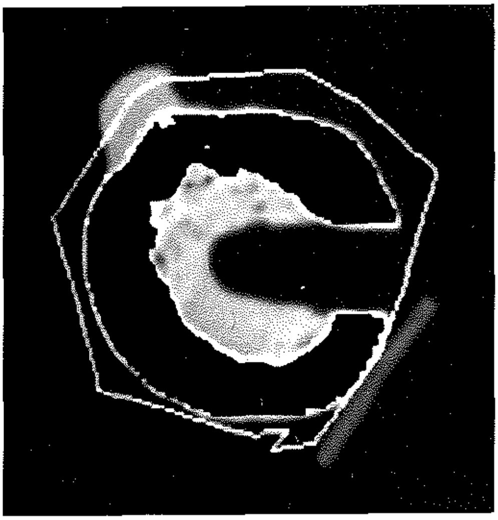


*Figure 2. Cross-sectional area in cortex of the femur with the use of QCT scan examination.*

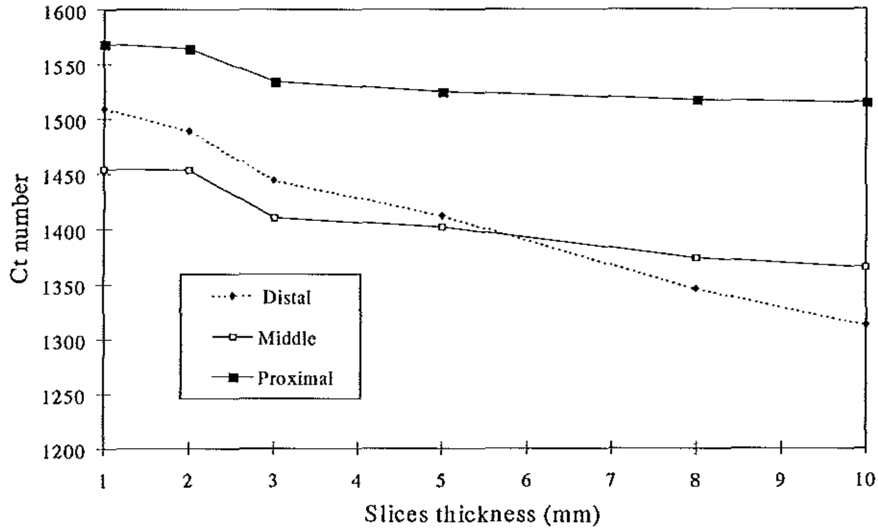


*Figure 4. Correlation between reduction of the CT number by increasing the slice thichness. This data was obtained from femur pair number 10, see for more information chapter 5.*

case of 5 mm slices an increase to 7% reduction in CT number value is found. It should be noticed that in literature this volume correction is often neglected. The HU in air condition is higher than in tissue, with the use of the Siemens Phantom a mean difference of 130 was found.[9] To correct for the increase of the HU between air and tissue condition, as seen above 200, measured with the calibration phantom Gammex RMI 465-1187, a reduction of 7.5% should be used in the CT data of the femora. According to the calibration phantoms described above the following formule for the conversion of the mean CT numbers in the range of 200 to 2000 HU (1 cm $^2$) to fysical density values measured by Somaton Plus 4 scanner was used (Figure 5):

$$\rho = ( (0.925 \times HU)-130) \times 0.00064 + 1.041$$

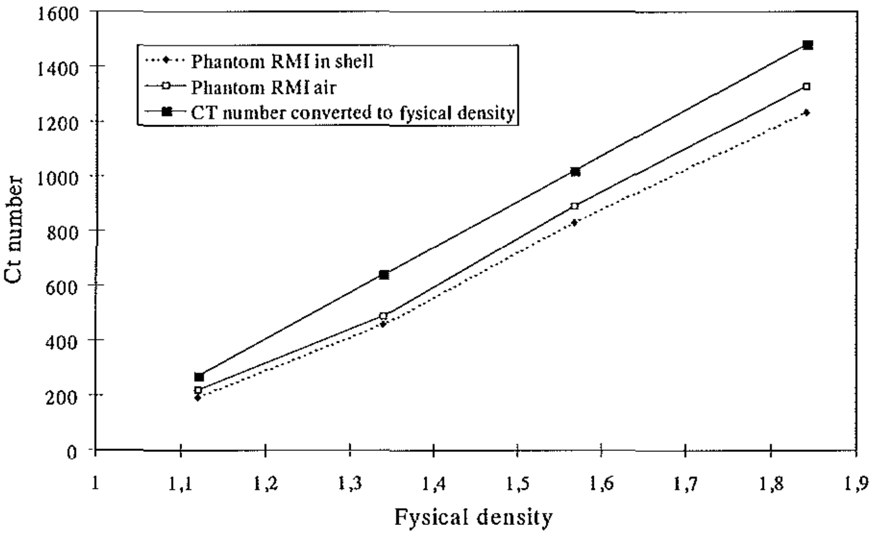


*Figure 5. Measurements of Phantom RMI in air and tissue conditions. Linear regressin line to convert CT numbers of experiement A to fysical density.*

## References

1 Singh M, Magrath AR, Maini PS. Changes in trabecular pattern of the upper end of the femur as an index of osteoporsis. J Bone Joint Surg 1970; 52 (Am): 457-467.

2 Leichter MS, Margulies JY, Weinreb A, et al. The relationship between bone density, mineral content, and mechanical strength in the femoral neck. Clin Orthop 1982; 163:272-281.

3 Wilson CR, Madsen M. Dichromatic absorptiometry of vertebral bone mineral content. Invest Radiol 1977; 12:180-187.

4 Madsen M, Peppler W, Mazess RB. Vertebral and total body bone minerla content by dual absorptiometry. Calc Tissue Res 1976; 21: 361-369.

5 Genant HK, Boyd D. Quantitative bone mineral analysis using dual energy computed energy computed tomography. Invest Radiol 1977; 12: 545-552.

6 Bradley JG, Huang HK, Ledley RS. Evaluation of calcium concentration in bones from CT scans. Radiology 1978; 128: 103-109.

7 Hipp JA, Springfield DS, Hayes WC. Predicting pathologic fracture risk in the management of metastatic bonr defects. Clin Orthop Rel Res 1995; 312: 120-135.

8 Snyder SM, Schneider E. Estimation of mechanical properties of cortical bone by computed tomography. J Orthop Res 1991; 9:422-431.

9 Riggs BL, Wahner HW, Seeman E, et al. Changes in bone mineral density of the proximal femur and spine with aging: differences between the postmenopausal and senile osteoporosis syndromes. J Clin Invest 1982; 70: 716-724.

10 Wahner HW, Riggs BL. Methods and apllication of bone densitometry in clinical diagnosis. CRC Critical reviews in clinical sciences 1986; 24: 217-233.

11 Hipp JA, Katz K, Hayes WC. Local demineralization as a model for bone strength reductions in lytic transcortical metastatic lesions. Invest Radiol 1991; 26:934-937.

12 Wahner HW, Dunn WL, Riggs BL. Assesment of bone mineral. J Nucl Med 1984; 25: 1241-1244.

13 Zerhouni EA, Spivey JF, Morgan RH, et al. Factors influencing quantitative CT measurements of solitary pulmonary modules. J Comput Assis Tomogr 1982; 6: 1075-1087.

14 Kalender W, et al. Vertebral bone mineral analysis: an intregrated approach with CT. Radiology 1987; 164: 419-423.

15 McCollough CH, Kaufmann RB, Cameron BC, et al. Electron-beam CT: Use of calibration phantom to reduce variabilty in calcium quantitation. Radiology 1995; 196: 159-165.

16 Cann CE, Genant HK. Precise measurement of vertebral mineral content using computed tomography. J Comput Assist Tomogr 1980; 4: 493-500.

17 Genant HK, et al. Appropriate use of bone densitometry. Radiology 1989; 170: 817-822.

18 Kalender WA, Suess C. A new calibration phantom for quantitative computed tomography. Med phys 1987; 14: 863-866.

19 Dambacher MA. Ruesgsegger P. Knochendischtemessungen und ihre indikationen. Orthopade 1994; 23: 38-44.

20 Hendee WR. The physical principles of computed tomography. Boston, Mass: Little, Brown 1983: pp 94-112.

# Appendix B

*Table 1. Strain gauges measurements in experiment A*

| No. | Ratio defect height/ bone diameter | C1 | C2 | C3 | C4 | C5 | C6 | C1 / C4 | C3 / C6 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.5 | 2.875 | 0.321 | -2.254 | 1.113 | -0.294 | -3.423 | 2.583 | 0.658 |
|  | control | -4.828 | -0.48 | 3.961 | -4.910 | 0.434 | 4.472 | 0.983 | 0.886 |
| 2 | 0.5 | 1.908 | -0.113 | -1.816 | 2.501 | 0.4 | -2.501 | 0.763 | 0.726 |
|  | control | -2.081 | 0.478 | 2.117 | -2.729 | 0.338 | 2.273 | 0.763 | 0.931 |
| 3 | 0.5 | 0.776 | -0.161 | -1.214 | 1.259 | -0.19 | -1.57 | 0.616 | 0.773 |
|  | control | -1.396 | -0.281 | 0.967 | -1.241 | -0.294 | 1.113 | 1.125 | 0.869 |
| 4 | 1 | 0.949 | -0.144 | -0.511 | 1.150 | 0.257 | -1.615 | 0.825 | 0.316 |
|  | control | 1.113 | 0.308 | -1.451 | 1.369 | 0.173 | -1.615 | 0.813 | 0.898 |
| 5 | 1 | -1.497 | 0.186 | 1.552 | -2.692 | 0.559 | 2.336 | 0.556 | 0.664 |
|  | control | 2.263 | -0.073 | -2.921 | 2.51 | -0.159 | -2.893 | 0.901 | 1.009 |
| 6 | 1 | 2.327 | -0.099 | -0.776 | 2.738 | -0.555 | -2.473 | 0.85 | 0.314 |
|  | control | -1.296 | 0.164 | 3.14 | -1.369 | -0.427 | 2.911 | 0.947 | 1.079 |
| 7 | 1 | 1.67 | 0.078 | -1.743 | 3.477 | -0.473 | -2.802 | 0.48 | 0.622 |
|  | control | -3.687 | -0.52 | 2.537 | -3.335 | -0.12 | 3.158 | 1.106 | 0.803 |
| 8 | 1.5 | 1.186 | -0.595 | -1.935 | 2.482 | -0.126 | -2.409 | 0.341 | 0.803 |
|  | control | -3.158 | -0.568 | 2.72 | -2.455 | -0.734 | 3.185 | 1.286 | 0.854 |
| 9 | 1.5 | 0.767 | -1.004 | -0.183 | 3.194 | -0.186 | -2.683 | 0.24 | 0.068 |
|  | control | 2.647 | 0.601 | -2.455 | 2.674 | 0.387 | -2.674 | 0.99 | 0.918 |
| 10 | 1.5 | -1.196 | -0.153 | 0.995 | -2.619 | -0.133 | 2.692 | 0.457 | 0.370 |
|  | control | 2.127 | -0.325 | -2.2 | 2.437 | 0.033 | -2.574 | 0.873 | 0.855 |
| 11 | 1.5 | d | 0.066 | 0.091 | -1.57 | -0.19 | 1.725 | d | 0.053 |
|  | control | d | -0.23 | -2.081 | 1.798 | -0.197 | -2.044 | d | 1.018 |
| 12 | 2 | -0.584 | d | -0.256 | 1.488 | 0.128 | -1.479 | 0.392 | 0.173 |
|  | control | 1.086 | d | -1.844 | 1.196 | -0.053 | -1.971 | 0.908 | 0.936 |
| 13 | 2 | 0.475 | -0.621 | -0.812 | 2.245 | 0.091 | -2.419 | 0.212 | 0.336 |
|  | control | 0.456 | 0.491 | -0.885 | 1.396 | 0.307 | -1.798 | 0.327 | 0.492 |
| 14 | 2 | 0.338 | -0.841 | -0.329 | 1.25 | 0.066 | -1.396 | 0.27 | 0.236 |
|  | control | -1.278 | 0.181 | 1.15 | -1.378 | 0.029 | 1.433 | 0.927 | 0.803 |

# Summary

Skeletal metastases are the most common form of malignant bone tumours and have probably occurred for many thousands of years. In three-quarters of the patients with skeletal metastases the primary tumour is mamma, bronchus, prostate or kidney carcinoma. The incidence increases due to prolonged survival as a result of more effective treatment of the primary tumours. With more than 61.000 new cases of cancer each year in the Netherlands, at least 7% to 27% of these patients develop a metastatic bone defect. Osteolytic metastases are the predominant types of bone lesions in most cancers. Pain is the main clinical sign in three-quarters of these patients. In 5%-10% an actual pathological fracture sustained. Although these patients usually not die of skeletal metastases, patients quality of life can greatly influenced. In the 20th century different surgical techniques were developed for osteosynthesis to treat pathological fractures. Conservative treatment, e.i. traction and cast fixation, had resorted in little effect in these patients. Because of this development the problem rises whether and when prophylactic internal fixation should be carried out. Nowadays, prophylactic fixation of impending fractures is generally preferred instead of treatment of actual fractures, because of important advantages; quick pain relief, earlier mobility, decreased hospital stay and reduction of operative complications. There is a lot of contradiction in the guidelines to prophylactic treatment of the long bones. These guidelines arose from several, often small, retrospective studies. As the number of people with osteoporosis and the number of people with cancer in the population increases, the incidence of impending and actual pathological fractures is likely to rise. The advances in cancer therapy allow longer survival for these patients. The aim of this thesis is to provide guidelines for prophylactic surgery of impending pathological fractures in the long bones, to develop a finite element model to predict this fracture risk and to compare different operation techniques.

A retrospective analysis of pain relief, mobilisation, short-term and long-term complications after surgery for pathological fractures of the long bone in 199 patients were studied. Chapter 2 presents these patients with 233 fractures, 161 actual and 72 impending, caused by bone metastasis in femur, humerus and tibia. A local resection of the tumour was followed by endoprothesis (n=52) and by internal plate osteosynthesis (n=167), and in 211 cases bone cement was added. Fourteen fractures were treated with intramedullary nails. Pain relief was achieved in about 90% after treatment. Three-quarters (n=145) of the patients who were treated for the lower extremity were able to walk again. There were 13 local complications. In 26 cases (11%) the implanted device failed, with a cumulative probability of 40% after five years. Seven weeks after treatment the fixation failed in 11 cases. The failure rate was 16% in the subtrochanteric region treated with an angled blade, with a cumulative probability of 70% after four years. The patients survival rate was 55% after six months and 20% at two years. In conclusion, despite the poor life expectancy, our results show that hemiartroplasty and osteosynthesis with bone cement for the treatment of pathological (impending) fractures are afe methods to restore limb function and to improve quality of life.

Chapter 3 presents two different methods for surgical treatment of pathological fractures of the humeral shaft due to bone metastases. In a retrospective study 37 patients were surgically treated for 38 fractures (27 actual and 11 impending). A comparison between plate osteosynthesis with bone cement (n=20) and intramedullary nailing (n=18) was made. There was no mortality related to the surgical procedure. The patients survival rate was 61% after 3 months and 44% after 6 months; six were alive after one year. Overall, a subjective and objective relief of pain was achieved in 92% and 79%, respectively. Restoration of arm function was improved in 95%. The operative course was complicated in six patients after plate osteosynthesis (three local and three systemic complications) and four patients after intramedullary nailing (one local and three systemic complications). Fixation failed in four patients, instability developed twice after intramedullary fixation without bipolar static locking. No significant difference in survival rate, pain relief, restoration of function and complications was associated with methods of treatment, nor with operation of actual or impending pathological fractures. Despite the pour life expectancy our results indicate that intramedullary nailing with bipolar static locking and post-operative irradiation or plate osteosynthesis with bone cement for treatment of pathological (impending) fractures of the humerus shaft are safe ways to restore arm function and improve quality of life.

We reported in Chapter 4 a radiographic review of 54 consecutive patients with 24 impending and 30 actual pathological fractures due to metastatic bone lesions in the subtrochanteric femoral region. In an attempt to develop criteria for metastatic lesions at risk of fracturing, the following variables based on anteroposterior and lateral radiographs were considered: appearance of the lesion, width of the lesion, ratio between width of the lesion and bone width, length of lesion, length of cortex involvement, proportion of transverse cortical bone destroyed and local pain. Nearly all of the lesions were radiographically classified as lytic. In 27 cases (50%) they were radiographically unmeasurable. Maximal length of cortical destruction was different in patients with either an actual or an impending fracture. Prophylactic internal fixation of pathologic subtrochanteric fractures due to metastatic lesions has to be considered in cases of increasing pain, intramedullary bone lesion width equal or greater than 30 mm, ratio metastasis width : bone width exceeding 0.9 and maximal length of cortical destruction equal or greater than 38 mm. If the conventional radiograph cannot be evaluated, a computed tomography scan has to be considered.

Analyses of torsional strength reduction on large longitudinal transcortical defects were made in an in vitro experiment. Fifteen fresh frozen femur pairs were collected from human cadavers. At random, in one femur an oblong hole was drilled in the cortex of the subtrochanteric region, the other served as control. The defect length (d) differed to bone diameter (D) in ratio 0.5, 1, 1.5 and 2. The width was one-quarters of the bone diameter. At each femur a torsional load with a low velocity angle was obtained to failure. Except three for femora, a spiral fracture occurred in the lesion. In the control group this was usually at the distal site of the bone. In a transcortical defect with a defect length once the bone diameter a small strength reduction was measured. In case of defect length twice the bone diameter a 50% strength reduction was estimated. No significant correlation was found between the ratio d/D 0.5 to 2 and strength reduction, deformation angle at failure and energy. No difference in rigidity occurred between intact bone and bone with a lesion. The location of maximum local stress points were strongly influenced by the defect length, depending on the helix angle at the initial fracture site. The helix angle changed from median $45^0$ in the smallest defects, to median 34 $^0$ in the largest defects. At the ratio d/D of 2 and in one case 1.5 the initial fracture median angle at defect site changed cardinal from $90^0$ shifting abruptly to the helix angle estimated. The corrected strain gauge value showed a significant correlation between the defect length and the increasing strain reduction. Bone mineral density (BMD) of the cortex was estimated by quantitative computed tomography scan measurements. A significant difference for the values of BMD concerning the region of the femur was estimated. The lowest BMD value was found at the proximal side of the femur, and the highest BMD values at middle part of the femur. The relation torque at failure versus BMD was significant for the proximal region of the control group. No correlation was found for cross-sectional area versus strength reduction. Influences of the site of the cortical defect and geometry of the femur were studied in another experiment of seven shortened paired femora, left after the first experiment. A significant rank-correlation between ratio d/D and strength reduction was estimated. The 50% torsional strength reduction shifted to ratio d/D 1. In conclusion, a progressive torsional strength reduction occurred when a transcortical defect at the subtrochanteric region of the femur with a ratio defect length to the bone diameter exceeds one, and this is a criterion for prophylactic internal fixation.

Thirty (orthopaedic) surgeons were asked to measure sizes and to predict torsional strength reduction on radiographs and computed tomography scans (CT) of three different cortical defects in the subtrochanteric region of the femur. In Chapter 6 these results were compared with real strength reduction measured with a torsional load test, with the same loading test method as described in Chapter 5. Two femora had a transcortical defect, while one femur had partial cortical destruction. The amount of cortical destruction was most frequently mentioned by the observers as a criterion of prophylactic surgery for impending pathologic fractures. All participants routinely made a radiograph in two directions, 50% of them asked for an additional radiograph and two-third a CT scan if necessary. In comparison to the in vitro sizes the radiographic and CT scan measurements of the cortical lesions showed differences in outcome with a median of 7% and 10%, respectively. The radiographic measurement with the largest difference was the width of the cortex destruction (26%) and for the CT scan measurement this was the height of the cortex destruction (25%). The highest standard deviation of mean for all cortical defects was found for radiographic and CT scan measurements for the height of the defect. Correlation between the measured outcome between radiographic and CT scan measurements held a close agreement for outer bone diameter and for the height of the defect a poor agreement. There was a significant correlation between the predicted mean torsional strength reduction in the radiographic group and CT scan group for all defects. Within a range of 20% accuracy, the percentage of observers who correctly predicted the strength reduction in the radiographic group was very low. The use of additional performed CT scans did not improve the prediction of strength reduction in the two cases with a transcortical defect, while there was a trend to improvement of outcome in case of the partial cortical destruction. This study showed that for cortical defects in the subtrochanteric region, surgeons cannot accurate measure the sizes of a cortical defect, they cannot estimate the torsional strength reduction from radiographs, and the supplementary use of CT scans does not improve these findings. Therefore, the application of the pervaded clinical guidelines to predict the fracture risk of a metastatic lesion in the long bones, using radiographic and CT scan measurements, should be done with caution.

Chapter 7 contents the theoretical base of the experiments described in Chapter 5 with subtrochanteric cortical defects in fresh frozen human femora loaded with torsion. Finite Element Model was used to analyses the fracture risk in relation to the length of transcortical defects, in order to produce better criteria for prophylactic surgery. FEM was based on one specimen used in the experimental study. CT scans were obtained to derive the transversal geometry. A semiautomatic contouring algorithm was used to digitize these CT scans. Three-dimensional FEM was generated, consisting four node tetraeder elements, three degrees of freedom per node and isotropic material properties. Linear analysis of the FEM and torsion load was applied. The finite element models were evaluated by determining the magnitude and the location of the maximum Von Mises stress in relation to the length of the cortical defect. The FEM predicted no strength reduction in a defect length of 0.5 the bone diameter and a maximal strength reduction of 60% in a defect length of 1.5 the bone diameter. Comparing the result of FEM to the experiment of the specimen used in this study, an error of 10% was found in the torsion strength. FEM shows the same torsion strength reduction pattern compared to the experiments. Nowadays, prophylactic surgery is accepted as a treatment when 50% circumferential cortex destruction occurred. This study shows that not only the width of the cortex destruction but also the transcortical defect length is an important fracture risk. A 50% torsion strength reduction occurrs when the defect length in the cortex is larger than the bone diameter.

Finally, in Chapter 8 we discussed the guidelines for prophylactic surgery for impending fractures of the long bones and the different types of surgical fixation. The importance of torsional loading on the femur during daily activities conditions is shown. The limitations and the effort of a multi-disciplinary approach in these patients treated with comfort care are described. The types of surgical treatment of impending and actual fractures according to their location in the long bones are evaluated. Futhermore, the management of a patient who is suspected of a metastatic lesion in the long bone is discussed.

# Samenvatting

Skelet metastasen zijn waarschijnlijk al vele duizenden jaren de meeste voorkomende vorm van kwaadaardige botttumoren. Bij driekwart van deze patienten is de primaire tumor een mamma-, bronchus-, prostaat- of niercarcinoom. De incidentie van botmetastasen neemt toe als gevolg van langere overleving door een effectievere behandeling van de primaire tumor. Ten minste 7%-27% van de meer dan 61.000 nieuwe kanker gevallen per jaar in Nederland, ontwikkelt (meestal lytische) botmetastasen. Bij driekwart van de patienten is pijn het belangrijkste symptoom. Bij 5%-10% komt een pathologische fractuur voor. Hoewel patienten met botmetastasen hier in het algemeen niet aan sterven, beinvloeden deze wel sterk de kwaliteit van leven. In de loop van de twintigste eeuw werden daarom verschillende technieken voor rigide interne fixatie ontwikkeld. Conservatieve methoden, zoals tractie en gipsimmobilisatie, hadden eerder weinig resultaat opgeleverd. Met deze ontwikkeling doet zich echter het probleem voor of en wanneer een prophylactische fixatie dient te worden uitgevoerd. Tegenwoordig geeft men voorkeur aan prophylactische operatie boven een behandeling van actuele fracturen wegens de voordelen van snelle pijn vermindering, eerdere mobilisatie, verkorte opname duur en minder complicaties. Er is echter nog veel onduidelijkheid over het juiste moment van opereren. De criteria die volgens de huidige richtlijnen dienen te worden gebruikt zijn slechts gebaseerd op kleine retrospectieve studies. Aangezien het aantal mensen met kans op een pathologische fractuur en hun levensverwachting stijgt, evenals het aantal mensen met osteoporose, is een juiste indicatie stelling van het grootste belang. Het doel van dit proefschrift is dan ook de huidige richtlijnen voor prophylactische chirurgie te verbeteren, een model te ontwikkelen om fractuur risico te voorspellen en de operatie technieken te vergelijken.

Om de pijnreductie, mate van mobilisatie en korte en lange termijn complicaties na chirurgische behandeling wegens een pathologische fractuur te analyseren werden in een retrospectieve studie gegevens verzameld van 199 patienten. In Hoofdstuk 2 worden deze patienten met 233 fracturen (161 actueel en 72 dreigend) veroorzaakt door botmetastasen van femur, humerus en tibia beschreven. Na uitruimen van de

tumor werd bij 219 patienten of een endoprothese geplaatst (n=52) of een plaatosteosynthese verricht (n=167), met in 211 fracturen toevoeging van botcement. Bij 14 fracturen werd een intramedullaire pen geplaatst. Van de patienten werd 90% pijnvrij, 145 patienten (76%) met een fractuur van de onderste extremiteit konden na behandeling weer lopen. In 13 gevallen trad een locale complicatie op. Bij 26 fracturen (11%) mislukte de fixatie (cumulatieve waarschijnlijkheid 40% na 60 maanden). Na 7 weken bleek bij 11 verrichte osteosynthesen de fixatie alsnog onvoldoende. Bij gebruik van een hoekplaat in het subtrochantaire gebied was de kans op mislukken 16% (cumulatieve waarschijnlijkheid 70% na 4 jaar). De totale overleving bedroeg 55% na 6 maanden en 20% na 2 jaar.
Geconcludeerd wordt dat, ondanks de slechte levensverwachting, hemiarthroplastiek of osteosynthese met botcement als behandeling voor (dreigende) pathologische fracturen een veilige manier is om de functie van de extremiteit te herstellen en de kwaliteit van leven te verbeteren.

In Hoofdstuk 3 worden verschillende methoden van chirurgische fixatie van pathologische fracturen van de humerusschacht ten gevolge van botmetastasen besproken. In een retrospectief onderzoek werden 37 patienten chirurgisch behandeld voor 38 fracturen (waarvan 27 actueel en 11 dreigend). Plaatosteosynthese met botcement (n=20) en intramedullaire fixatie door middel van een pen (n=18) werden met elkaar vergeleken. Er was geen peroperatieve mortaliteit. De overleving bedroeg 61% na 3 maanden en 44% na 6 maanden; 6 patienten waren na 1 jaar nog in leven. Objectief en subjectief werd pijnstilling bereikt bij respectievelijk 92% en 79%. De armfunctie verbeterde bij 95%. Complicaties traden op bij 4 patienten na intramedullaire fixatie en bij 6 patienten na plaatosteosynthese. Fixatie mislukte bij 4 patienten, er ontwikkelde zich 2 maal instabiliteit na intramedullaire fixatie zonder bipolaire statische vergrendeling. Geen significant verschil in overleving, pijnstilling, functieherstel en complicaties tussen beide methoden kon worden aangetoond. Ondanks de korte levensverwachting blijkt uit de resultaten dat zowel intramedullaire fixatie met een grendelpen en postoperatieve bestraling, als plaatosteosynthese met behulp van botcement veilige methoden zijn om bij (dreigende) pathologische fracturen een goede armfunctie te verkrijgen en de kwaliteit van leven te verbeteren.

We beschrijven in Hoofdstuk 4 een overzicht van 54 patienten met 25 dreigende en 30 actuele pathologische fracturen door botmetastasen in het subtrochantaire femur. In een poging criteria te ontwikkelen wat betreft fractuurrisico bij deze botdefecten werden de volgende variabelen, gebaseerd op anteroposterior en laterale röntgenopnamen, bepaald: verschijningsvorm van het defect, breedte van het defect, de ratio tussen defectbreedte en botdiameter, lengte van het defect, sagittale lengte van het corticale defect, de transversale corticale destructie en locale pijn. Bijna alle laesies werden radiologisch geclassificeerd als lytische haarden. In 27 gevallen (50%) bleken de defecten op de röntgenopnamen niet goed meetbaar. Er werd geen relatie gevonden tussen voorgaande variabelen en de histologische classificatie. Wel werd een verschil gezien in longitudinale corticale destructie tussen patienten met een actuele dan wel een dreigende fractuur. Prophylactische interne fixatie van dreigende pathologische subtrochantaire fracturen door botmetastasen moet worden overwogen bij progressie van de pijn, een intramedullair botdefect met een breedte groter dan of gelijk aan 30 mm, een ratio tussen breedte metastase en botdiameter groter dan of gelijk aan 0.9 of een maximale longitudinale corticale destructie van groter of gelijk aan 38 mm. Als een röntgenopname niet te beoordelen is dient een CT scan te worden overwogen.

Om het effect van sterkte reduktie bij grote longitudinale transcorticale defecten met torsie belasting te meten werd een in vitro experiment opgezet. Er werden 15 paar ingevroren humane femora gebruikt. At random werd in 1 femur per paar een defect subtrochantair aangebracht, de ander diende als controle. Elk femur onderging een torsie belasting met lage draaisnelheid, totdat het brak. Met uitzondering van 3 femora trad een spiraal fractuur op door de laesie, in de controle groep meestal distaal. Er werd bij een transcorticaal defect tot een lengte van 1× de botdiameter een minimale sterktereduktie gemeten, terwijl bij een defect met een lengte van 2× de botdiameter 50% sterktereduktie werd gemeten. Er werd geen significante correlatie gevonden tussen de verschillende defect lengtes van 0.5 - 2 × de botdiameter en de sterktereduktie, de hoekverdraaiing bij breken, en de energie. Geen verschil trad op in de rigiditeit tussen de gelaedeerde en intacte femora. De locatie van het maximale spanningspunt bij het defect werd sterk beinvloed door de lengte. Dit werd afgeleid van de afname van de (mediaan) helix hoek van de spiraal fractuur die van $45^0$ bij het kleinste defect daalde naar $34^0$ bij het grootste defect. Een opvallend fenomeen trad op bij alle lengtes van het defect van meer dan 2 × de botdiameter en in een defect lengte van 1.5 × de botdiameter, waar in het eerste gedeelte de fractuur lijn initieel $90^0$ verloopt en abrupt veranderd in de helix hoek. Tevens werden rekstrook metingen verricht waaruit bleek dat voor de gecorrigeerde rekstrook metingen een significante correlatie bestond tussen de lengte van het defect en de toegenomen spanningsafname. Met behulp van quantitatieve CT scan metingen werd de bot mineraal dichtheid (BMD) voor alleen de cortex bepaald. De mediane waarde van BMD was significant verschillend voor de gemeten locatie van het femur, met de laagste waarde voor het proximale gedeelte en de hoogste waarde voor het middelste gedeelte. Alleen in het proximale gedeelte van de controle groep was er sprake van een significante correlatie tussen BMD en sterktereduktie. Er werd geen correlatie gevonden tussen de gemeten transversale corticale oppervlakten en de sterkte reduktie. Om de invloed van de locatie van het defect en de geometrie van het femur te bepalen, werd in een tweede experiment bij 7 ingekorte femur paren opnieuw onder torsiebelasting gebroken. Er werd een verschuiving van de 50% sterktereduktie naar de defect lengte van 1 × de botdiameter geconstateerd. Deze studie toont aan dat onder torsiebelasting een transcorticaal defect met een lengte van meer dan 1 × de botdiameter in het subtrochantaire gedeelte van het femur een progressieve sterkte reductie plaats vindt, en dat bij deze laesie een prophylactische chirurgische behandeling dient plaats te vinden.

Dertig (orthopedisch) chirurgen zijn benaderd om de sterktereductie te schatten bij torsiebelasting en afmetingen te bepalen met behulp van röntgenopnamen en CT scan bij drie verschillende corticale defecten in het subtrochantaire gedeelte van het femur. Deze resultaten werden vergeleken met de waarden van de uitkomsten in vitro experimenten, zoals deze in hoofdstuk 5 zijn beschreven. Inventarisatie van door hen toegepaste richtlijnen voor prophylactische chirurgische fixatie gaf aan dat de mate van cortexdestructie het meest gebruikt wordt. Standaard worden röntgenopnamen in 2 richtingen gemaakt, 50% maken additionele opnamen en tweederde maakt, indien nodig, aanvullend een CT scan. Twee femora hadden een transcorticaal defect en een had een partiele cortex destructie.

De aan de hand van röntgen- en CT opnamen gemeten maten van het defect bleken respectievelijk 7% en 10% af te wijken van de werkelijke grootte. Bij de röntgenopnamen werd het grootste verschil gemeten bij de breedte van de cortex destructie (26%), terwijl dit bij de CT scan opnamen voor de hoogte van de cortex destructie was (25%). De grootste standaard deviatie voor de röntgen- en CT scan bepalingen waren voor de hoogte van het corticale defect. Een sterke overeenkomst in de waarde in de röntgen groep en CT scan groep werd gemeten voor bot diameter, een zwakke overeenkomst werd bij de gemeten defect lengte geconstateerd. Er bleek een significante correlatie te bestaan tussen de schatting van de sterktereductie in de röntgengroep en CT scan groep. Een CT scan opname resulteerde bij de transcorticale defecten niet in een betere voorspelbaarheid van de sterkte reductie, bij de partiele corticale destructie was een trend tot een betere schatting.
Geconcludeerd kan worden dat bij een subtrochantair corticaal defect de (orthopedisch) chirurg de afmetingen en de sterktereductie in het geval van torsiebelasting niet juist kan schatten met behulp van röntgenopnamen; een CT scan heeft weinig aanvullende waarde. Het toepassen van de huidige richtlijnen betreffende het risico op een pathologische fractuur zal dus met enige voorzichtigheid moeten plaatsvinden.

Wegens de gebrekkige kennis over fractuurrisico bij grotere metastatische botdefecten werden de in hoofdstuk 5 beschreven experimenten met humane femora en corticale defecten in het subtrochantaire gedeelte onder torsiebelasting uitgevoerd. Hoofdstuk 7 behandelt de theoretische ondersteuning van deze experimenten. Met behulp van Finite Element Modelling werd het fractuurrisico in relatie tot de grootte van het defect geanalyseerd met als uiteindelijk doel een verbetering van de criteria voor prophylactische chirurgie. Het FEM model werd gebaseerd op data van een van de femora uit de experimentele studie. CT scans werden gebruikt om de transversale afmetingen vast te leggen. De gebruikte elementen, 4 tetraeder- knooppunten, hadden een lineaire interpolatiefunctie; er waren 3 vrijheidsgraden per knooppunt met isotropische materiaal eigenschappen. Een lineaire analyse werd uitgevoerd voor torsie. De invloed van de lengte van het corticale defect op de von Mises spanning bij falen werd onderzocht. Het FEM model voorspelde geen sterktereductie bij een defect tot een lengte van 0.5 x de botdiameter en een maximale sterktereductie van 60% bij een defect van 1.5 x de botdiameter. Bij de vergelijking van de resultaten van het FEM model en de experimenten werd een zelfde sterktereductie patroon gevonden. Het FEM model voorspelt vrij nauwkeurig de sterktereductie in het gebruikte bot, er werd een verschil van slechts 10% gevonden. Volgens de huidige richtlijnen is bij destructie van 50% van de omtrek van de cortex prophylactische stabilisatie nodig. Deze studie toont echter aan dat niet alleen de breedte van de cortexdestructie van belang is maar ook de lengte: een defect met een lengte van meer dan de botdiameter zal de torsiesterkte met ongeveer 50% doen verminderen.

Ten slotte worden in hoofdstuk 8 de richtlijnen voor prophylactische chirurgie van dreigende fracturen in de lange pijpbeenderen en de verschillende soorten chirurgische behandeling besproken. Tevens worden er enkele kanttekeningen over deze vorm van palliatieve zorg gemaakt.

# Dankwoord

Aan de totstandkoming van dit proefschrift hebben velen de afgelopen jaren bijgedragen. Zonder hen was het niet gelukt. Bedankt allemaal !

Allereerst dr T. Wiggers, beste Theo; van af het eerste uur dat ik kennis maakte met de kliniek, toen nog als co-assistent, heb je mij geïnteresseerd voor de traumatologie bij de oncologische patient. Jouw geweldige enthousiasme voor wetenschappelijk onderzoek en jouw toewijding om deze klus te klaren wist je perfect op mij over te brengen. Naast onze samenwerking op het wetenschappelijk terrein hebben we in deze periode ook als vrienden veel gedeeld.

Prof. Dr Ir C.J. Snijders, beste Chris; jouw altijd opgewekte instelling om wetenschappelijke of organisatorische problemen op te lossen werkte zeer aanstekelijk. Het vertrouwen dat je van het begin af aan in mij stelde heb ik altijd enorm gewaardeerd.

Prof. dr J. Jeekel, Prof. dr J.A.N. Verhaar en Prof. dr ir L.J. Ernst wil ik bedanken voor de bereidheid het manuscript te beoordelen en zitting te nemen in de commissie.

Marielle ten Have; volgens mij zijn er weinig studenten technische mechanica geweest die tijdens hun afstudeerproject zoveel het 'Zwick laboratorium by night' hebben gezien. Bedankt voor je onuitputtelijke inzet en succes met je eigen finite element modelling bedrijfje.

Gert Jan Kleinrensink, na onze produktieve samenwerking met de 'Oirschot trial' kwam jij met de gouden tip in het labyrint van vakgroepen en universiteiten. Je onstuitbare fascinatie voor wetenschappelijk onderzoek heeft zijn vruchten afgeworpen. Als verse doctor is de rol als paranymf voor jouw weggelegd.

Enerieke van der Zwaag, met grote interesse en voortvarendheid heb jij tussen je co-schappen door gezorgd voor voldoende deelnemers aan de enquête.

Prof. dr J.W.J.L. Stapert, beste Jouwert; met veel plezier heb ik met jou samengewerkt. Vele facetten van het gebruik van de intramedullaire pen techniek zijn me sindsdien pas duidelijk geworden.

Dr M. Oudkerk wil ik bedanken voor de perfecte organisatie en volledige medewerking van zijn afdeling radiologie. Er is geen lytische lesie in het femur onopgemerkt aan U voorbij gegaan.

Arie Munne en Dani Kraus, jullie kwaliteit en inzet bij het verzamelen en verzenden van de radiologische data, op de meest ongunstige tijdstippen, was essentieel voor de voortgang van het onderzoek.

Henk Swarte wil ik bedanken voor zijn heldere kijk op de theoretische en praktische kanten van het gebruik van fantomen.

Paul Mulder, bedankt voor je ondersteuning, en een ding weet ik zeker; geen statistische vraag is voor jouw te moeilijk.

Dr van Geel, beste Bert; het was even wennen die eerste 'dead line', maar na enkele overwonnen te hebben werd het zelfs prettig om naar toe te werken.

Dr Boxma, beste Han; gedurende mijn vooropleiding heeft je enthousiasme voor de traumatologie, zowel klinisch als wetenschappelijk, een grote indruk op mij gemaakt.

De maatschap heelkunde van het Zuiderziekenhuis in Rotterdam bedank ik voor de stimulerende sfeer binnen de kliniek die als uitstekende voedingsbodem gediend heeft voor het leggen voor een solide basis van mijn orthopedische opleiding en het onderzoek. De arts-assistenten stonden dag en nacht borg voor een perfecte sfeer, bedankt!

Natuurlijk ook de maatschap orthopedie en mijn mede-assistenten van het Westeinde ziekenhuis in Den Haag wil ik bedanken voor het begrip voor niet alleen mijn fysieke afwezigheid, maar ook mijn getaande geestelijke kracht na weer eens een nachtje achter de computer te hebben door gebracht.

Als spil in het onderzoek waren de secretaresses, met name Ria, Marja, Marinka, Barbara niet weg te denken, zij worden bedankt voor hun inspanningen.

Nicoline van den Brûle, de accuratesse in het 'last-minute' opsporen van de meest oude en obscure publikaties zijn jouw parels in de referentielijsten.

De mensen die werkzaam waren in het mortuarium wil ik bedanken voor hun hulp.

De groep van de afdeling technische mechanica en van het 'Zwick' laboratorium aan de technische universiteit Delft wil ik hartelijk danken voor de technische en organisatorische ondersteuning. Leo van de Drift en Jan Sterk, de mannen van het laboratorium, zij wisten altijd en overal wel een praktische oplossing op.

Fred van Keulen, jouw scherpe biomechanische analyses en creatieve finite element modeleringen waren zeer verhelderend voor mij als leek tussen zoveel technische informatie.

Zonder de bereidwillige medewerking van de nabestaanden van patienten die zijn overleden in het Zuider en het Westeinde ziekenhuis, had er geen enkel experiment kunnen plaats vinden.

De professoren, orthopeden, chirurgen en mede-assistenten uit de verschillende ziekenhuizen in de regio Zuid-Holland die hebben geparticipeerd in de enquête wil ik bij deze hartelijk danken.

Harry Kooijman, jij die al vroeg in je jeugd de jonge onderzoeker aan het spelen was, vaak samen met mij, bent mij met promoveren te snel af geweest. Ondanks de huidige grote geografische afstand was je betrokkenheid indrukwekkend. Als ex-paranymf blijf je hopelijk in de toekomst ook zo vaak e-mailen. Sharon Sweeney, het moet voor een chemicus een grote kluif geweest zijn om deze teksten te corrigeren op het engels. Bedankt voor jullie inzet.

Mama, lieve Marian; ik wil je bedanken voor je altijd toegewijde steun en liefde. Het is diep triest dat mijn vader die met veel interesse aan de wieg stond van het experimentele deel van het onderzoek, door zijn vroegtijdig overlijden de afronding van mijn proefschrift niet heeft kunnen meemaken. Ik mis hem.

Tot slot, lieve Marie Lou; jij bent mijn stille kracht gedurende het onderzoek geweest. Helaas won de computer het vele nachten van jou. Toch bleef je met bijzonder veel liefde steunen. Het wordt tijd voor een lange strandwandeling...........

# Curriculum Vitae

Sander Dijkstra werd geboren op 24 april 1966 te Voorburg. Hij volgde het VWO aan het Wessel Gansfort College te Zoetermeer. In 1984 begon hij met de studie geneeskunde aan de Erasmus Universiteit Rotterdam. Als student-assistent was hij in de periode 1985-1987 verbonden aan de afdeling Medische Psychologie van de Erasmus Universiteit Rotterdam. Het doctoraalexamen werd behaald in 1989, waarna een stage aan de Atma Jaya Universiteit te Jakarta volgde. Hij rondde zijn studie af in 1992. Zijn afstudeeronderzoek onder leiding van dr T. Wiggers verbonden aan de dr Daniel den Hoed kliniek te Rotterdam, was de aanzet tot dit proefschrift. Na het vervullen van zijn dienstplicht als arts bij het "131 zwaar chirurgisch veldhospitaal" te Ermelo kwam hij in 1993 als wetenschappelijk medewerker in dienst van de dr Daniel den Hoed kliniek te Rotterdam. In datzelfde jaar kwam hij in opleiding voor orthopaedie. De vooropleiding werd in de periode 1993-1996 bij opleider dr K.J. Brouwer van de afdeling Heelkunde in het Zuiderziekenhuis te Rotterdam gevolgd. Vanaf 1996 is bovengenoemde werkzaam in het Westeinde Ziekenhuis te Den Haag bij opleider dr R. Sanders.