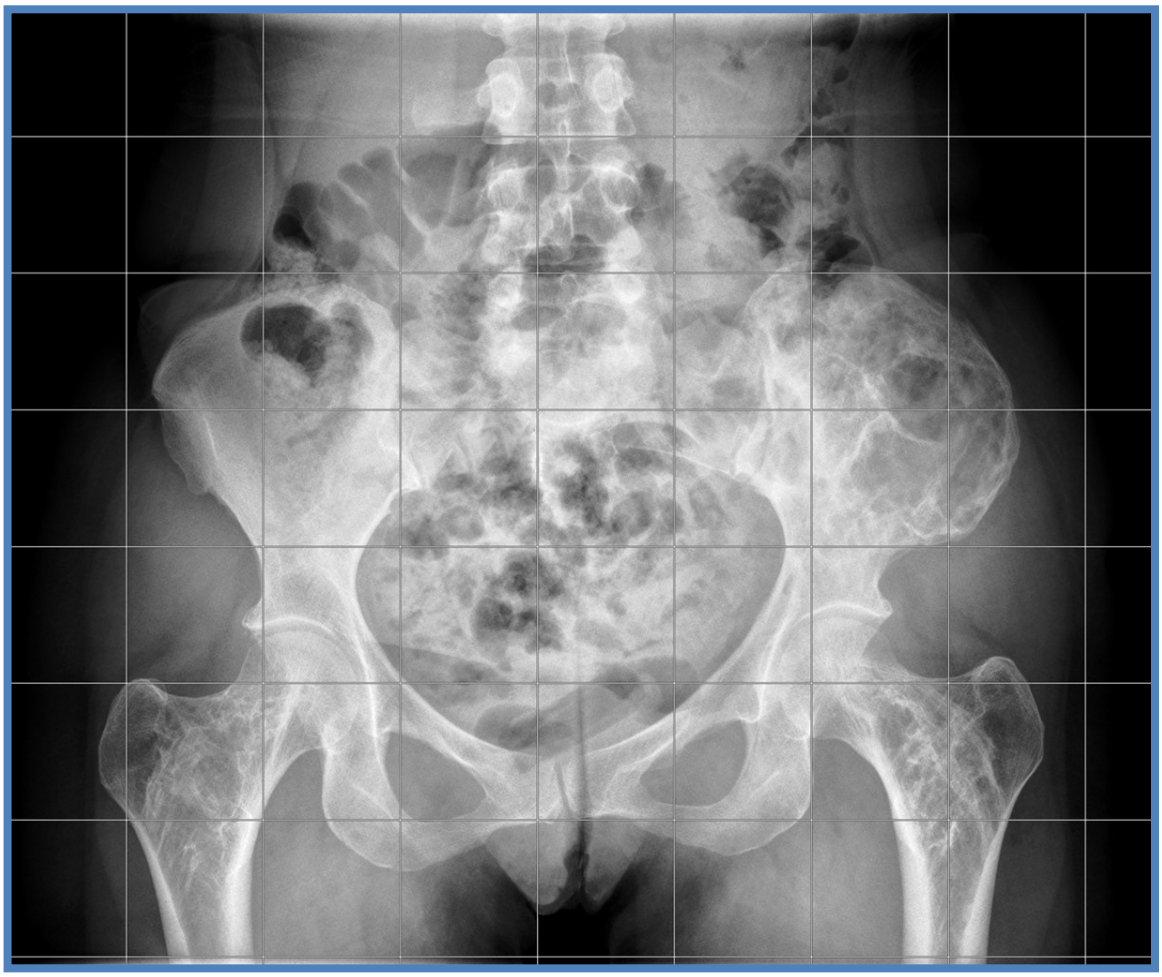
FOLLOW UP AND CURRENT STATUS OF 124 PATIENTS WITH FIBROUS DYSPLASIA FOCUSING ON INDIVIDUAL PAIN COURSE.



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Diploma thesis

Follow up and current status of 124 patients with Fibrous Dysplasia focusing on individual pain course.

submitted by

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October 6, 2010

Affidavit

I, hereby, declare that the following diploma thesis has been written only by the undersigned and without any assistance from third parties. Furthermore, I confirm that no sources have been used in the preparation of this thesis other than those indicated in the thesis itself.

Graz, October 6, 2010

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Graz, am 06. Oktober 2010

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Abstract

Abstract (English)

Follow up and current status of 124 patients with Fibrous Dysplasia focusing on individual pain course.

Fibrous Dysplasia (FD) is a rare, sporadically occurring, benign disease of the bone which is caused by a point mutation in the GNAS gene and characterised by the replacement of normal bone material through fibrous tissue. Apart from asymptomatic cases, FD clinically appears mainly in pain, pathological fractures and bone deformities. Sometimes it manifests in addition with neurological or endocrinological complications as a part of a syndrome (Mazabraud and McCune Albright Syndrome).
If in the past surgical procedures were the only possible treatment, since 1994 there has been a medicinal treatment approach with intravenous bisphosphonate application within experimental studies, which has been reported to provide pain reduction.

This manuscript aims to conduct a status quo ascertainment and a comparative illustration through a retrospective data analysis of 124 patients who have been diagnosed with Fibrous Dysplasia. Concerning the individual pain course and the treatment so far, the findings will be used in order to create a database which is to be used for further research.

The analysis of data from the clinical records and from a structured enquiry by telephone using an elaborate questionnaire was documented in an Excel file. Furthermore a comparative illustration was conducted and statistically evaluated. The main focus hereby was on the individual's perception of pain.

The total group showed significant differences with regard to craniofacial and non-craniofacial localisation of the disease, the age distribution, as well as to monostotic and polyostotic forms. Among the 88 patients who were compared by the pain score differences were found regarding pain intensity and course of the disease: In polyostotic and non-craniofacial patients the mean value of pain during their acute phase of disease was about three points higher than in their reference groups (Craniofacial versus non-craniofacial: p=0.015; Monostotic versus polyostotic: p=0.001). Pain in different age-groups showed a higher mean value in adults in their acute phase of the disease than in children (p=0.028). In our study population 14% of the patients were suffering from constant pain at a mean follow-up of 11.1 years (range 2-26).

In conclusion it is to be said that FD is a disease with a wide variability concerning clinical symptoms and individual pain course which ranges from complete absence of symptoms to very painful cases. Pain is one of the main clinical features in symptomatic forms of FD. Therefore further research focusing on pain agents and pain treatment options needs to be considered.

Abstract (German)

Follow-up und Status-quo Erhebung für 124 Patienten mit der Diagnose "Fibröse Dysplasie" im Zeitraum von 1984 – 2008 mit Fokus auf die individuelle Schmerzsymptomatik.

Die „Fibröse Dysplasie“ (FD) ist eine seltene, sporadisch auftretende, gutartige Erkrankung des Knochens, verursacht durch eine Punktmutation im GNAS-Gen und gekennzeichnet durch den Austausch von normaler Knochenstruktur durch fibröses, unreif verkalktes Gewebe. Klinisch manifestiert sich die FD neben asymptomatischen, meist als Zufallsbefund diagnostizierten Fällen, vor allem durch Schmerzen, pathologische Frakturen, Knochendeformitäten, aber auch in Kombination mit neurologischen oder endokrinologischen Komplikationen im Rahmen von Syndromen (Mazabraud Syndrom und McCune Albright Syndrom).
Waren in der Vergangenheit chirurgische Maßnahmen die einzige Behandlungsmöglichkeit, ist seit 1994 ein medikamentöser Ansatz der Behandlung unter Verwendung von intravenösen Bisphosphonaten aufgezeigt worden, durch die eine Schmerzreduktion nachgewiesen werden konnte.

Das Ziel dieser Diplomarbeit ist es, durch eine retrospektive Datenerhebung unter Verwendung der Krankenakten von 124 PatientInnen mit der Diagnose „Fibröse Dysplasie“ und eine aktuelle telefonische Befragung der PatientInnen, eine Status quo-Erhebung und Vergleichsdarstellung im Hinblick auf die Schmerzsituation, den Schmerzverlauf und die bisher erfolgten therapeutischen Maßnahmen durchzuführen. Die dabei erhobenen Daten werden in eine Datenbank eingebracht und sollen als Grundlage für weiterführende Studien dienen.

Die Daten aus den vorliegenden Krankengeschichten bzw. aus einer telefonischen, strukturierten Befragung anhand eines ausgearbeiteten Erhebungsbogens, wurden in einer Excel-Datei dokumentiert. Im Weiteren wurde eine Vergleichsdarstellung durchgeführt und die Ergebnisse wurden statistisch ausge-

wertet. Hauptzielgröße dabei war das individuelle Schmerzempfinden bzw. die klinische Schmerzintensität im Verlauf.

Im Gesamtkollektiv zeigten sich signifikante Unterschiede bezüglich Schmerzsymptomatik im Hinblick auf folgende Parameter: Kraniofaziale versus nicht-kraniofaziale Lokalisation der Erkrankung, im Altersvergleich sowie auch bei der Unterscheidung zwischen monostotischen und polyostotischen Formen. Innerhalb der 88 PatientInnen, die mittels Schmerzscore miteinander verglichen werden konnten, fanden sich Unterschiede in der Schmerzintensität zwischen den einzelnen Gruppen sowie im Verlauf ihrer Erkrankung: PatientInnen mit polyostotischen und kraniofazialen Befall an FD erreichten einen höheren Schmerzmittelwert von 3 Punkten im Vergleich zu ihrer Referenzgruppe (Kraniofazial versus nicht-kraniofazial: p=0,015; Monostotisch versus polyototisch: p=0,001).
Auch in der Erwachsenengruppe konnte eine signifikant erhöhte Schmerzintensität in der Akutphase der Erkrankung dargestellt werden als bei den Kindern (p=0,028).
In unserem PatientInnenkollektiv litten sogar 14% der Befragten nach therapeutischen Interventionen und einer Follow-up-Zeit von durchschnittlich 11,1 Jahren (zwischen 2 und 26 Jahren) an ständigen Schmerzen.

Zusammenfassend ist festzuhalten, dass die FD eine Erkrankung mit sehr hoher Variabilität im klinischen Erscheinungsbild und Verlauf ist. Die Symptomatik reicht von vollständiger Beschwerdefreiheit bis zu schwer verlaufenden Fällen. Bei den symptomatischen Formen der FD ist Schmerz eines der Hauptsymptome. Aus diesem Grund sind weitere Forschungsarbeiten zum Thema Schmerz und FD erforderlich, um zusätzliche, effiziente und sichere Behandlungsstrategien entwickeln zu können.

Abbreviations

ABC	Aneurysmal bone cyst
CF	Craniofacial
Cur	Curettage
et al.	Et alia
etc.	Et cetera
FESS	Functional endoscopic sinus surgery
FD	Fibrous Dysplasia
Fig.	Figure
GH	Growth hormone
GNAS	Guanine nucleotide binding, alpha stimulating
ID	Identification number of patients
IR	Intramedullary rods
MAS	McCune-Albright syndrome
Metal	Plates, screws
MFD	Monostotic Fibrous Dysplasia
n	Sum
n.s.	Not specified
no.	Number
NCF	Non craniofacial
NSAIDs	Non-steroidal anti-inflammatory drugs
OFD	Osteofibrous Dysplasia
PE	Probe excision
PFD	Polyostotic Fibrous Dysplasia
Phenol	Adjuvant phenol treatment
PNRS	Pain numeric rating scale (NRS-11)
Spongostan	Gelatine sponge
Syn	Synthetic bone grafts
VAS	Visual Analogue Scale
WHO	World Health Organization
y	Years

°	Mazabraud Syndrome
*	McCune Albright Syndrome
%	Percent
+	Positive family history

Table of Content

1. Introduction

Fibrous Dysplasia (FD) is a rare benign disease of the bone (at the maximum 7% of the benign bone tumours) [1, 2].

FD is characterized by a high variability in the course of disease and a wide clinical spectrum: A wide range of symptoms has been reported, from asymptomatic effects and low symptoms to severe forms with life-long effects for the patients like intermittent phases of pain or deforming deviations of the bone. These symptoms can be highly distinctive as they cause not only somatic but even mental problems [3].

1.1. Aim

The aim of this diploma thesis is a retrospective 24-year evaluation of all patients with diagnosed FD, who were described in the registry of the Institute of Pathology of the Medical University of Graz. The primary group of interest were patients with severe, periodic pain attacks with particular consideration of pain intensity and pain course. The thesis will also point out and compare possible varieties of FD patients with different localisations (craniofacial versus non-craniofacial and monostotic versus polyostotic bone lesions) of their disease and therapeutic interventions.

This data collection should serve as a basis for further studies with special interrogations.

2. Clinical theory

2.1. Fibrous Dysplasia

2.1.1. Definition

Fibrous Dysplasia was first described by Lichtenstein and Jaffé in 1943 [1] and is defined according to the World Health Organization (WHO) as in "*a benign medullary fibrous-osseous lesion which may involve one or more bones*." [4]. Synonyms for FD are Jaffé-Lichtenstein syndrome [6] and Fibrocartilaginous Dysplasia [4]. If FD is limited to a single bone it's a monostotic form, when several bones are involved it's called polyostotic [1, 5].

McCune-Albright Syndrome (MAS) is defined by the triad of polyostotic form of FD, café-au-lait spots (melanotic skin maculae) and hyperfunctioning endocrinopathies [7]. Pseudo-precocious puberty, cushing syndrome [8], pituitary adenoma, hyperthyroidism [9], growth hormone (GH) hypersecretion [10], renal phosphate wasting [11] class among to those endocrinopathies.

In **Mazabraud Syndrome** the polyostotic FD (PFD) is predominantly combined with intramuscular myxomas [12]. FD is diagnosed in childhood and adolescence, myxomas are exposed in adult-age [13].

2.1.2. Epidemiology

FD is a rare non hereditary, congenital disease of children and adults [14]. In the literature there are no reliable descriptions of the prevalence of the disease due to the different clinical appearance [6]. According to the WHO there is an equal sexual distribution, with no differences in race and origin [4]. The polyostotic form

arises less frequently (monostotic:polyostotic = 6:1) [4], but occurs as a more severe phenotype [14].

Asymptomatic Fibrous Dysplasia is often diagnosed coincidentally, mostly in the age of puberty. Severe forms (polyostotic form and McCune-Albright Syndrome) are detected earlier in the early childhood. The Mazabraud syndrome is adult-onset [14]. (Table 1)

Table 1: Forms of Presentation of Fibrous Dysplasia.

	Bone Involvement		Skin Involvement	Endocrine Disorders	Soft-Tissue	Onset	
	single	multiple				Child	Adult
Monostotic	X						X
Polyostotic		X				X	
MAS		X	X	X		X	
Mazabraud Syndrome		X			X		X

Legend: MAS = McCune-Albright Syndrome

2.1.3. Sites of involvement

FD is a disease affecting any skeletal bone. The most common predilection site is the femur, particularly the proximal part of the bone [15]. In decreasing order FD is found in the tibia, the craniofacial bones, the ribs, the humerus, the pelvis. On rare occasions and almost only in extensive polyostotic cases FD is located in hands and feet. Claviculae, scapulae and vertebrae are seldomly involved as well [14]. Polyostotic lesions have a disposition to affect one side of the body [1], one bone can be afflicted in several areas, which may be separated by the normal structure of the bone [6]. In women all long bones are favourably afflicted whereas in men the ribs and the skull are more susceptible [15].

2.1.4. Aetiology

Aetiologically important is the miss-sense mutation of the GNAS complex (**g**uanine **n**ucleotide binding, **a**lpha **s**timulating - complex) in chromosome 20q13. This com-

plex imprints the α-subunit of the heterotrimeric Guanine-protein (G-protein) [8]. The result of this mutation is a lack of the intrinsic GTPase activity, which causes osteoblastic differentiation defects, and the increase of the secretion of interleukin-6 (IL-6) [16]: On the one hand a high number of abnormally-differentiated pre-osteoblastic cells are produced and the differentiation to normal osteoblastic cells is interrupted: Instead of the normal formation of the bone a fibrous tissue is built. On the other hand surrounding osteoclasts are activated whereby the resorption of normal bone is increased. Embryonic stem cells are involved in the mutation [17] and the severity of the disease depends on the time of mutation. The earlier the mutation, the more pronounced is the clinical appearance [18]; even other organs are likely to be involved, as all three germ layers (ectoderm, endoderm and mesoderm) can be affected. In these cases it's possible to find endocrine dysfunctions and skin spots. This phenotype corresponds to the characteristics of the McCune Albright Syndrome [9, 17, 19].

2.1.5. Clinical findings

Monostotic FD (MFD) is often presented clinically quiescent, therefore the diagnosis is made accidentally, very often after an examination with x-rays for another reason [20].

2.1.5.1. Pain

The pain course appears in different graduations: From no remarkable pain over severe to excruciating pain. It is often caused by a fatigue fracture with spontaneous appearance or triggered by a minimal trauma, especially in weight-bearing areas [14, 18]. The pain is brought on by selective pressure. Sometimes it imitates an inflammation and swelling can be induced [21]. There are differences in how patients from different age groups experience that pain: It can be difficult to detect this pain in children as they more easily accept chronic pain than adults do [22, 23].

2.1.5.2. Bone deformities

Predilection sites of bone deformities are craniofacial bones and long bones. A typical alteration is the so called shepherd´s crook deviation (a varus deviation) which is found in the proximal femur. In patients suffering from polyostotic FD even the spine can be involved which can result in scoliosis [24]. Even after patients have reached their full height a progressive tendency can be detected (in contradiction to idiopathic scoliosis) [17, 25].
If the skull and facial bones are involved swelling and consequential asymmetry emerge on the head and in the face.

2.1.5.3. Fracture

FD is often clinically exposed in pathological fractures. These fractures present a problematic issue and are caused by the reduction of cortical thickness of the bone due to osteolytic activity [21].

2.1.5.4. Neurological complications

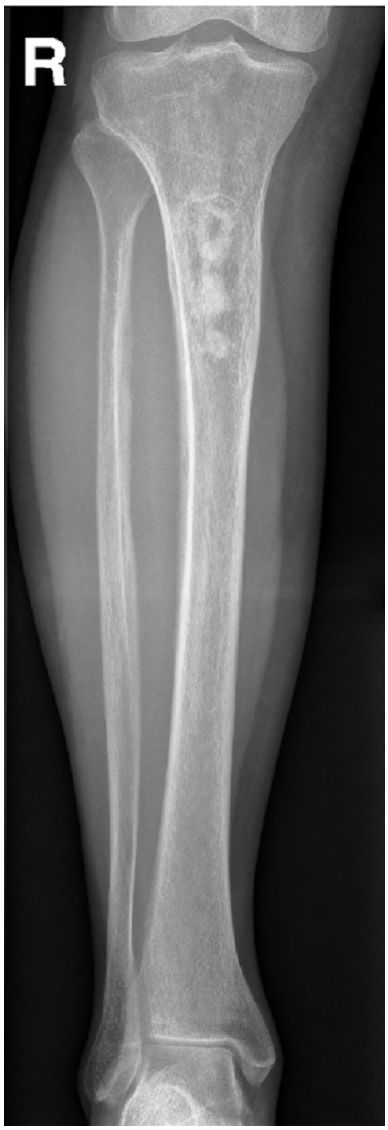
If bones in the craniomaxillofacial area are involved with FD, visual and acoustical loss may be found, caused by compression of the optic and acoustic nerve due to the expansion of the lesions. Likewise substantially involved vertebral bodies lead to spinal cord compression. Without adequate therapy the damage could be irreversible [26].

2.1.6. Diagnostic features

Due to the fact, that it sometimes might be difficult to diagnose FD it is important to examine patients clinically and radiologically and ascertain pathological findings [21].

2.1.6.1. Radiological findings

A safe statement due to the diagnosis FD and dissociation of malignant bony deformations depends on the proportion and distribution of bone and fibrous tissue within a lesion. Typical radiological appearances are the enlargement and the expansion of the bone, which mostly assumes from the medulla in a concentric or eccentric way, the thinning of the cortical bone in this area and the ground glass appearance [5, 6, 17]. (Figure 1)
Lichtenstein et al. [1] describes this rarefication of the bone and pseudotrabeculated phenomenon as “soap bubble” shadow.



In 1980 Lodwick et al. [27] postulated a radiologically grading classification in which tumours are scaled due to the gravity of the bone destruction and other characteristics into grade I (benign), II and III (malign) [28]. (Figure 2,Table 2)
In MFD the lesion is bounded by a sclerotic rim and the substantia compacta sometimes is protruded.
According to the radiologically grading scale mentioned above the MFD lesions are within grade IA and IB.
In PFD bigger lesions with a more blurred surrounding are found. Due to the diameter deformations are more often: The shepherd´s crook deviation of the femur is a typical example. PFD is typically classified in grade IB and IC in the Lodwick system [6].

Figure 1: X-ray of the right lower leg of a 39-year old male patient with histologically verified monostotic FD: It shows the loss of the normal trabecular pattern in several bones of his right leg.

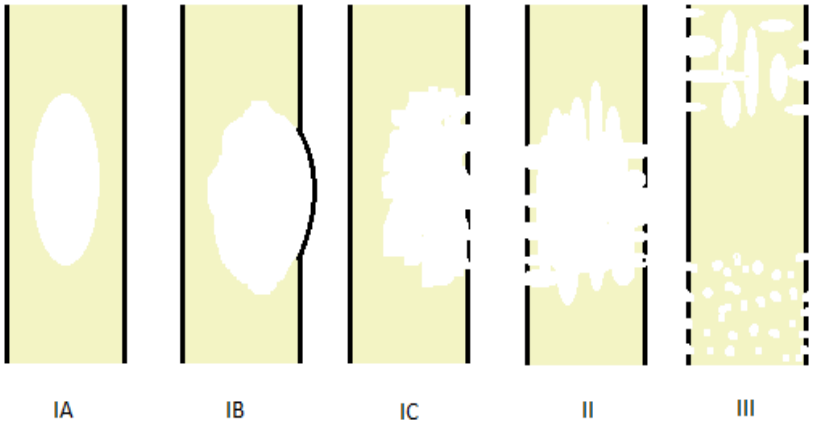


Figure 2: Schematic representation of the grades IA to III of the classification to Lodwick (Referring to Freyschmidt et al. [56]).

Table 2: Lodwick-classification: Grading with destruction of bone [27].

Radiographic pattern	IA	IB	IC	II	III
Destruction	Mandatory geographic	Mandatory geographic	Mandatory geographic	Moth-Eaten or geographic	Mandatory permeated
Edge characteristic	Regular or lobulated or multicentric	Regular or lobulated or multicentric or ragged/ poorly defined	Regular or lobulated or multicentric or ragged/ poorly defined or moth-eaten	If geographic, mandatory, moth-eaten edge greater than 1 cm	Any edge
Penetration of cortex	None or partial	None or partial	Mandatory total	Total by definition	Total by definition
Sclerotic rim	Mandatory	Optional	Optional	Optional but unlikely	Optional but unlikely
Expanded shell	Optional only 1 cm or less	If sclerotic rim present, expanded shell must be > 1 cm	Optional	Optional but unlikely	Optional but unlikely

2.1.6.2. Histopathological findings

Usually FD mutated bones are histologically well circumscribed and are composed of fibrous and bony components, which shows variable conglomerates from one to another and even within a lesion:
Following characteristics belong to the main signs: Finely immature bone-spicules with absence of osteoblastic framing, fibroblastic stroma with primitive mesenchymal spindle-like cells without malignity signs and less or no collagenous fibrils. Bony components mainly appear as irregularly curvilinear woven trabeculae, in rare cases also linearly [4, 29].
In substantia compacta a cortical thinning due to a high activity of osteoclasts is found [17].
In 1999 Riminucci et al. [30] detected in CF and NCF FD areas histological diversities in the distribution of compact to cancellous bone and described different types associating various regions: There is a higher amount of substantia compacta in CF lesions. According to the histological findings three types are postulated: Pagetoid Fibrous Dysplasia, Hypercellular Fibrous Dysplasia and ‘Chinese writing’ Fibrous Dysplasia.
Riminucci et al. traced these differences back to a more likely neuroectodermal origin in CF bones, whereas in other bones mesodermal parts are predominant [30].

2.1.7. Differential diagnosis

The diagnosis as well as the differential diagnosis are mainly based on radiological imaging. In cases of doubt a biopsy is necessary.
To get an overview, the most important differential diagnoses are mentioned in the following part:

2.1.7.1. Simple (juvenile) bone cyst

The simple bone cyst is a benign unicameral lesion, which is mostly filled with straw-coloured (serous or sero-sanguineous) fluid. In comparison to FD this cystic variance is more radiolucent and shows a larger spatial extent. Long bones, pelvis and calcaneus are mainly involved [29, 31].

2.1.7.2. Paget disease

Paget disease breaks out in adult age and is primarily located in the skull [32]. It is characterized with plump irregular woven trabeculae and coniform flame-like boarders. Histological findings show typical mosaic patterns and vascularised stroma [14].
The radiological differentiation between FD and Paget disease is difficult, because in both there are during the course of the diseases hyperostosis in substantia compacta and phases of increased alteration of bones. Whereas the histological finding of intranuclear inclusions in Paget disease are not to be found in FD [33].

2.1.7.3. Osteofibrous Dysplasia (Kempson-Campanacci lesion)

Osteofibrous Dysplasia (OFD) typically is a disease of the childhood and is localised in the tibia, seldom in the fibula. Histologically on bony trabeculae a prominent osteoblastic rim is found and diagnostic imaging shows a multicentric and vesicular extension with sclerotic areas [6, 34].

2.1.7.4. Adamantinoma

The Adamantinoma depends on the low-grade sarcomas and is primarily located in the proximal tibia. The radiology aspect often mimics FD and Osteofibrous Dysplasia. The Adamantinoma is a disease of the adult, but occurs in the first decade, too [6, 67].

2.1.7.5. Low-grade intramedullary osteosarcoma

The differentiation between this malign tumour and FD is rather difficult due to the fact, that there are similar histological and radiological features: The microscopic appearance of the tissue imitates the “Chinese writing” FD form and spindle-formed cells with rare mitotic figures are seen. The predilection site of Osteosarcoma is the lower limb. In many cases the diagnosis can be confirmed only in the course of repeated examination [14, 35, 36].

2.1.8. Prognostic factors

The prognosis for this benign disease is good. Patients progressing from monostotic and polyostotic FD to malignant transformations are rarely recorded.
Most lesions remain clinically silent with the increasing age of the patient, however some of these FD lesions may be activated over the time. Thus normal hormonal changes in lifetime could affect the disease as well [4, 20, 25].

2.1.9. Treatment

Small lesions which are found coincidentally during clinical examinations or x-ray are often clinically inconspicuous and don’t require any form of therapy. They often show typical characteristics on radiographs, therefore a biopsy is not necessary. Observance and regular check-ups are indicated [29].

2.1.9.1. Conservative therapy

2.1.9.1.1. Pain killers

Non-steroidal anti-inflammatory drugs (NSAIDs) are used only for symptomatic treatment in mild bone pain and are suited to be an adequate therapy of this pain. More severe pain even demands narcotic analgesics [22].

2.1.9.1.2. Bisphosphonates

With the development of modern bisphosphonates in the end of 1980s new possibilities in the range of conservative therapy were opened [37]: The antiresorptive potency of nitrogenous bisphosphonates of the 2nd and 3rd generation ascended by several decimal powers and undesirable side effects were reduced to a minimum [38].

A high bone turn-over, great quantities of serum alkaline phosphatase and urinary hydroxyproline are characteristic for FD. Thus open trials with calcitonin and entidronate were started being a counteractive therapy. These trials showed that there is neither an improvement of the laboratory findings mentioned above nor a clinical or radiological change [39]. So in 1994 Liens et al. [40] first described the short term-effects of pamidronate, a bisphosphonate, which was chosen because of its positive effect on bone: Due to its phosphorous-carbon-phosphorous (P-C-P) structure, it is binding on bone materials and hinders the formation and dissolution of crystals including calcium and phosphate [41]. Bone resorption is restricted, less osteoclasts are built and their apoptosis rate is enhanced [38].
Osteoblasts are formed and activate a factor which inhibits the building of osteoclasts [38, 40, 42]. Patients treated with this therapy stated a decreased pain intensity and radiographs show a thickening of cortices [40, 43], a filling of radiolucent lesions, due to an ossification and a reduction of the diameter of the lesions.

Pathological fractures are not mentioned and there is a functional improvement in patients [44, 45].
As already mentioned side-effects are less common: After starting a bisphosphonate therapy sometimes flu-like symptoms like fever, bone pain, headache and fatigue can be found. In further treatment these symptoms become less or disappear. Other side-effects to be mentioned are mineralization defects, hypomagnesaemia, hypocalcaemia, renal an ocular changes [38]. Due to mineralization problem regular monitoring is important especially in young patients [29, 46].

2.1.9.1.3. Calcium and vitamin D

Calcium and vitamin D supplements are subscribed to avoid the development of secondary hyperparathyroidism and enhance the effect of a therapy with bisphosphonates [38, 47, 48].

2.1.9.2. Surgical intervention

Surgical intervention is required for patients with constant episodes of pain, frequent bone fractures and initiating bone deformations. Often early appropriate surgical treatment can prevent or keep deformities in a minimal form [23]. The choice of treatment options depends on the age of the patient, the localisation of FD, and the expansion and the biological behaviour of the disease. Patients with FD in their upper limbs have less functional restrictions than patients where the disease focuses on their weight-bearing bones [29]. The range of surgical interventions stretches from open biopsy, simple curettage, curettage and bone grafts (cancellous/cortical allogenic or autologous grafts), plates, screws, wires, pins to intermedullar fixations, osteotomy or amputations. In literature there are various approaches to these possibilities [23, 29, 49, 50]. A simple curettage is to be omitted due to the risk of a recurrence of the disease [29]. In rare cases an adequate surgical therapy is impossible. This depends on the localisation of the lesion: The pelvis for example is difficult to handle. In the main cases the purpose is pain reduction [23, 49].

Craniofacial located FD shows an exceptional position: In asymptomatic forms the maxim is wait and see, but if there is a functional limitation or psychical pressure surgery is utilized. Cause of modern navigation-based re-constructions the length of the operation and physical load are reduced [51].

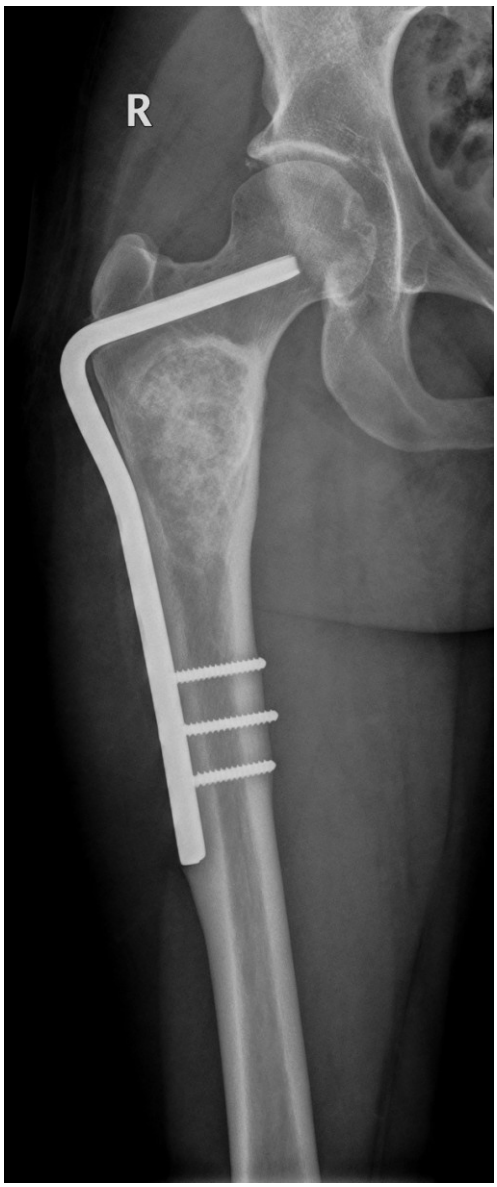


Figure 3: X-ray of the right proximal femur of a 22-year old woman after an open curettage, refilling the lesion with a synthetic bone graft and cancellous bone of the iliac crest and stabilisation with an angle plate.

3. Materials and Methods

3.1. Study design

This study is an analysis of patients' with the diagnosis "Fibrous Dysplasia", "McCune-Albright syndrome" and "Mazabraud syndrome", who were registered in the period from 1984 to 2008 by the Institute of Pathology. Patients' data were retrospectively collected by a personal consultation. The study was approved by the Ethics Committee, Medical University of Graz.

3.1.1. Patients

The recruitment of patients was made by a direct query from the central patient database of the Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz with the documentation system AURAweb: It was a search for all histological probes and a tabulation of corresponding patients with the diagnosis mentioned above (see 3.1) of Medical University of Graz and Styrian state hospitals in the period from 01.01.1984 to 30.11.2008. Patients were sorted alphabetically and considering additional information about date of birth, age at diagnosis, location of the biopsy, histological diagnosis and in which hospital the patient was treated.

As a result 138 patients corresponded to these hallmarks. According to the present study protocol criterions for inclusion in the study have been histological evidenced FD in all locations, all ages and no sexual discrimination. Criterions for exclusion from the study have been missing validation of the diagnosis.
After reviewing the patients' files 14 patients had to be cancelled because the diagnosis wasn't confirmed. The remaining 124 patients were included in the study.

Out of these 124 patients in 109 (87.9%) patients the disease was presented in a monostotic infestation and in 15 patients (12.1%) it was a polyostotic form. In all

124 cases patients' samples fixed in paraffin are available. The histological diagnosis and disease classification was done according to WHO guidelines.

To ensure a long-term follow up, a personal contact with patients was required. It was possible to get 88 (71.0%) patients on the phone, respectively assented to participate this study (see Appendix).

3.1.2. Methods

3.1.2.1. Case Report Form (CRF)

The basis to the following statistical compilation was the CRF (see Appendix). In addition to general information about the patients the collected data rested on diagnostic findings, the location of the disease, family history, previous interventions and therapy. The main focus of this work was the quality and intensity of the pain. The "Pain Numeric Rating Scale" (PNRS, in literature NRS-11 too, see Figure 4) was used, because pain intensity can be measured quantitatively:

According to Hartrick et al. [52] this score is proved in clinical trials because of its easy handling:
On a scale from 0 to 10 patients were asked to rate their pain intensity, when 0 means no pain and 10 the worst pain possible.

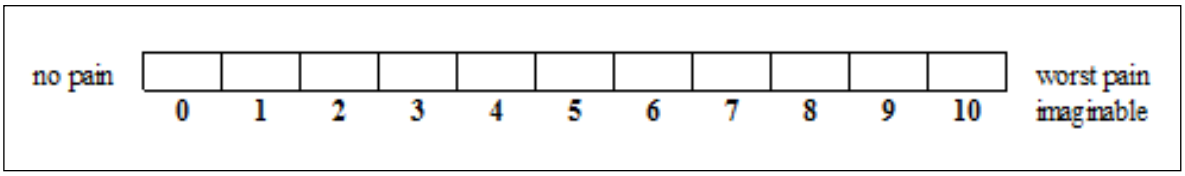


Figure 4: NRS-11.

This score was required for three different issues: The current intensity of the pain, the best and worst pain level during the disease.

In addition further questions were relevant for this work: Does the pain exist unbroken or is it intermittent and are there any causes and points of time for its appearance? Do the patients feel aggrieved?

All given answers were collected in the CRF.

3.1.2.2. Database

The data out of the CRF were entered into a computerized database (Excel 2007, Microsoft Corporation, Redmond, Washington) in order to do further statistical evaluations.

3.1.2.3. Analysis

Out of the data record the following questions were compiled in this thesis: (see 4. Results)

a. Is there a distinction between the CF and NCF localisation of the disease?
b. Which conclusion can be made out of the comparison of MFD and PFD?
c. Can a familial clustering be realized?
d. Are there any differences in the individual pain course of the patients?
e. Variations of the previous therapeutic measures.
f. Where are the difficulties in the distinction between the diagnosis FD and its differential diagnoses?

All relevant data were analyzed statistically with SPSS Statistics 17.0 (IBM Company, Chicago, Illinois): Crosstabs (Chi-square-test) and Independent-samples t-tests were chosen as the most important tools for comparison of the recorded data and p-results smaller than 0.05 have been counted as significant. Diagrams were drawn with Excel 2007 (Microsoft Corporation, Redmond, Washington).

The research of literature was made by a direct query through the database PubMed, in books and journals.

4. Results

4.1. **Patients collective** (Table 3)

Out of 124 patients with the histological confirmed diagnosis of FD, there were 53 male (42.7%) and 71 female (57.3%) patients with a mean age at diagnosis of 35.7 years and a range from 6 to 82 years. Sixteen patients (12.9%) were younger than 19 years (from 6 to 16 years) and 108 patients (87.1%) were between 19 and 82 years at the time of their first diagnosis. Information about patients' reasons to consult a doctor was known in 104 cases and were on the one hand painful periods or permanent pain on the afflicted spots (44.2%; 46/104), an increasing indolent swelling (10.6%; 11/104), any fractures (5.8%; 6/104), deviations (1.0%; 1/104) and hearing impairment (1.0%; 1/104). On the other hand it was a coincidental finding (37.5%; 39/104) mostly in radiological examinations. (Figure 5)

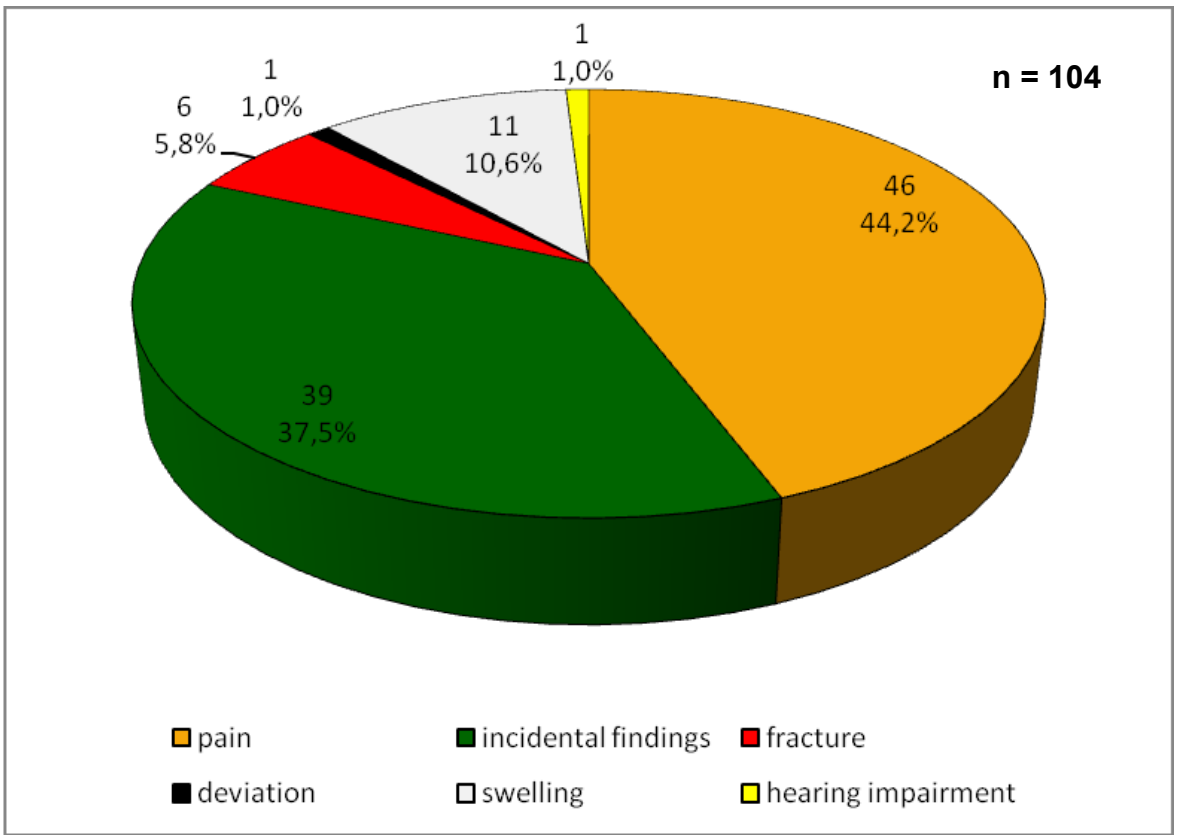


Figure 5: Initial presentation of FD.

FD affected many parts of the skeleton, thus to facilitate the analysis the lesions were classified into two groups: Craniofacial (CF) and Non-craniofacial (NCF). Lesions in the spine, costae, humerus, radius, ulna and carpal bone, pelvis, femur, tibia, fibula and tarsal bone belong to the NCF area. In 42 (33.9%) patients CF-lesions were found and in 80 patients (64.5%) they were particularly multiple in NCF areas. Two patients (1.6%) did not match these two groups because FD was diagnosed both in CF and NCF.

Monostotic FD was diagnosed in 109 patients (87.9%) and in 15 patients (12.1%) the polyostotic form of FD was found. In one male patient the polyostotic affliction in his right tibia and femur and a café-au-lait spot in the area of the thoracic spine indicated MAS. A female patient suffered from Mazabraud Syndrome (lesions in her spine, pelvis, left and right femur, left tibia and upper arm and three intramuscular myxomas in her left thigh).

Table 3: Patient demographics.

Demographic		Value
Number of patients		124
Sex, n (%)		
	Female	71 (57.3%)
	Male	53 (42.7%)
Age (y) at time of diagnosis		
	Mean	35.7
	Range	6 – 82
Age groups, n (%)		
	Child (≤18 y)	16 (12.9%)
	Adult (>18y)	108 (87.1%)
FD distribution, n (%)		
	Monostotic	109 (87.9%)
	Polyostotic	15 (12.1%)
FD associated with a syndrome, n (%)		
	McCune Albright Syndrome	1 (0.8%)
	Mazabraud Syndrome	1 (0.8%)
Localisation, n (%)		
	Craniofacial	42 (33.9%)
	Non – Craniofacial	80 (64.5%)
	Both (CF + NCF)	2 (1.6%)

4.2. Monostotic FD versus polyostotic FD

Out of 124 patients in 87.9% (109/124) a single FD lesion was found, in 12.1% (15/124) at least a second one was seen. In Figure 6 the localisation of patients' tumour was pooled and shown separately in monostotic and polyostotic afflicted patients. MFD patients' mean peak of age at the time of diagnosis was 35.5 years (range from 7 to 82), PFD patients were older (37.1 years; range from 6 to 80). The initial presentation presented next to a high rate of main symptom pain in both groups, in monostotic forms patients were worried about a swelling or lesions were discovered by accident, whereas polyostotic patients were presented with fractures and deviations. (χ^2=15.868[a], p=0.007)

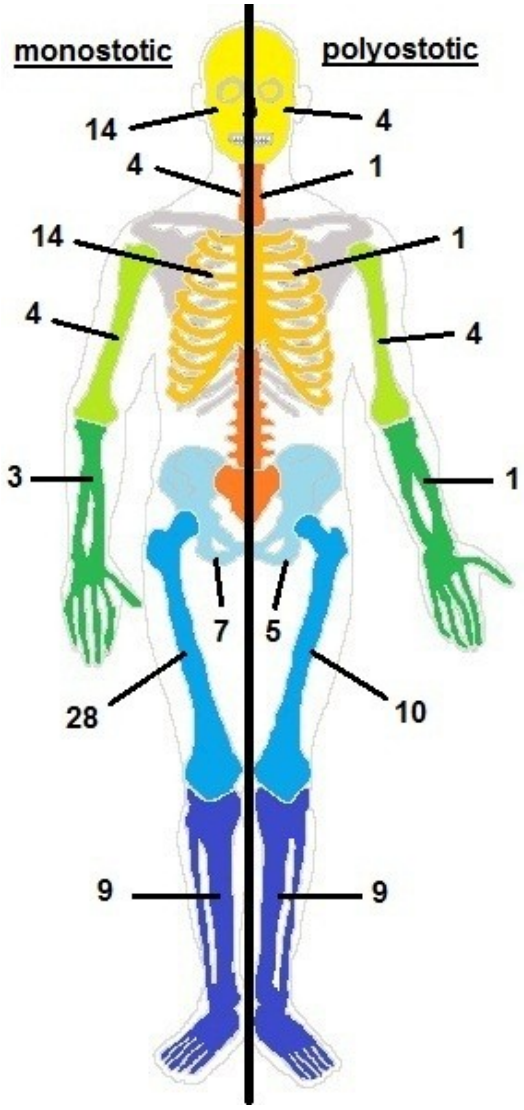


Figure 6: Localisation of the tumour.

A significant difference in sexual distribution could not be observed just as a slight tendency towards more limitations of patients with PFD (χ^2=2.763[a], p=0.096). As regarded syndrome-associating FD was found in the polyostotic form (χ^2=12.887[a], p=0.002).

4.3. CF and NCF localisation

All 124 patients were separated into two groups, 42 patients (33.9%) belonged into CF group and 80 patients (64.5%) into NCF group. Two patients (1.6%) could not

be matched into a specific group thus they were not valued in the statistical analysis.

Regarding the sex distribution within both groups, there were significantly more female CF-patients (73.8%; 31/42) than male (11/42) and more male NCF-patients (51.3%; 41/80; χ^2=7.072[a], p=0.008). The mean age was 36.7 years with the range from 6 to 82 in NCF group and 33.4 years (range from 8 to 63) in the other group.

Only one bone was involved in 95.2% (40/42) of CF-patients, in two (4.8%) patients there were several bones afflicted, and in NCF patients a monostotic form was found in 86.3% (69/80) and the polyostotic form in 13.8% (11/80).

NCF-patients presented themselves in 53.4% (39/73) with pain, whereas 44.8% (13/29) of the patients in the second category did not have any complaints and the diagnosis was made by accident. (Table 4)

Table 4: Primary complaints.

	pain	fracture	swelling	hearing impairment	incidental findings	total
CF	6	0	9	1	13	29
NCF	39	6	2	0	26	73

Further 81.5% (22/27) of CF-patients stated to have no limitations in their daily life (χ^2=3.867[a], p=0.049)

4.4. Familial clustering

In 95 patients a declaration about the family history was made: In three patients out of them, the same disorder was stated anamnestically in their relatives (two siblings and one cousin). To confirm these statements no files were available.

Statistically no evidence for a familial clustering was found (χ^2=83.379[a], p=0.000).

4.5. Individual pain course

There were records about the pain situation in 97 patients' files (78.2%) out of 124 cases. 63.9% (62/97) complained of pain during the course of their disease, 28.2% (35/97) were painless. According to sexual distribution there hardly was any difference as well in the pain rate as in the pain intensity.

After 88 patients could be contacted by phone, following statements about their individual pain course could be collected and illustrated in Figure 7:

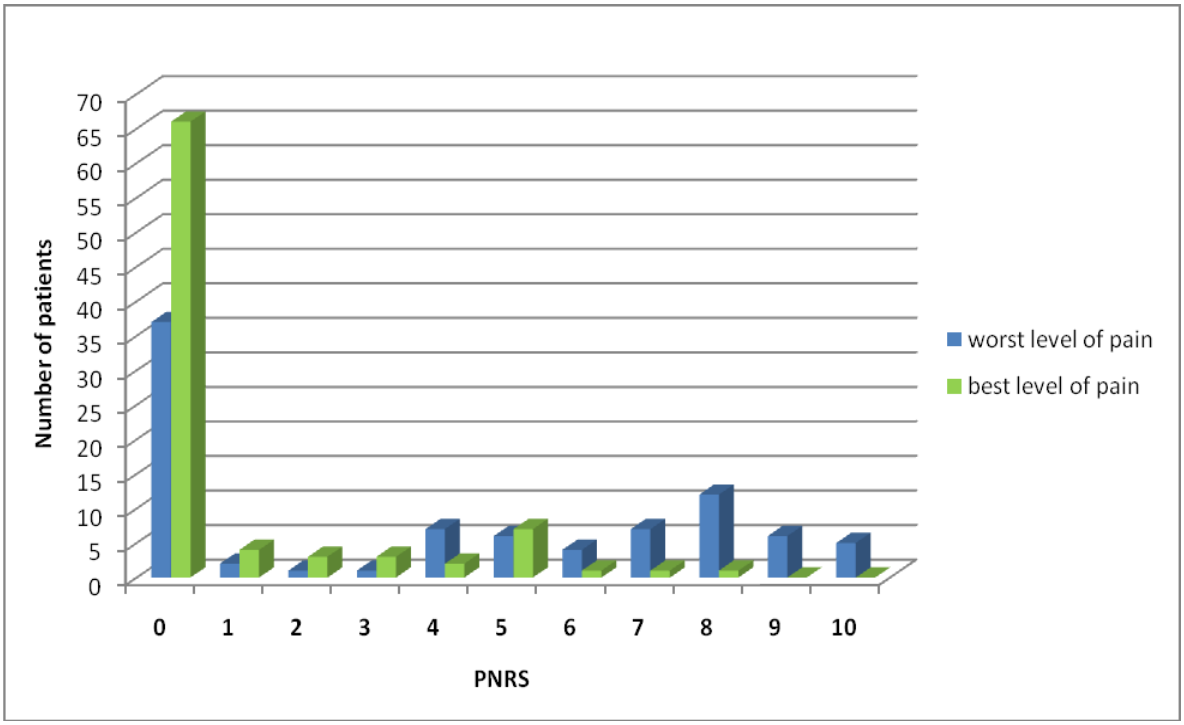


Figure 7: The comparison of the worst and best pain level in the acute-phase.
(Legend: PNRS = Pain numeric rating scale)

Regarding pain in the acute-phase of the disease 42.0% (37/88) of the patients were without pain, in 19.3% (17/88) the worst pain level was slight to moderate (pain scale from 1 to 5) and 32.5% (29/88) claimed for pain on the PNR-Scale from 6 to 9. In the remaining patients (four women and one man; 5.7%) the pain was such excruciating, no harder pain was imaginable (PNRS: 10). To sum up, there was a mean value of 3.84 of worst pain intensity on the pain scale.

In comparison to the best level of pain: 75% (66/88) were painless, in 19 patients (21.6%) the pain was between 1 and 5 on the ranking scale and in three cases (3.4%) it was more severe. The mean value was 0.94.

All patients were also asked about their current condition:
The average follow-up period after the time of diagnosis was 11.1 years (range from 2 to 26 years). At the moment of call 75.0% (66/88) did not feel any pain in the area of their former lesion and 20.5% (18/88) of patients stated a well tolerable pain (PNRS: 1 to 5), 4.5% (4/88) a more awful one. (Figure 8) The mean value resulted in 1.00 on the ranking scale.

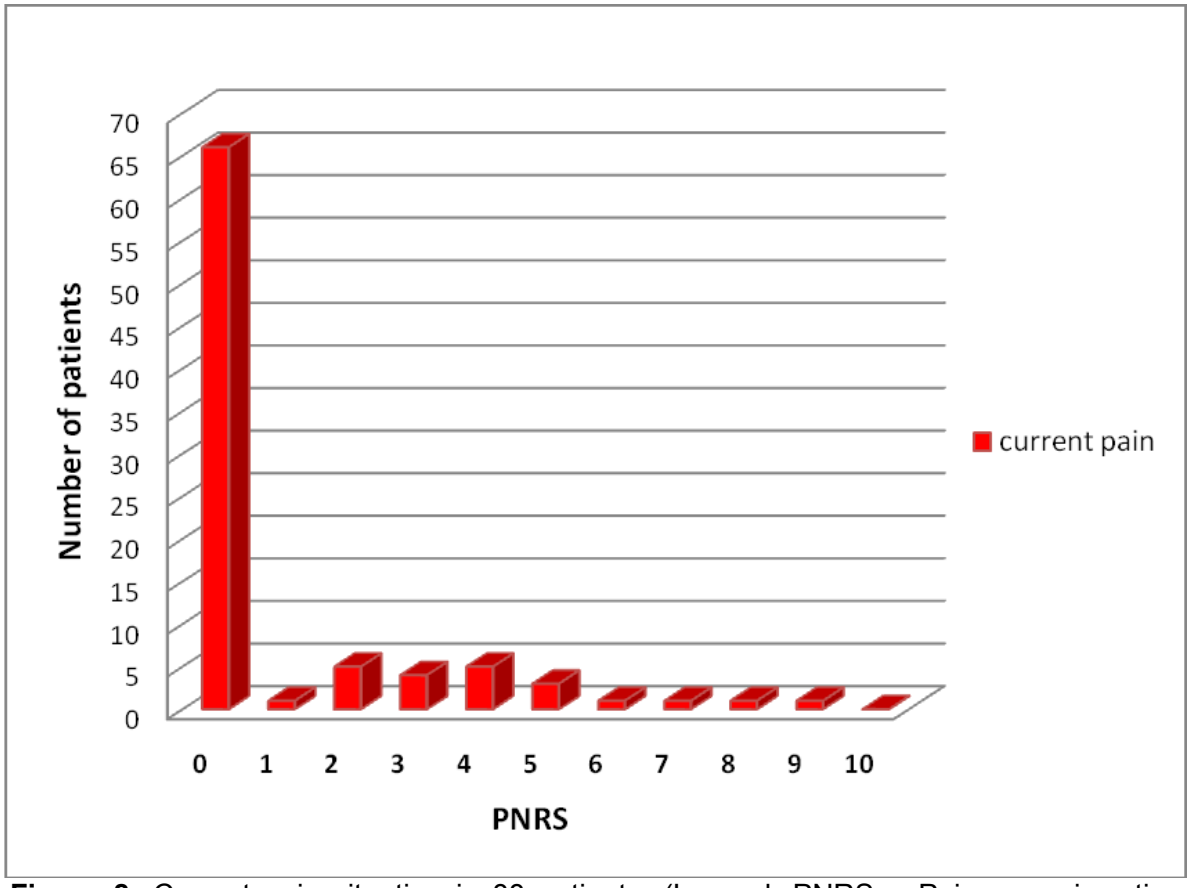


Figure 8: Current pain situation in 88 patients. (Legend: PNRS = Pain numeric rating scale)

Normally 55.7% (49/88) were pain-free but on the other side 13.6% (12/88) experienced pain the whole time and 30.7% (27/88) sporadically. Pain was brought up with partially multiple factors: In rest, in night and in stress. Twenty-eight patients (31.8%) were sensitive to changes in the weather.

In 73 cases statements about treatment and pain were available: (see Figure 9)
There were two patients with exclusive pharmacological treatment (one with bisphosphonate and one with NSAIDs), 63 patients with surgical intervention and eight patients treated with both.
After treatment, patients without pain increased and the rate of permanent or intermitted pain became less.

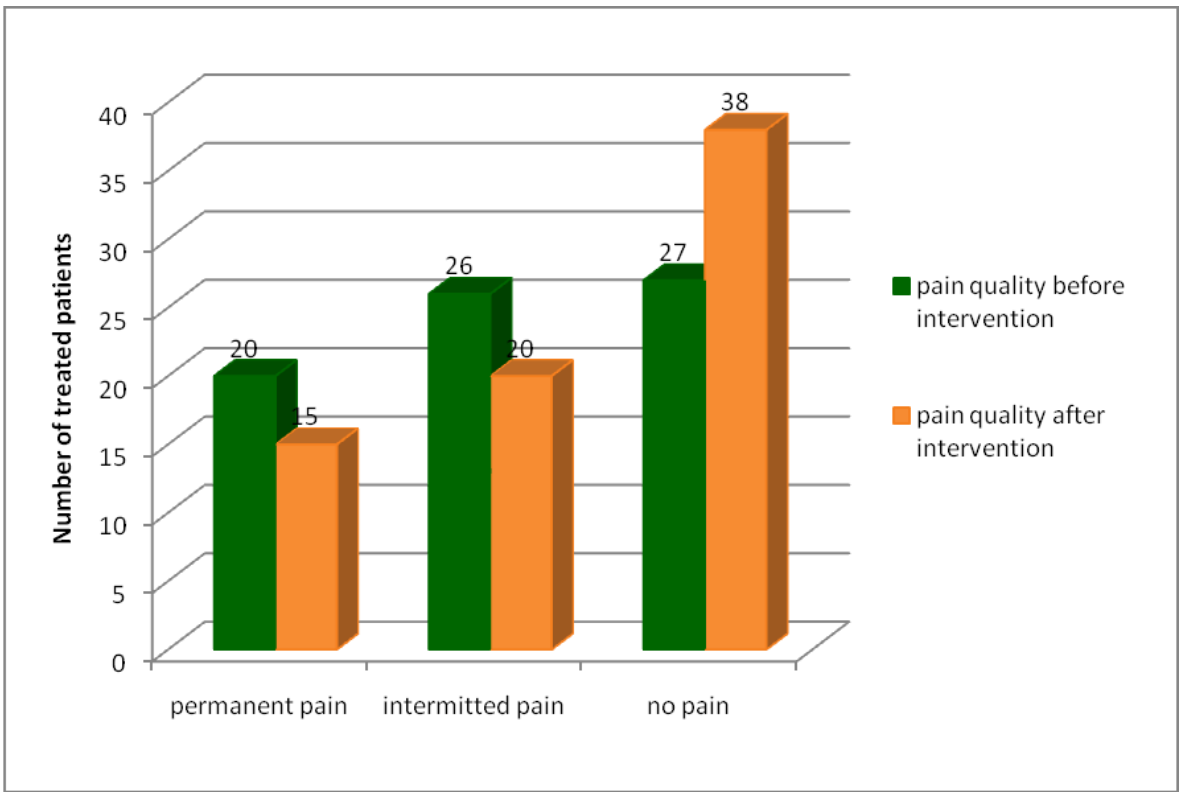


Figure 9: Information about pain before and after therapy.

4.5.1. Pain in MFD/PFD patients

Concerning the pain numeric rating scale and in comparison of monostotic and polyostotic disorder, the average pain intensity at present and during the acute phase was illustrated in Figure 10. The mean value of the pain intensity showed significant differences in monostotic and polyostotic patients in regards to a current ($t86=-2.288$, $p=0.025$) and the worst pain level ($t86=-2.483$, $p=0.015$) but only by tendency in the best level of pain ($t86=-1.698$; $p=0.093$).

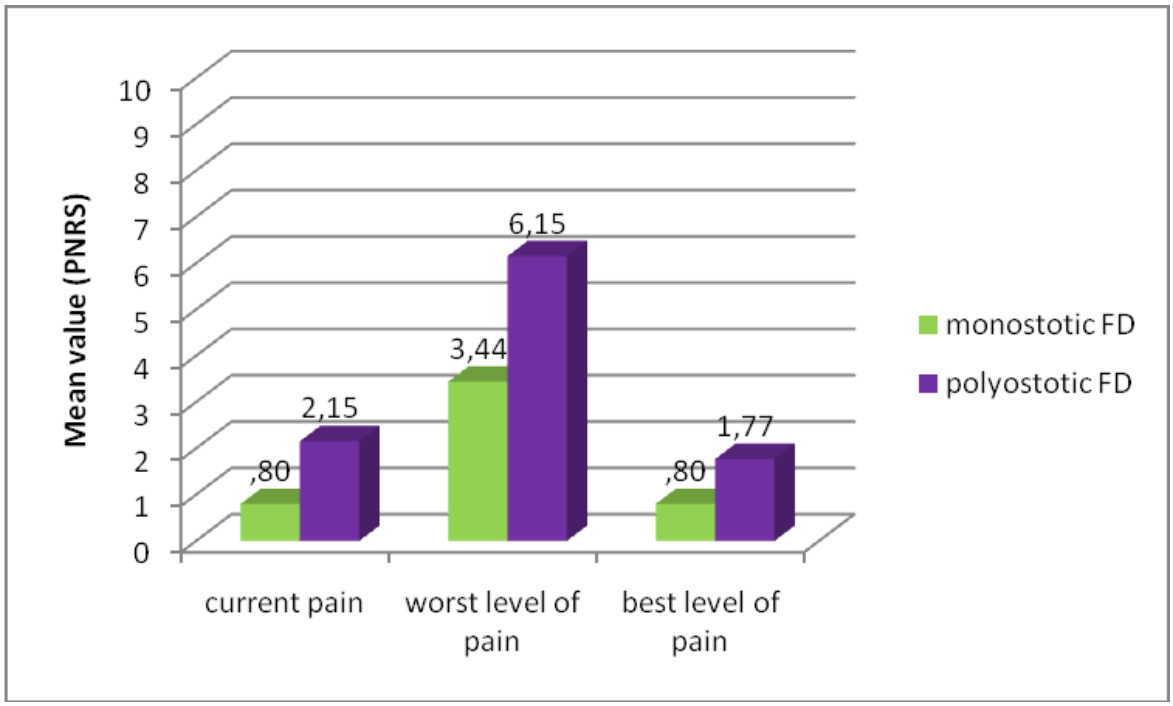


Figure 10: Mean value declaration of pain intensity (MFD/PFD).

4.5.2. Pain in CF/NCF patients

Pain was significantly detected in the NCF group (76.5%; 52/68), whereas only one out of three (33.3%; 9/27) of all CF patients felt pain (χ^2=15.649[a], p=0.049).

The collected facts out of the PNRS separated in CF and NCF patients regarded a definite difference in pain intensity: In NCF-patients the mean value of the worst pain during their disease course was higher than in CF patients (mean worst level of pain NCF=4.81; mean worst level of pain CF= 1.85; t84=-3.619, p=0.001). For the best level of pain during illness and for the current pain status there were no descriptive differences.

Figure 11 shows a comparative illustration of mean values within these different groups:

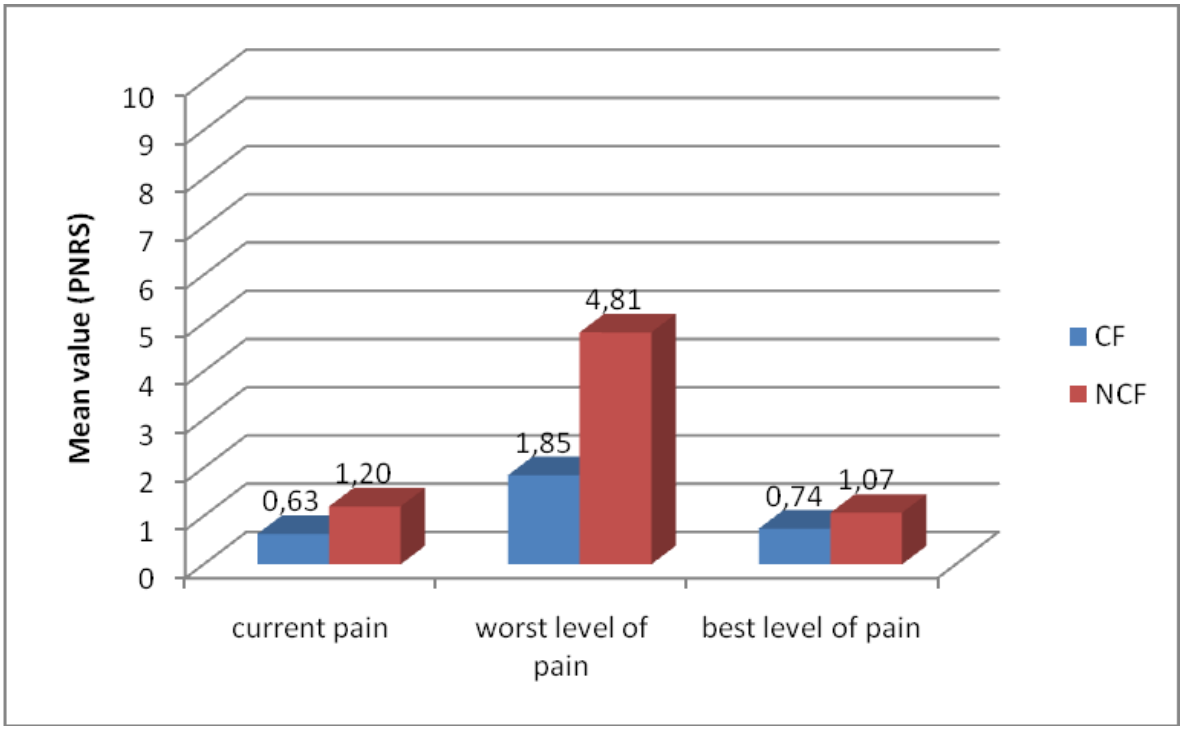


Figure 11: Mean value declaration of pain intensity (CF/NCF).

In Figure 12 the distribution of FD lesions in our 52 NCF pain patients is illustrated, which shows a predominant involvement of the lower limb:

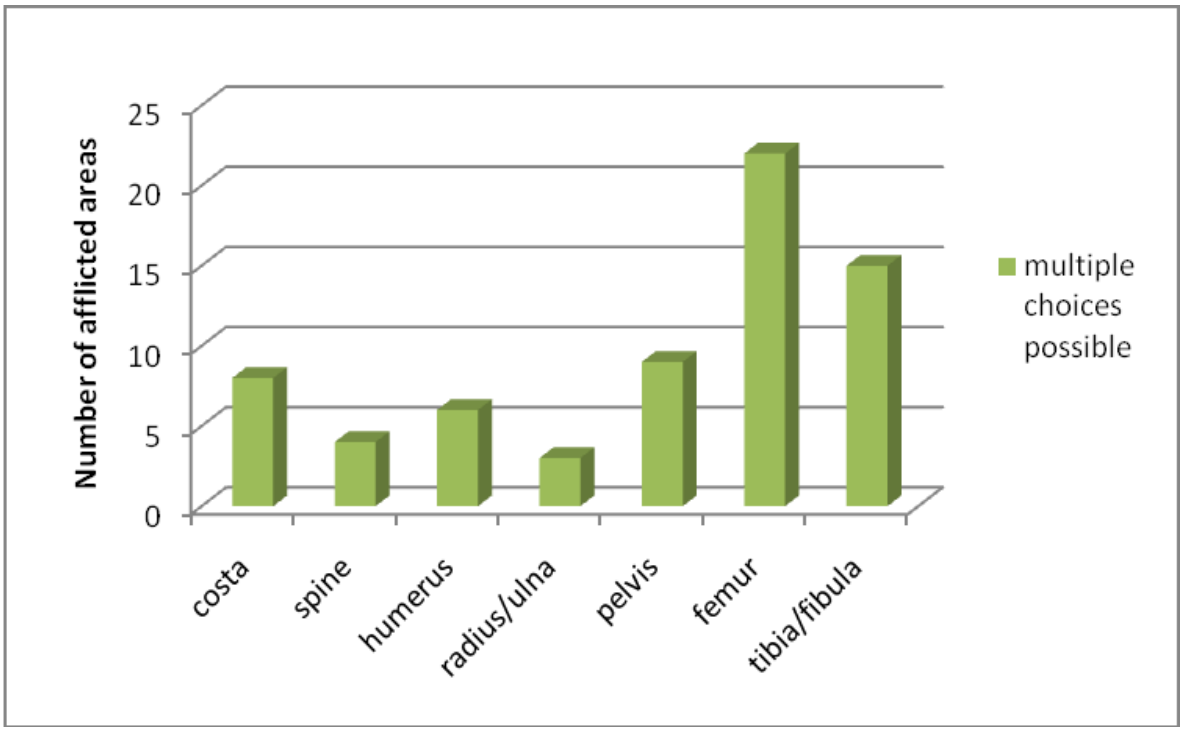


Figure 12: FD located NCF areas in patients with pain.

4.5.3. Pain in different age groups

A separation of our 88 patients concerning their age at the time of diagnosis into children (all patients ≤18 years) and adults (>18 years) and the analyses of painful periods during their course of disease showed an explicit picture: Children indicated less frequently pain during the course of the disease than adults. In 80% (8/10) the patients of the child-group never felt any pain, whereas only 37.2% (29/78) of the adults are totally painless during the whole time (χ^2=7.696[a], p=0.021). At the moment of call all patients (10/10) of the child-group were painless, but only barely half (48.7%, 38/78) of the patients in the adult-group (χ^2=9.402[a], p=0.009). In 34.6% (27/78) they were still suffering intermitted pain periods.

Regarding the pain intensity children reported significantly less pain in the acute phase: The mean value of the worst level of pain was 1.40 in the child-group, but about three points higher in the reference group (mean value: 4.15; t_{86}=-2.660, p=0.028). In Figure 13 the mean values are compared illustrated:

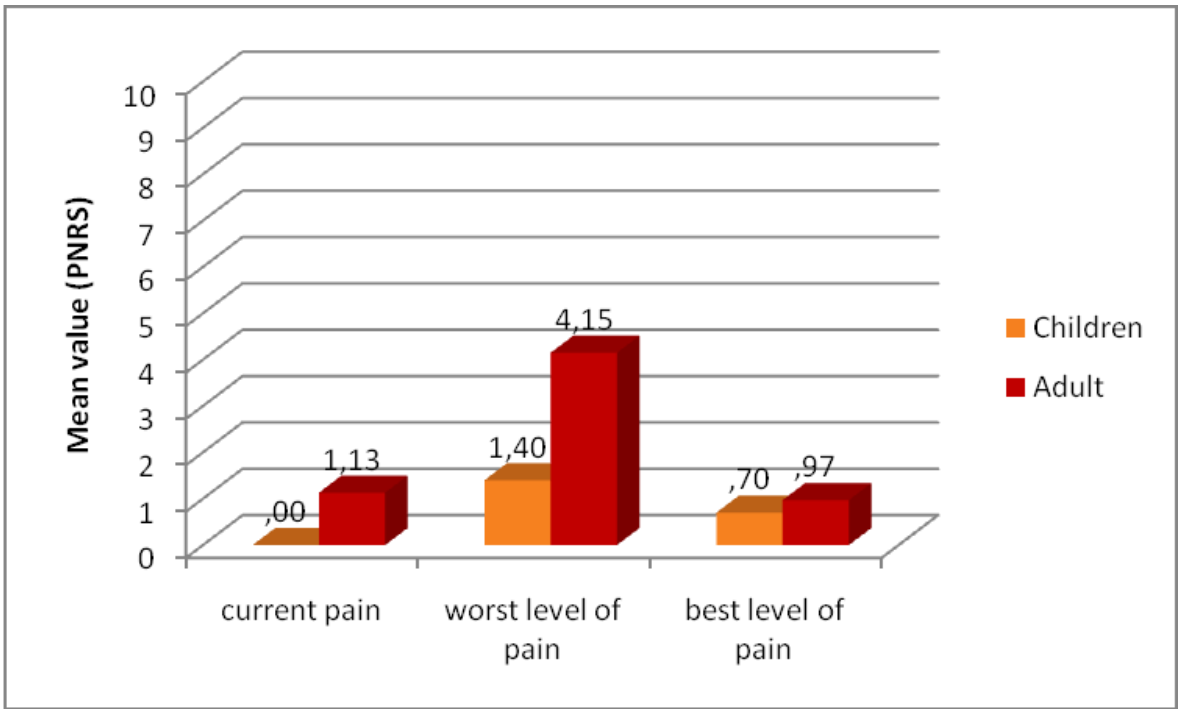


Figure 13: Mean value declaration of pain intensity in different age groups (Child/Adult).

4.6. Therapeutic interventions

4.6.1. Incisional biopsy

Histological probes of 124 patients were available:
In 18 cases (14.5%) there was no further information about the method of specimen excision and no other surgical intervention beside an exploratory excision in 22 patients(17.7%). In the other patients (67.8%; 84/124) the probe finding took place with biopsy and/or curettage, respectively within their surgical treatment.

4.6.2. Surgical intervention

Due to the missing treatment information in 18 patients (14.5%; 18/124), the follow up of the remaining 106 patients (85.5%) was possible:

No further surgical treatment except for histological diagnostics was necessary in 43.4% (46/106). Pharmacological therapy and/or supervision were sufficient.
Otherwise one or more surgical interventions were required in 60 patients (56.6%).

In Figure 14 all details were summarized:
A biological autologous or allogenic cancellous bone-grafting was used in 31 cases. The autologous tissue was mainly taken from the iliac crest of the patient.
In 19 times synthetic cancellous bone was implanted in order to refill the curetted area. For adjuvant therapy, phenol was applied in 13 cases. The use of gelatine sponge (Spongostan® [Johnson&Johnson Medical, New Brunswick, New Jersey], three cases) and bone cement (four cases) was rarely indicated.
For internal fixation and stabilisation a variety of osteosynthesis techniques were stated: Bone intramedullary rods in seven cases, plates (dynamic compression plates, angle plates, etc.) and screws in 19 cases.
Particularly if ribs were affected, a resection or partial resection was performed (11 patients).

In six CF patients a functional endoscopic sinus surgery (FESS) was done and after the affected tissue in the jaw bone was scraped out, the lesion was refilled with autologous blood in two persons.

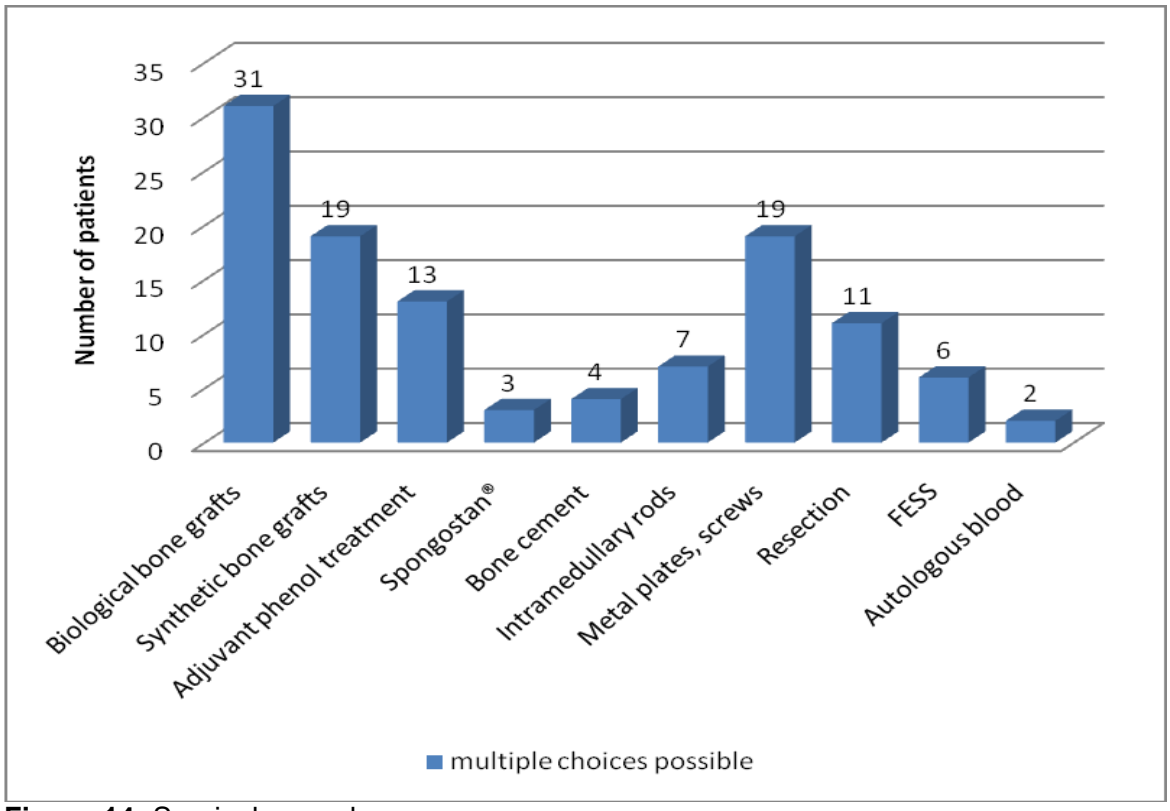


Figure 14: Surgical procedures.

4.6.3. Conservative intervention

The main indication of pharmacological therapy is its analgesic effect. In early times NSAIDs and narcotic medicaments were used for symptomatic therapy, but with the development of a new generation of bisphosphonates this group of drugs was increasingly prescribed for pain-relieving and stabilisation of the disease [40].

Analysing all existing data details about the conservative therapy in 72.6% of the patients (90/124) were found:
Out of these 90 patients 78 (86.7%) did not consume any remedies, six patients (6.7%) took bisphosphonates, five (5.6%) NSAIDs and one (1.1%) a combination of bisphosphonates and NSAIDs.

Especially focused on patients with bisphosphonate therapy the following message was found: Out of seven cases treated with bisphosphonates, in five patients (71.4%) the polyostotic form and two times (28.6%) the monostotic form was found. In the non bisphosphonate-treated contrary group of 83 patients, eight cases (9.6%) were polyostotic and 75 (90.4%) were monostotic involved (χ^2=19.944[a], p=0.000).

In one of seven times (14.3%) it was enough to handle the disease only with bisphosphonate therapy, in six patients (85.7%) additional surgery was necessary.

One of the seven bisphosphonate patients again never had any pain during the course of their disease. Regarding the pain mean value, patients treated with bisphosphonates claimed of significantly more pain (mean: 7.57) in their worst level before treatment than the comparison group (mean: 3.52) of patients without a bisphosphonates therapy (t_{86}=-2.858, p=0.005). In the current evaluation after treatment the mean value of pain in the bisphosphonate group was 4.57 and in the second group 0.69 (t_{86}=-5.697, p=0.000). (Figure 15)

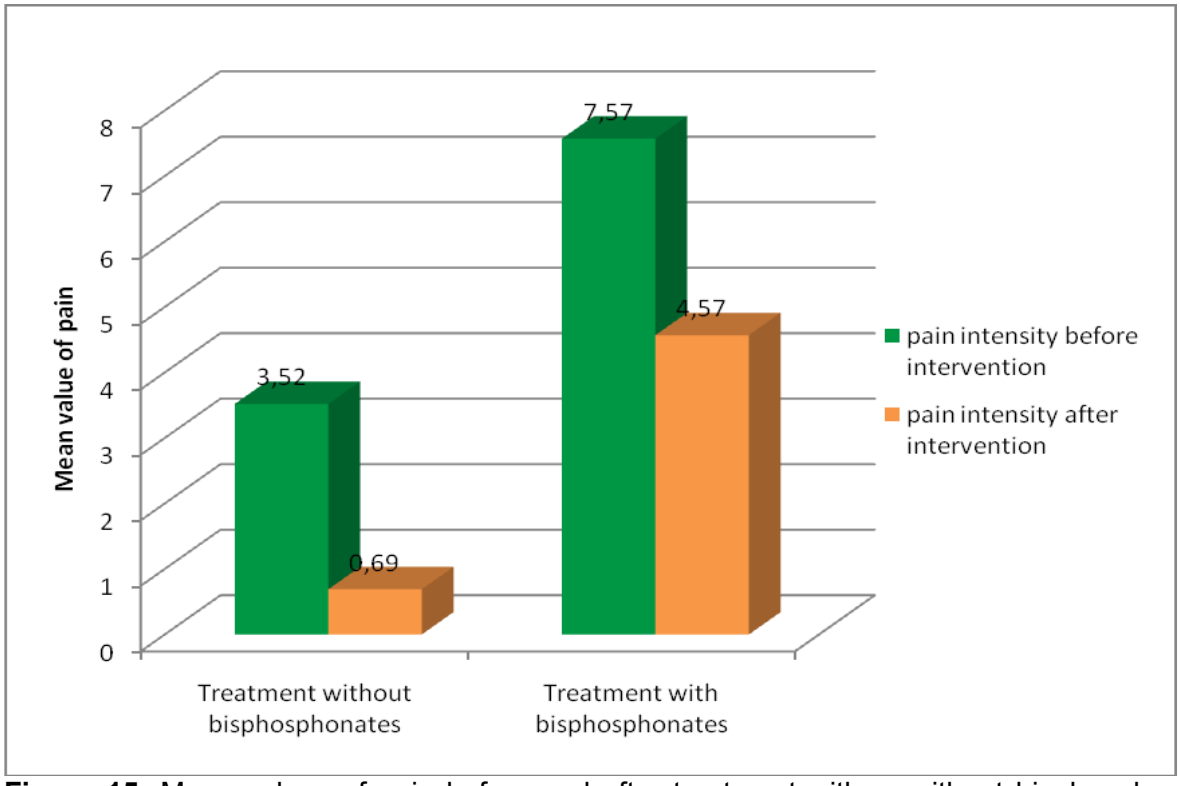


Figure 15: Mean values of pain before and after treatment with or without bisphosphonates.

4.7. Difficulties in diagnostic procedure

As previously mentioned (see 3.1.1) our patients were found by a computer-assisted query through the central patient database of the Medical University of Graz: Corresponding to the hallmarks 138 patients were filtered. After rechecking the results, we found in 14 patients no correct match with the diagnosis FD. These patients had to be excluded out of the study.

In more exact search the problem of these false positive findings in seven patients (patients no. 2, 3, 22, 49, 55, 108, 134) could be realized:
The automatic search of a computer through patients' profiles for the words "Fibröse Dysplasie" was also finding patients with "*Osteofibröse Dysplasie*" (compare 2.1.7.2 OFD) and histological descriptions in which the differential diagnosis FD was excluded (patient no. 49: *[...] Das Bild der Fibrösen Dysplasie liegt nicht vor. [...]*)

The other seven cases I want to elucidate in a short way:

Patient no. 7:
A female patient, 61 years at the entrance clinical examination, motion-dependent pain since three months and swelling in this area since two months.
02/2005: exploratory excision with suspected FD, which was histologically verified.
10/2005: biopsy out of a supposed FD recurrence: 1) Histologically verified FD, but x-ray and clinical finding was not conforming to this diagnosis. 2) Second and third histological opinion were obtained with the result: Low-grade intramedullary osteosarcoma.

Patient no. 56:
Eleven-year old female patient.
06/1986: Histological diagnosis: Osteoidosteoma with differential diagnosis FD, in further examination Osteoiosteoma was validated.

Patient no. 82:

A female patient, 21 years at the time of first diagnosis, painless swelling in the lower part of her left thigh.

02/2004: Aneurysmal bone cyst with parts of fibrous and osseous tissue (Non-ossifying fibroma), but FD and a giant cell tumour were not to be excluded due to missing radiological images.

03/2004: Second and third opinion: Non-ossifying fibroma with aneurysmal bone cyst.

Patient no. 86:

A woman (22 years) complained of a remarkable lesion on her sternum since one year, which shows a recently painful swelling.

12/2001: Benign fibrous histiocytoma.

01/2002: Finding re-evaluation: A morphological differentiation of benign fibrous histiocytoma and FD impossible. Radiological findings were absent.

01/05: Benign fibrous histiocytoma.

Patient no. 91:

A 46 year old female patient, progressive capacity restraint disorders on her right thigh.

04/2001: Probe excision: FD. Curettage and refilling of the lesion with autologous bone graft and fixation with plates, but the clinical diagnosis could not be established. Second and third opinion: FD, fourth opinion: Malign fibrous histiocytoma.

05/2001: Malign fibrous histiocytoma.

06/2001: Malign fibrous histiocytoma and wide resection.

Patient no. 100:

A female patient, 23 years at the entrance clinical examination.

06/2003: No clear histological diagnosis possible (differential diagnosis: intraosseus lipoma, FD, bone infarction). There was no x-ray at hand.

07/2003: Re-biopsy due to the increase of the lesion. Histological differential diagnosis: Small-cell osteosarcoma and Ewing tumour. After genetic examination the diagnosis Ewing sarcoma was confirmed.

Patient No. 103:

A three years old boy.

03/1992: FD.

07/1996: Osteofibrous Dysplasia.

5. Discussion

This rare disorder, first described by Lichtenstein [5] in 1938, entitled “Polyostotic Fibrous Dysplasia” and after discovering monostotic forms too, retitled in “Fibrous Dysplasia of bone” by Lichtenstein and Jaffé [1] in 1942, shows characteristic changes within the bone.

5.1. Patients collective

In the more recent literature there are no sexual differences in the patients’ collective reported [4, 17, 53]. In contradiction Jaffé [54] spoke about a definitive overhang into the female direction and Unni [15] only about a slight one. In our collective the rate of the sexual distribution was 1:1.3 (male:female).
In many cases the manifestation of the disease is in the adult age (60% upon the 40 year of age) [15, 53]. Whereas Chapurlat et al. [17] reported the beginning of initial symptoms already in childhood, but bone pain and fractures occured in adulthood. Harris et al. [18] spoke about the onset of symptoms before the 10^{th} year of age in two-thirds of their cases. The mean age of our patients at diagnosis was 35.7 years (range from 6 to 82).

An interesting aspect in the research of literature is the outstanding high thematisation of syndrome-associated FD (MAS and Mazabraud Syndrome) by contrast with the real rate of appearance. That results in a wrong impression (see Henry [20]) of their indeed incidence: Epidemiological descriptions of MAS suppose prevalence between 1:100,000 and 1:1,000,000 [2]. Pollandt [13] summarized that up to 2002 there are 52 cases of Mazabraud found in literature at all. In my work one patient was afflicted to MAS, another one to Mazabraud Syndrome.

5.2. Monostotic FD versus polyostotic FD

MFD is more common than PFD. General information fluctuate between 9:1 to 3:2 (monostotic versus polyostotic) [4, 17, 53, 55]. Our collective showed a dominant distribution in the monostotic direction, it was about 7.3 times more common.
Monostotic forms are often asymptomatic and are detected by accident. The initial presentation age is between twenty and forty years, whereas in PFD symptoms arise earlier in childhood [56]. In our office population the mean age of patients, who sought advice, was in the monostotic group 35.5 years and in the other group 37.1 years. This is according with Pollandt's outcome [53].

5.3. CF and NCF localisation

We could not find a separation of patients in CF and NCF and a comparing exposition in orthopaedic literature in the same way we did it. The idea to divide our population in these groups grew out of Riminucci's findings [30] according to different histological appearance of FD in CF bones and bones elsewhere. Therefore we looked for possible clinical differences.
In literature patients with lesions in skull and jaw are very well pooled in CF patients, while on the one hand FD in NCF-locations is treated for each region separately, on the other hand CF and NCF lesions are summarized in one group, because the researchers are more interested in differences MFD to PFD.

Our study showed a sexual distribution towards more female patients with lesions in the CF area than male with the ratio 3:1. This result is equivalent to the outcome of Kruse et al. [57], but Lustig et al. [58] described a male to female ratio of 2:1. On the contrary, in our collective more male than female patients belonged to NCF group. The analysis of the mean age at diagnosis was in NCF patients 36.8 years and in our CF 33.4 years. CF-Patients in the study of Kruse et al. [57] and Valentini et al. [59] were about nine to eleven years younger.

In their analysis Valentini et al.[59] reported about 68 CF patients: An affliction of only one bone was seen in 76%, the polyostotic form in 24%. This is conforming to our results: In our CF cohort (42 patients) there were definitively more patients (95.2%; 40/42) FD presenting themselves in monostotic form. As opposed to these results other authors mentioned an overflow in polyostotic direction in CF patients [58].

5.4. Familial clustering

Due to a sporadic stem cell mutation FD is a non-hereditary disorder [14]. As well as in the study of Dämmrich et al. [51] in our patient population was no significant prevalence found.

5.5. Individual pain course

Effectively in most FD papers, which are available for us, pain is declared as a common clinical symptom. Thus, it was surprising, that there are little studies, which contain pain by itself as subject related to an individual pain course of patients. We even found only one study where pain is the main theme of the analysis: Kelly et al. [22]: *Pain in Fibrous Dysplasia of bone: age-related changes and anatomical distribution of skeletal lesions.*

The same pain score (PNRS), we used in our analysis, was utilized by two other authors too [22, 44]. Chao et al. [60] and Egner et al. [68] applied the “Visual Analogue Scale” (VAS) and Chapurlat et al. [46, 48] even created their own pain scale (0 = no pain, 1 = low pain, 2 = moderate pain, 3 = medium pain, 4 = severe pain).

Interestingly, in our study participants declared in 28.2% (35/97) that they had never had any pain during their course of disorder. On the other hand, considering the average follow up period of 11.1 years (range 2 to 26) 13.6% (12/88) were hit by permanent pain.

Berkley [61] postulated in her work sex differences in the perception of pain, namely " [...] *female often have lower thresholds, greater ability to discriminate, higher pain ratings and less tolerance of noxious stimuli than male*". This is conforming to our findings: Five patients stated a pain intensity of 10, which was the worst pain level. Four out of these were women.
Whereas in the sexual distribution of all pain patients the ratio was nearly 1:1, like the population of patients in the work of Kelly et al. [22].
The same authors discussed in their paper age-related differences with following results: Adults suffered from more and severe pain than children (mean value of pain intensity (PNRS) in adults is 4.1 and in children 2.8) although the disorder in many cases seemed to be quiescent. In our study these results are reflected: The mean pain intensity according to the PNRS in the acute phase of the disease was 4.15 in adults and 1.4 in children. Next, Kelly et al. [22] described, that less than the half of their CF patients complained about pain. The same picture is shown in our subjects: Only one out of three CF patients stated pain in the course of their disease. Compared with in more than three-quarters of our NCF cases there were statements of painful episodes whereby in aspect of the localisation, the lower limbs were more dominant.

As supposed polyostotic patients in our collective showed due to the multiple affliction of bones more pain severity as well in the course of disease as in current status compared to the monostotic group. Whereas Kelly et al. [22] described, that the pain intensity in their patients' group did not fit with the expansion of the lesions.

As previously mentioned above (2.1.9.1.2 Bisphosphonates) a medical therapy with bisphosphonates expresses a good value in pain regulation. Chapurlat et al. [46] presented a significant decrease of pain severity in 13 cases, but noted in eight of them no permanent improvement. Several treatment series were necessary, which were successful. Furthermore, the same research team [48] reported their outcomes of 44 pain patients: There was a reduction in pain intensity in 41% of cases after treatment with intravenous bisphosphonates. Egner et al. [68] also described the therapeutical achievement in pain management in their study with PFD-patients, treated with intravenous bisphosphonates.

Lane et al. [44] described a therapy with combining bisphosphonates in intravenous and oral form in comparison to oral therapy alone and his results showed a reduction of pain in both groups, but there was a better outcome within the combination therapy.
Chao and Katznelson [60] pointed out the positive effect of high-dose oral bisphosphonate therapy in a case report of three patients with initial severe pain (VAS-score).
The results of our data ascertainment showed that the indication for bisphosphonates were patients with severe pain. In all cases there was a diminishing in the pain severity after treatment, whereas in our patients bisphosphonates therapy was predominantly used in addition to a surgical intervention.

5.6. Therapeutic interventions

Until the development of bisphosphonates (especially their new generation) surgical intervention was the sole way of a curative therapy. Restrictively, I have to note, that particularly in PFD no healing can be reached, only a prevention of deformities and fractures due to stabilisation measures can be achieved [23].
Chapurlat and Meunier [21] postulated following five headings concerning the management of FD: "*To confirm the diagnosis, to look for other sites, to establish prognosis, Medical treatment in practice, Orthopaedic treatment [...]".* The authors' intention was to declare the importance of an adequate and accurate investigation before any medical or surgical treatment is started.
This exact dealing with each singular patient is essential because each case is unique due to the sporadic genetic mutation in different points of time and development phases. Thus even the regime of therapy is different to each single person. Treatment options are increased in the last years by improving the surgical and medical treatment [62].
The first use of bisphosphonates by Liens et al. [40] revolutionized the initial pharmacological treatment of FD: For the first time a direct interference in the course of disease was possible: A lot of investigations approved the positive effect on pain [17, 21, 37, 44, 46, 48, 60, 63, 64] and there is no hint in orthopaedic literature casting doubt on this.

The effect of bisphosphonates on refilling osteolytic lesions and increasing the bone mineral density, which Liens et al. [40] first described, is controversially discussed. Some of the authors were able to verify this activity of the substance [21, 29, 37, 45, 46, 48]. Plotkin et al. [63] and Glorieux et al. [64] doubted on these positive effects on dysplastic lesions.
Looking through our patient collective there was a relative small number of patients treated with bisphosphonates (seven patients – two monostotic afflicted, five polyostotic). Our results showed, that patients with more severe pain in comparison to the control group were treated with bisphosphonates and their therapeutic effect was reached, because pain could be significantly reduced.

5.7. Difficulties in diagnostic procedure

In the literature the problematic case of diagnostic findings is manifoldly discussed: Already in 1946 Jaffé [54] recognised that a single X-ray diagnostic in PFD might be convincing, whereas in monostotic forms at least further tissue examinations are useful, because the differentiation to other benign bone lesions is more difficult. Kärjä and Räsänen [65] reported about great variations in their histochemical and histopathological examinations within their CF-patients.
The histological dissociation of FD to high-differentiated tumours was according to Campanacci [14] difficult to realise.
Wagner et al. [33] found out in their exploration between FD, Morbus Paget and bone tumours, that simple radiological and scintigraphic screenings are insufficient. They demanded additional histological diagnostic investigations; in certain cases even a genetic analysis was required. Proschek et al. [66] pointed out the mainly asymptomatic clinical aspect in adulthood, which complicated the diagnostic and they marked the importance of a biopsy besides conventional X-rays.
The conclusion of our seven cases with differential diagnostic difficulties (see chapter 4.7) showed the problems to find the right diagnosis, to which solitary histological finding was insufficient. The histological image in FD is similar to its differential diagnosis, thus the clinical course and a synopsis of histological, radiological and clinical findings have to be observed.

6. Conclusion

Since FD is a very rare disease of the bone, it is, in our opinion, justified to pool data from patients treated in Styrian hospitals who have been diagnosed with FD in a time frame of 24 years. Thus a basis for further research is created.

In clinical experience the main problem for a part of these patients in question is distinctive pain with changing intensity. Apart from established surgical procedures this pain can be treated with bisphosphonate therapy which is still being in evaluation.

Therefore the main focus of this paper has been on the symptom pain. In conclusion this study shows that part of the patients actually suffer from considerable pain. This pain situation has been individually analyzed using a standardized 11-step pain score (PNRS) whereby we were able to observe that especially PFD and NCF patients are exposed to significantly higher pain. We believe that this is the reason that NCF patients were more likely to report being impaired in their life situation than CF patients. At the moment almost 15% of the probands still suffer from constant pain after a follow-up of 11.1 years in average. It is surprising that bisphosphonate therapy which is being highly acclaimed in literature throughout the past years has been applied only rarely in this group of patients. Still our evaluation shows improvement in the average pain intensity curve of the patients who have been subject to the mentioned therapy. The majority of the patients have been treated surgically. Also, this analysis shows that the group of patients treated with bisphosphonate indicate higher average pain intensity before treatment than the rest of the group.

Therefore, we are prone to believe that research especially regarding pain treatment for FD patients needs to be continued.

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8. Figures and Tables

8.1. Legend to Figures

8.2. Legend to Tables

9. Appendix

9.1. Case report form

CRF Fibröse Dysplasie Telefonabfrage

PatientInnennummer:
Nachname: Vorname: Geburtsdatum:

Telefon: _____
aktuelle Adresse:_____

Alter _____
Gewicht _____
Körpergröße _____

Geschlecht o m o w

Datum der ersten Beschwerden _____ o Schwellung
o Schmerzen
Datum der Erstdiagnose_____ o Fraktur
o Zufallsbefund

ED durch:

Röntgen	o ja	o nein	
Histologie	o ja	o nein	
	o Offene Inzisionsbiopsie		
	o Stanzbiopsie		
	o Offene Exzisionsbiopsie / Curettage		
Sonstiges	o _____		

Bisherige **Bildgebung**

MRT	o ja	o nein	o auswärtig
CT	o ja	o nein	o auswärtig
Szintigraphie	o ja	o nein	o auswärtig

Diagnose

- o Monostotisch
- o Polyostotisch
- o Sek. AKZ
- o Sek. Malignom
- o Begleiterkrankungen

Lokalisation

_____
_____
_____

Syndrom assoziiert

McCune Albright Syndrom	o ja	o nein
Mazabraud Syndrom	o ja	o nein

Familienanamnese o leer o Mutter
o Vater
o Geschwister
o Kinder

Bisherige Intervention:

- o Keine
- o Chirurgisch
  - o Biopsie
  - o Curettage
  - o Mit biologischer Rekonstruktion
  - o Mit VITOSS
    - o Mit Zementplombe
  - o Mit Verbundosteosynthese
  - o Andere

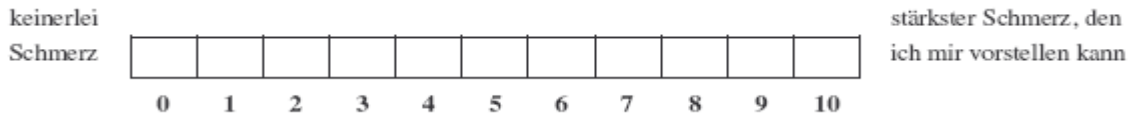
o Medikamente o ja o nein

Details _____

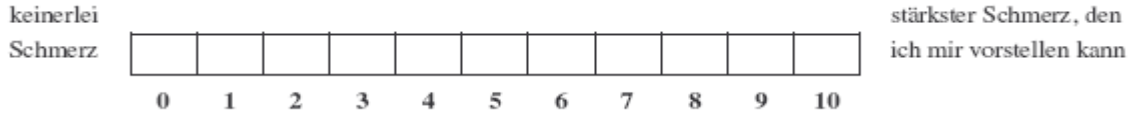
- o Bisphosphonat
- o NSAR

Schmerzscore

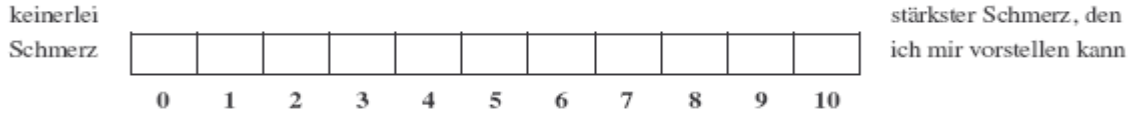
Schmerzscore PNRS aktuell



Schmerzscore PNRS maximal



Schmerzscore PNRS minimal



Lokalisation

_____
_____
_____
_____

Wann
- o Ruhe
- o Nacht
- o Belastung
- o Wetterfühligkeit

Dauer
- o permanent
- o Intermittierend

Subjektive Bewegungseinschränkung o ja o nein

9.2. Patients collective (124 patients)

Table 5: Patients collective (124 patients with Fibrous Dysplasia): A - E

A

ID	Sex	Age at diagnosis (years)	Age now (years)	Follow up years	Initial symptoms	Localisation		Therapeutic intervention		Pain[1]
								Surgical intervention	Mediacation	
1	male	44	70	26	n.d.	monostotic	femur	n.d.	n.d.	n.d.
4	male	28	40	12	incidental findings	monostotic	CF	Curretage, Metal, FESS	no	no
5	male	39	42	3	deviation	polyostotic	CF, pelvis, femur, tibia	Biopsy, Curretage, Metal	Bisphosphonate	no
6	female	15	22	7	fracture	monostotic	femur	Biopsy, Curretage, Rod, Metal	no	no
8	male	51	61	10	pain	monostotic	femur	Biopsy	no	yes
9	male	6	23	17	pain	polyostotic *	femur, tibia	Curretage, Rod	no	yes
10	male	39	45	6	incidental findings	monostotic	costa	Biopsy, Curretage	no	yes
11	male	27	52	25	n.d.	monostotic	CF	n.d.	n.d.	n.d.
12	male	46	51	5	pain	polyostotic	pelvis, femur	Biopsy, Curretage, Graft II, Phenol, Metal	no	yes
13	female	21	41	20	n.d.	monostotic	CF	Curretage, Graft I, Resection	no	n.d.
14	female	37	51	14	pain	polyostotic	CF	Curretage	no	yes
15	male	33	38	5	pain	monostotic	femur	Biopsy, Curretage, Graft II, Metal	no	yes
16	female	51	56	5	incidental findings	monostotic	femur	Curretage, Graft II, Metal	no	yes
17	female	47	58	11	incidental findings	monostotic	costa	Biopsy, Curretage	no	yes
18	female	35	61	26	incidental findings	monostotic	costa	Curretage, Resection	no	no
19	male	35	40	5	pain	monostotic	femur	Biopsy, Curretage, Graft II	no	yes
20	male	19	40	21	pain	monostotic	tibia	Biopsy, Curretage, Graft I	no	yes
21	female	32	48	16	n.d.	monostotic	CF	n.d.	n.d.	n.d.
23	male	65	70	5	incidental findings	monostotic	costa	Biopsy	no	no
24	male	21	34	13	pain	monostotic	tibia	Curretage, Graft I, Phenol	no	yes
25	male	46	66	20	swelling	monostotic	CF	Curretage, Graft I	no	no
26	male	30	41	11	incidental findings	polyostotic	humerus, radius	Biopsy	no	no
27	male	16	24	8	swelling	monostotic	CF	Curretage, FESS	no	no
28	female	26	29	3	swelling	monostotic	CF	FESS	no	no
29	female	45	63	18	swelling	monostotic	CF	Biopsy	no	no
30	female	44	46	2	swelling	monostotic	CF	Biopsy	no	no

B

ID	Sex	Age at diagnosis (years)	Age now (years)	Follow up years	Initial symptoms	Localisation		Therapeutic intervention		Pain[1]
								Surgical intervention	Mediacation	
31	female	35	56	21	n.d.	monostotic	CF	n.d.	n.d.	n.d.
32	female	23	45	22	incidental findings	monostotic	costa	Resection	no	no
33	female	10	13	3	swelling	monostotic	tibia	Biopsy, Curretage, Graft I, Graft II, Phenol	no	no
34	female	43	49	6	pain	polyostotic	CF, pelvis, femur, tibia	Curretage, Graft I, Metal	no	yes
35	female	51	62	11	pain	polyostotic	costa, spine	Curretage, Resection	Bisphosphonate	yes
36	female	47	58	11	pain	monostotic	spine	Curretage, Graft I	no	yes
37	female	43	49	6	incidental findings	monostotic	spine	Biopsy, Curretage, Graft I	Bisphosphonate	yes
38	female	12	14	2	pain	monostotic	femur	Biopsy, Curretage, Graft II, Rod	no	yes
39	male	56	64	8	swelling	monostotic	costa	Biopsy, Resection	NSAID	yes
40	female	35	53	18	n.d.	monostotic	CF	n.d.	n.d.	n.d.
41	male	14	37	23	swelling	monostotic	CF	n.d.	n.d.	n.d.
42	male	69	92	23	n.d.	monostotic	femur	n.d.	n.d.	n.d.
43	female *	22	24	2	pain	monostotic	femur	Biopsy, Curretage, Graft I, Graft II, Metal	no	yes
44	female	32	43	11	incidental findings	monostotic	CF	Biopsy	no	no
45	female	80	90	10	fracture	polyostotic	pelvis, femur, tibia	n.d.	n.d.	n.d.
46	female	43	47	4	incidental findings	monostotic	CF	Biopsy	no	yes
47	male	27	31	4	n.d.	monostotic	CF	n.d.	n.d.	n.d.
48	male	41	47	6	pain	monostotic	pelvis	Biopsy	no	yes
50	female	22	26	4	incidental findings	polyostotic	humerus, radius	Biopsy, Curretage, Graft I	no	yes
51	female	30	40	10	pain	monostotic	humerus	Curretage, Graft I, Graft II	no	yes
52	female	37	63	26	n.d.	monostotic	CF	n.d.	n.d.	n.d.
53	female	52	60	8	pain	polyostotic °	humerus, pelvis, femur, tibia	Biopsy	Bisphosphonate	yes
54	male	11	14	3	pain	monostotic	femur	Biopsy, Curretage, Rod, Phenol	no	yes
57	male	37	49	12	incidental findings	monostotic	humerus	Biopsy, Curretage, Graft I, Metal	no	n.d.
58	male	43	50	7	incidental findings	monostotic	radius	Curretage, Graft I, Phenol	no	yes
59	male	55	62	7	n.d.	monostotic	costa	Curretage, Resection	no	n.d.
60	female	72	81	9	pain	monostotic	tibia	Biopsy, Curretage	no	yes

C

ID	Sex	Age at diagnosis (years)	Age now (years)	Follow up years	Initial symptoms	Localisation		Therapeutic intervention		Pain[1]
								Surgical intervention	Mediacation	
61	female	44	65	21	pain	monostotic	costa	Biopsy, Curretage, Resection	no	yes
62	female	44	69	25	pain	monostotic	femur	Curretage, Graft I	no	yes
63	female	28	32	4	pain	monostotic	CF	Biopsy	NSAID	yes
64	female	43	49	6	pain	monostotic	tibia	Biopsy, Curretage, Graft II	no	yes
65	female	37	45	8	n.d.	monostotic	CF	Biopsy	no	n.d.
66	female	8	22	14	incidental findings	monostotic	CF	Biopsy, Curretage, Graft I, Metal	no	no
67	male	8	32	24	swelling	monostotic	CF	Resection	no	no
68	female	29	55	26	pain	monostotic	radius	Biopsy, Curretage, Graft I	no	yes
69	female	33	41	8	n.d.	monostotic	CF	n.d.	n.d.	n.d.
70	male	28	31	3	swelling	monostotic	CF	Curretage, FESS	no	no
71	female	22	29	7	incidental findings	monostotic	CF	Curretage, Blood	no	n.d.
72	female	59	64	5	incidental findings	monostotic	tibia	Biopsy, Curretage, Graft II, Metal	no	yes
73	male	72	78	6	incidental findings	monostotic	costa	Biopsy	no	yes
74	female	38	53	15	pain	monostotic	CF	FESS	NSAID	yes
75	female	27	29	2	pain	monostotic	tibia	Biopsy, Curretage, Graft I, Graft II	no	yes
76	male	23	40	17	n.d.	monostotic	CF	n.d.	n.d.	n.d.
77	female	30	38	8	swelling	monostotic	CF	Curretage, Blood	no	no
78	male	40	57	17	incidental findings	monostotic	femur	Curretage, Graft I, Phenol	no	no
79	female	19	24	5	incidental findings	monostotic	CF	FESS	no	no
80	female	43	62	19	swelling	monostotic	CF	Biopsy	no	no
81	male	23	31	8	pain	monostotic	femur	Curretage, Cement	no	yes
83	male	7	11	4	pain	monostotic	femur	Biopsy, Curretage, Rod	no	yes
84	male	42	46	4	pain	monostotic	spine	Curretage, Graft I, Metal	no	yes
85	female	39	47	8	n.d.	monostotic	CF	n.d.	n.d.	n.d.
87	male	38	46	8	fracture	polyostotic	femur, tibia	Curretage, Cement, Metal	Bisphosphonate	yes
88	female	37	48	11	pain	monostotic	humerus	Biopsy, Curretage, Spongostan	no	yes
89	female	31	40	9	incidental findings	monostotic	pelvis	Curretage, Phenol	no	n.d.

D

ID	Sex	Age at diagnosis (years)	Age now (years)	Follow up years	Initial symptoms	Localisation		Therapeutic intervention		Pain[1]
								Surgical intervention	Mediacation	
90	female	12	25	13	incidental findings	monostotic	femur	Curretage, Graft I, Graft II, Metal	no	no
92	male	60	63	3	incidental findings	polyostotic	CF	Biopsy	no	yes
93	female	39	48	9	pain	monostotic	CF	Curretage	no	yes
94	male	36	60	24	incidental findings	monostotic	ulna	Curretage, Graft I	no	no
95	male	45	64	19	pain	monostotic	costa	Curretage, Resection	Bisphosphonate, NSAID	yes
96	female	21	40	19	n.d.	monostotic	femur	n.d.	n.d.	n.d.
97	male	8	27	19	fracture	polyostotic	humerus, femur, ulna	Curretage, Rod	no	yes
98	female	37	62	25	pain	monostotic	pelvis	Curretage, Graft I	NSAR	yes
99	female *	26	38	12	pain	monostotic	pelvis	Curretage, Graft I, Cement, Phenol, Metal	no	yes
101	male	24	34	10	pain	polyostotic	femur, tarsal bone	Biopsy, Curretage, Phenol	Bisphosphonate	yes
102	female	25	30	5	pain	monostotic	humerus	Biopsy, Curretage, Graft I, Graft II, Phenol	no	yes
104	male	82	104	22	n.d.	monostotic	femur	n.d.	n.d.	n.d.
105	male	20	25	5	incidental findings	monostotic	femur	Curretage	no	no
106	female	63	78	15	pain	monostotic	CF	Biopsy	no	yes
107	male	13	18	5	fracture	monostotic	femur	Biopsy, Curretage, Spongostan, Rod	no	n.d.
109	male	38	48	10	pain	monostotic	pelvis	Curretage, Graft I	no	yes
110	male	31	55	24	incidental findings	monostotic	tibia	Biopsy	no	yes
111	female *	46	49	3	pain	monostotic	femur	Biopsy, Curretage, Cement	no	yes
112	female	29	35	6	pain	monostotic	femur	Biopsy, Curretage, Graft II, Metal	no	yes
113	male	51	54	3	incidental findings	monostotic	CF	Biopsy	no	no
114	female	16	21	5	incidental findings	monostotic	CF	Biopsy	no	no
115	female	34	47	13	incidental findings	monostotic	CF	Biopsy	no	no
116	female	63	80	17	incidental findings	monostotic	costa	Curretage, Resection	no	no
117	male	44	65	21	incidental findings	monostotic	femur	Curretage, Graft I, Graft II	no	yes
118	female	21	35	14	hearing impairment	monostotic	CF	Biopsy, Curretage, Graft I	NSAID	yes
119	female	22	34	12	pain	polyostotic	femur, tibia	Curretage, Graft I, Metal	no	yes
120	female	33	56	23	n.d.	monostotic	costa	n.d.	n.d.	n.d.

E

ID	Sex	Age at diagnosis (years)	Age now (years)	Follow up years	Initial symptoms	Localisation		Therapeutic intervention		Pain[1]
								Surgical intervention	Mediacation	
121	female	45	60	15	incidental findings	monostotic	femur	Curretage	no	no
122	female	31	41	10	n.d.	monostotic	CF	n.d.	n.d.	n.d.
123	male	14	24	10	fracture	monostotic	femur	Biopsy, Curretage, Graft I, Graft II	no	yes
124	female	54	57	3	incidental findings	monostotic	CF	Curretage, Spongostan	no	no
125	male	12	20	8	incidental findings	monostotic	femur	Biopsy, Curretage, Graft II, Phenol	no	no
126	female	38	63	25	n.d.	monostotic	CF	n.d.	n.d.	n.d.
127	female	46	57	11	incidental findings	monostotic	femur	Curretage, Phenol	no	no
128	female	37	49	12	n.d.	monostotic	costa	Curretage, Resection	no	n.d.
129	female	39	49	10	pain	monostotic	costa	Biopsy	no	yes
130	male	48	54	6	incidental findings	monostotic	spine	Curretage, Metal	no	no
131	male	50	63	13	pain	monostotic	femur	Curretage, Graft I, Metal	no	yes
132	male	41	59	18	incidental findings	monostotic	femur	Biopsy, Curretage, Graft I	no	no
133	female	63	66	3	incidental findings	monostotic	CF	Curretage	no	no
135	male	40	65	25	pain	monostotic	pelvis	Graft II	no	yes
136	male	32	48	16	pain	monostotic	pelvis	Biopsy, Curretage	no	yes
137	female	33	49	16	pain	monostotic	femur	Curretage, Graft II, Phenol	no	yes
138	female	33	54	21	incidental findings	monostotic	CF	Curretage	no	yes

Legend: ID = Identification number of the patients; pain[1]= Pain at any time in the course of disease; * = McCune Albright Syndrome; ° = Mazabraud Syndrome; [+] = Positive family history; n.d. = No data; CF = Craniofacial bone; Graft I = Biological bone grafts; Graft II = Synthetic bone grafts; Spongostan = Gelatine sponge; Cement = Bone Cement; Rod = Intramedullary rod; Metal = Plates, screws; FESS = Functional endoscopic sinus surgery; Blood = Autologous blood; Phenol = Adjuvant phenol treatment; NSAID = Non-steroidal anti-inflammatory drugs;

9.3. Eighty-eight patients: PNRS

Table 6: Eighty-eight interviewed FD patients: Further information about their individual pain course. (F – I)

F

ID	Sex	Follow up years	Localisation	Painscore (PNRS)			Current situation	Factors which brings up pain	Limitation[1]
				Worst pain level	Best pain level	Current pain level			
4	male	12	monostotic	0	0	0	no pain		no
5	male	3	polyostotic	0	0	0	no pain		yes
6	female	7	monostotic	0	0	0	no pain		no
8	male	10	monostotic	5	0	0	no pain		no
9	male	17	polyostotic *	6	5	0	no pain		yes
10	male	6	monostotic	4	0	0	intermittend pain		no
12	male	5	polyostotic	8	0	0	no pain		no
14	female	14	polyostotic	6	5	0	intermittend pain	stress	yes
15	male	5	monostotic	1	0	0	no pain		no
16	female	5	monostotic	5	2	3	permanent pain	stress, meteoropathy	yes
17	female	11	monostotic	7	1	4	permanent pain	rest, night, meteoropathy	no
18	female	26	monostotic	0	0	0	no pain		no
19	male	5	monostotic	8	0	0	intermittend pain	stress, meteoropathy	no
20	male	21	monostotic	9	0	0	intermittend pain	meteoropathy	no
23	male	5	monostotic	0	0	0	no pain		no
24	male	13	monostotic	8	6	0	no pain		yes
25	male	20	monostotic	0	0	0	intermittend pain	meteoropathy	no
26	male	11	polyostotic	0	0	0	no pain		no
27	male	8	monostotic	0	0	0	no pain		no
28	female	3	monostotic	0	0	0	no pain; itsching	stress, meteoropathy	no
29	female	18	monostotic	0	0	0	no pain		no
30	female	2	monostotic	0	0	0	no pain		no
32	female	22	monostotic	0	0	0	no pain		no
33	female	3	monostotic	0	0	0	no pain		no
34	female	6	polyostotic	4	0	0	intermittend pain	stress, meteoropathy	no
35	female	11	polyostotic	10	8	5	permanent pain	rest, stress, meteoropathy	yes

G

ID	Sex	Follow up years	Localisation	Painscore (PNRS)			Current situation	Factors which brings up pain	Limitation[1]
				Worst pain level	Best pain level	Current pain level			
36	female	11	monostotic	8	0	0	no pain		no
37	female	6	monostotic	7	0	3	intermittend pain	stress	yes
39	male	8	monostotic	8	3	6	permanent pain	rest, night, stress, meteoropathy	yes
43	female *	2	monostotic	5	0	1	intermittend pain	stress, meteoropathy	no
44	female	11	monostotic	0	0	0	intermittend pain	meteoropathy	no
46	female	4	monostotic	0	0	2	intermittend pain	meteoropathy	no
50	female	4	polyostotic	5	0	0	intermittend pain	stress, meteoropathy	no
51	female	10	monostotic	8	0	0	intermittend pain	meteoropathy	no
53	female	8	polyostotic °	10	4	5	permanent pain	stress, meteoropathy	yes
58	male	7	monostotic	4	0	0	intermittend pain	stress, meteoropathy	no
60	female	9	monostotic	4	0	2	intermittend pain	meteoropathy	no
61	female	21	monostotic	10	0	0	no pain		yes
62	female	25	monostotic	7	0	0	no pain		yes
63	female	4	monostotic	7	0	0	no pain		yes
64	female	6	monostotic	2	0	2	intermittend pain	meteoropathy	no
66	female	14	monostotic	0	0	0	no pain		no
67	male	24	monostotic	0	0	0	no pain		no
68	female	26	monostotic	6	5	0	intermittend pain	rest, stress	yes
70	male	3	monostotic	0	0	0	no pain		no
72	female	5	monostotic	7	0	5	intermittend pain	night, meteoropathy	no
73	male	6	monostotic	1	0	0	intermittend pain	meteoropathy	no
74	female	15	monostotic	10	4	8	permanent pain	rest, stress	yes
75	female	2	monostotic	4	0	0	intermittend pain	stress	yes
77	female	8	monostotic	0	0	0	no pain		no
78	male	17	monostotic	0	0	0	no pain		no
79	female	5	monostotic	0	0	0	no pain		no
80	female	19	monostotic	0	0	0	no pain		no

H

ID	Sex	Follow up years	Localisation	Painscore (PNRS)			Current situation	Factors which brings up pain	Limitation[1]
				Worst pain level	Best pain level	Current pain level			
87	male	8	polyostotic	9	1	9	permanent pain	night, meteoropathy	yes
90	female	13	monostotic	0	0	0	no pain		no
92	male	3	polyostotic	5	0	0	intermittend pain	stress, meteoropathy	no
93	female	9	monostotic	9	5	0	no pain		yes
94	male	24	monostotic	0	0	0	no pain		no
95	male	19	monostotic	9	5	3	permanent pain	stress	yes
98	female	25	monostotic	4	1	0	intermittend pain	night	yes
99	female *	12	monostotic	8	5	4	permanent pain	rest, stress	yes
101	male	10	polyostotic	8	0	7	intermittend pain	meteoropathy	yes
102	female	5	monostotic	3	0	0	no pain		no
105	male	5	monostotic	0	0	0	no pain		no
106	female	15	monostotic	5	1	0	no pain		no
109	male	10	monostotic	6	2	4	intermittend pain	stress, meteoropathy	yes
110	male	24	monostotic	7	3	0	intermittend pain	stress	yes
111	female *	3	monostotic	9	0	2	permanent pain	meteoropathy	no
112	female	6	monostotic	4	0	0	no pain		yes
113	male	3	monostotic	0	0	0	no pain		no
114	female	5	monostotic	0	0	0	no pain		no
115	female	13	monostotic	0	0	0	no pain		no
116	female	17	monostotic	0	0	0	no pain		no
117	male	21	monostotic	8	3	4	permanent pain	rest, night, stress	yes
118	female	14	monostotic	8	5	3	permanent pain	rest, stress, meteoropathy	yes
119	female	12	polyostotic	9	0	2	intermittend pain	rest, night, stress, meteoropathy	no
121	female	15	monostotic	0	0	0	no pain		no
123	male	10	monostotic	8	2	0	no pain		yes
124	female	3	monostotic	0	0	0	no pain		no
125	male	8	monostotic	0	0	0	no pain		no

ID	Sex	Follow up years	Localisation	Painscore (PNRS)			Current situation	Factors which brings up pain	Limitation[1]
				Worst pain level	Best pain level	Current pain level			
127	female	11	monostotic	0	0	0	no pain		no
130	male	6	monostotic	0	0	0	no pain		yes
132	male	18	monostotic	0	0	0	no pain		no
133	female	3	monostotic	0	0	0	no pain		no
135	male	25	monostotic	7	0	0	intermittend pain	rest, stress	no
136	male	16	monostotic	10	7	0	no pain		yes
137	female	16	monostotic	8	0	0	no pain		yes
138	female	21	monostotic	5	0	4	intermittend pain	meteoropathy	no

Legend: ID = Identification number of the patients; PNRS = Pain numeric rating scale; * = McCune Albright Syndrome; ° = Mazabraud Syndrome; [+] = positive family history; Limitation[1] = Patients' statement about limitation in daily life;

10. Curriculum Vitae

PERSONAL INFORMATION

Name:	Eva Traunmüller
Address:	Strassoldogasse 4, A-8010 Graz
	Welserstr.6, A-4070 Eferding
E-Mail:	eva.traunmueller@stud.medunigraz.at
Date of birth:	8th July 1986
Place of birth:	Grieskirchen
Citizenship:	Austrian

SCHOOL EDUCATION & ACADEMIC STUDIES

Since 10/2004	Medical Studies, Medical University of Graz
09/1996 – 06/2004	Grammar school, Gymnasium Dachsberg, Prambachkirchen
09/1992 – 07/1996	Elementary school, Eferding

PROFESSIONAL EXPERIENCE

Practical year:

08/2010 – 09/2010	Department of Orthopaedic Surgery and Trauma Surgery, Charité, Berlin
07/2010	Department of Gynaecology, Charité, Berlin
06/2010	Internship General practitioner Dr. Pätzold
04/2010 – 05/2010	Department of Internal Medicine, Clinical centre Passau

Clinical electives:

03/2010	Department of Gastroenterology, Clinical centre Wels-Grieskirchen
09/2009	Department of Gynaecology, Hospital of the Barmherzigen Brüder, Linz
07/2009	Department of Orthopaedic Surgery and Trauma Surgery, Charité, Berlin
02/2009	Department of Cardiology, Clinical centre Wels-Grieskirchen
09/2008	Department of Cardiology, General hospital Linz
08/2008	Department of Gynaecology, Clinical centre Wels-Grieskirchen
07/2007	Department of Ophthalmology, Clinical centre Wels-Grieskirchen

Courses and lectures next to my studies:

01/2010	Elective subject: Case reports: Instruction to scientific work
06/2009	Elective subject: Tumour orthopaedic
06/2009	Elective subject: English in the Clinical Practice 1
04/2009	Special study module: Surgical instruction
02/2009	Winter school, LKH Stolzalpe: Practical Orthopaedics
07/2008	Special study module: Emergency medicine
11/2007	Special study module: Cased-based Learning
01/2007	Special study module: Clinical topographic anatomy
08/2006	Paramedic, Red Cross, Eferding

Scientific work:

Traunmueller E, Maurer-Ertl W, Kuerzl G, Froehlich E, Ghaffari-Tabrizi N, Bodo K, Liegl B, Leithner A. Fibrous dysplasia and pain status in 88 patients. Abstract book of the 23rd EMSOS Meeting 2010. 2010 May;79-80.-23rd EMSOS Meeting; MAY 5-7, 2010; Birmingham, UNITED KINGDOM. [Poster]

ADDITIONAL SKILLS

Languages:	German (mother tongue), English, French, Latin
EDV:	MS Office (ECDL core 2002)
Driving licence:	B, F

PERSONAL INTERESTS

Playing the French horn, choral singing, rescue service