Thesis

PROPORTION OF FRACTURES IN TUMOUR PATIENTS WITHOUT HISTOLOGICAL EVIDENCE OF MALIGNANT TISSUE IN THE FRACTURE AREA

A retrospective, descriptive study of atypical and pathological fractures of the humerus and femur

submitted by

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Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, 19th of June 2024 *Felix Schretthauser m.p*

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Zusammenfassung

Einleitung: Bei Tumorpatient*innen kann der natürliche Knochenstoffwechsel durch verschiedene Faktoren gestört sein. Primäre und sekundäre Knochentumore, lebensverlängernde Therapien oder allgemeine Komorbiditäten sollten hier als Beispiele angeführt werden. Die Verabreichung von bone modifying agents (BMA) als Therapie von skeletal related events (SRE) bei Knochenmetastasen wird als Risiko für atypische Femurfrakturen (AFF) gesehen. Da sich die Lebenserwartung von Krebspatient*innen verlängert und die Dosierung von Bisphosphonaten (BP) und Denosumab bei Tumorpatient*innen relativ hoch ist, wird ein Anstieg an AFF befürchtet. Das Ziel dieser Arbeit ist es, den Anteil von nicht tumorösen Humerus- und Femurfrakturen zu bestimmen und so den Anteil von AFF und atypische Humerusfrakturen (AHF) zu schätzen.

Material und Methoden: Es wurde eine retrospektive, deskriptive Studie durchgeführt. 362 Krebspatient*innen wurden analysiert, die zwischen 2006 und 2020 der traumatologischen Notaufnahme der Abteilung für Orthopädie und Traumatologie an der Medizinischen Universität Graz zugewiesen wurden. Die Tumorpatient*innen wurden mit der Verdachtsdiagnose einer atypischen oder pathologischen Fraktur aufgenommen. Folgende Daten wurden erhoben und analysiert: Demographische Daten, Aufnahmedatum, Lokalisation der Fraktur, Diagnosezeitpunkt der Tumorerkrankung, deren Entität und Art der Therapie, Verschreibung von BMA, Glukokortikoiden und Vitamin D_3 und Komorbiditäten.

Ergebnisse: Von den 362 Patient*innen, waren 57.18% weiblich und 42.81% männlich. Das mittlere Alter zum Zeitpunkt der Fraktur betrug 67.44 Jahre. Die Diagnose des Primärtumors konnte bei 345 Patient*innen bestimmt werden. 64 Patient*innen hatten Brustkrebs, 56 hämatologische Neoplasien, 47 pulmologische Neoplasien, 46 urologische, 28 Neoplasien des Knochens und Weichgewebes, 15 hatten nicht tumoröse Läsionen und 37 andere Neoplasien. Bei 80 Patient*innen konnte kein Tumorgewebe im Frakturspalt gefunden werden. Die histologischen Daten der Frakturspaltanalyse waren bei 78 Patient*innen ergebnislos. Es wurden 108 Humerus- und 242 Femurfrakturen identifiziert. Von denen waren 7 nicht tumoröse, diaphysäre Humerus- und 6 nicht tumoröse, diaphysäre Femurfrakturen. The mittlere Zeit vom Zeitpunkt der Diagnose des

Primärtumors bis zum Auftreten der Fraktur betrug 47.90 Monate. 70 Patient*innen unterzogen sich einer BMA-Therapie.

Diskussion: Die Anzahl an nicht tumorösen, diaphysären Frakturen des Humerus und Femurs werden als Schätzung von atypischen Frakturen angesehen, wohl wissend, dass atypische Frakturen nur durch die Analyse einer radiologischen Bildgebung bestimmt werden können. Die Ergebnisse dieser Studie sollten aufgrund von fehlenden Daten nur mit Limitation interpretiert werden. Zukünftige großangelegte Studien könnten Risikoprofile für Krebspatient*innen hervorbringen, um dadurch Frakturen zu vermeiden und die Lebensqualität der Patient*innen zu verbessern.

Abstract

Introduction: In tumour patients, healthy bone metabolism can be disrupted by various factors. Primary and secondary bone tumours, life prolonging therapies or general comorbidities should be mentioned here as examples. Administration of bone modifying agents (BMA) for treatment of skeletal related events (SRE) in bone metastases is shown to be a risk factor for atypical femoral fractures (AFF). Since life expectancy in tumour patients is increasing and dosages of bisphosphonates (BP) and denosumab in tumour patients is relatively high, an increase of AFF is feared. The aim of the thesis is to determine the proportion of non-tumorous humeral and femoral fractures, to estimate the proportion of AFF and atypical humeral fractures (AHF).

Material and Methods: A retrospective, descriptive study was performed. 362 cancer patients, admitted from 2006 to 2020 to the Level I Trauma Center of the Department of Orthopaedics and Trauma at the Medical University of Graz were analysed. The tumour patients had a suspected diagnosis of a pathological or atypical fracture. Following data was collected and analysed: demographic data, admission date, location of fracture, time of diagnosis of the tumour diseases, their entity and manner of treatment, administration of BMA, glucocorticoids, vitamin D_3, and comorbidities.

Results: Of the 362 patients, 57.18% were female and 42.81% were male. Mean age at the time of fracture was 67.44 years. The diagnosis of primary tumours could be determined in 345 patients. 64 with breast cancer, 56 with haematological neoplasms, 47 with pulmonary neoplasms, 46 with urological, 28 with neoplasms of the bone and soft tissue, 15 with non-tumorous lesions and 37 with other neoplasms. No tumorous tissue could be found in the fracture gap of 80 patients. The histological data of the fracture gap analysis was inconclusive in 78 patients. 108 humerus and 242 femur fractures were identified. Of these there were 7 non tumorous diaphyseal humeral and 6 non tumorous diaphyseal femoral fractures. The mean time from the diagnosis of the primary tumour until fracture occurred, was 47.90 months. 70 Patients underwent BMA therapy.

Conclusion: The number of non-tumorous diaphyseal fractures of the humerus and femur is seen as an estimation of atypical fractures, well knowing that proof of atypical fractures

only can be provided by analysing radiologic images. The results of this study should be interpreted with limitations due to missing patient data. Future large-scale studies could provide risk profiles for cancer patients, preventing fractures and thus improve patients' quality of life (QoL).

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Abbreviations

AFF	atypical femoral fracture
AHF	atypical humeral fracture
ASBMR	American Society of Bone and Mineral Research
BMA	bone modifying agent
BMD	bone mineral density
BMP	bone morphogenetic proteins
BMU	basic multicellular unit
BP	bisphosphonate(s)
COPD	chronic obstructive pulmonary disease
FDA	Food and Drug Administration
HR	hazard ratio
GH	growth hormone
HSC	haematopoietic stem cell
IGF-1	insulin like growth factor 1
IL	interleukin
M-CSF	macrophage colony-stimulating factor
OPG	osteoprotegerin
ONJ	osteonecrosis of the jaw
PGE_2	prostaglandin E2
PTH	parathyroid hormone
QoL	quality of life
RANKL	receptor activator of NF-kB ligand
RR	relative risk
Runx2	runt-related transcription factor 2
SRE	skeletal related events
TGF β1	transforming growth factor beta 1
TNF	tumour necrosis factor alpha

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1 Introduction and Background

1.1 Physiological remodelling of bone tissue

The functions and tasks of bone tissue are exceedingly diverse. On the one hand it provides supporting and protecting functions of inner organs and bone marrow and serves as a part of the locomotor system, on the other hand it is essential for the homeostasis of calcium metabolism. (1)

1.1.1 Basic multicellular unit

To maintain these physiological structures and functions of the skeleton, the bone is constantly remodelling itself. (2) By doing so, a complex, cyclic, three stage process is applied. First of all, older tissue is resorbed by osteoclasts. Secondly a transition period from resorption to formation can be observed. As a last step, new bone tissue is formed by osteoblasts. (3)

In addition, there are two other bone cell types that play an important role in remodelling bone tissue. Osteocytes can broadly be described as mechanosensors and central coordinators of the process of bone remodelling. Whereas bone lining cells, described as inoperative osteoblasts coating bone surfaces, seem to be crucial for bone resorption and bone formation. (3)

These four cells shape into a so called basic multicellular unit (BMU), a momentary existing anatomical structure. In this BMU remodelling processes, precisely tailored to the respective cells, run phase-specifically and are coordinated with each other. (3)

In contrast to this explanation, recent knowledge suggests that different BMU components affect the process of remodelling, regardless of the chronological phase. In addition to that remodelling process is also affected by the specific differentiation stage of the cells and various cellular messengers and signals. (4)

1.1.2 Reasons for bone modelling and remodelling

The term “modelling” is generally understood to mean the process of changing the bones’ shape as a response to biomechanical forces and the formation of bone tissue. This leads to an incremental adjustment of load bearing bones to the respective tensile and compressive force. (5) This circumstance was first described in 1892 as Wolff’s law. (6) Adjustment takes place by removing or adding bone tissue via osteoblasts respectively osteoclasts. (5)

The process of bone modelling is predominant during childhood and adolescence, as well as after a fracture. (7)

Bone remodelling in contrast, is commonly defined as the removal and substitution of old bone tissue with newly created bone throughout the embryonic period until death. (7) Due to the influence of constant physical forces, microtraumas occur in the bone. They are to be regarded as a physiological, functional strategy of the bone to absorb these forces and thus prevent complete fracture of the bone. (8) These microtraumas are constantly repaired through bone remodelling. As a consequence, this equilibrium of damage and repair prevents accumulation of microtraumas and the development of stress fractures. (9)

1.1.3 Osteoblast

Osteoblasts are responsible for the formation of new bone and arise from pluripotent mesenchymal stem cells which, depending on the influence of transcription factors, can also differentiate into adipocytes, myocytes or chondrocytes. (7)

The proteins Runt-related transcriptions factor 2 (Runx2) and osterix (Sp7) act as transcriptions factors on osteochondrogenitor cells to induce differentiation into osteoblasts. In addition, other signalling proteins (β-catenin, Wnt) are required to ensure the survival and differentiation of the progenitor cells to mature osteoblasts which make up to 46% of all bone cells and are active for two to three months. These mature cubic blasts are characterised by a prominent endoplasmic reticulum and Golgi apparatus, indicating high protein production and secretion. (10)

In the first step of bone formation, type I collagen is produced, which serves as the main component of the newly formed bone matrix (osteoid). Secondly, osteoblasts contribute to the mineralization of the bone matrix by secreting phosphate vesicles. Together with calcium from extracellular fluid, the solution precipitates into hydroxyapatite crystals. The ratio of hydroxyapatite and organic type I collagen determines the rigidity and flexibility of the skeleton. (7)

1.1.4 Osteoclast

Osteoclasts originate from the monocyte macrophage lineage and develop from mononuclear progenitor cells to multinucleated giant cells. (7) The main task of these polarized cells is to decompose bone tissue. (10)

Additionally, they open niches in the bone marrow for development of haematopoietic stem cells, contribute to the endocrine function of bone by activating osteocalcin and induce angiogenesis. (10)

Osteoclasts are able to form so-called sealing zones around the resorption lacunae with their podocyte extensions, in order to degrade the bone. Protons collect within this closed resorption compartment. The pH drops, making apatite soluble. This acidic environment also promotes degradation of the organic matrix (osteoid) by osteoclast-secreted proteases, instancing cathepsin K. (11)

Maciel et al. (10) list three signalling proteins among various signalling pathways influencing the differentiation of osteoclasts: Macrophage colony-stimulating factor (M-CSF), receptor activator of NF-kB ligand (RANKL) and osteoprotegerin (OPG).

M-CSF is crucial for the differentiation of preosteoclasts from haematopoietic stem cells. It triggers signalling pathways that ultimately lead to cell division of preosteoclasts and in the same way prevent their apoptosis. Furthermore, it leads to the formation of RANK-receptors in progenitor cells of osteoclasts, promoting osteoclastogenesis when the receptor connects with its ligand. (10)

RANKL is generated from osteoblasts, osteocytes and T-cells. Once RANKL interacts with RANK, various signalling pathways are activated, allowing the transformation of monocytes into mature osteoclasts and subsequently to maintain in active state. (12)

Differentiation of osteoclasts is prevented by binding of OPG to RANKL, making OPG an inhibitor of osteoclast formation. (13)

1.1.5 Osteocyte

Some Osteoblasts remain behind during the formation of new bone tissue. They become immured in the newly formed osteoid and osteocytes are formed as a result of the final differentiation of osteoblasts. Consequently, these engulfed osteoblasts completely change their morphology as well as their function and become with over 90% the most common type of bone cell. (7)

Osteocytes develop long dendritic processes by which they communicate with other osteocytes and osteoblasts, forming a large network through the mineralized bone via canaliculi. (10) They thus change their function from secerning and producing cells to sensing and coordinating cells, which now act as the grand orchestrators of bone metabolism. (14)

Osteocytes can detect mechanical forces, bones are exposed to during body movement. (7) They use appropriate signalling molecules to induce bone remodelling process at the exact required location.(10) Sclerostin and Wnt antagonists are produced by Osteocytes. They thereby inhibit differentiation of osteoblasts and consequently bone formation. On the other hand, activation of Wnt signalling pathway in osteocytes leads to an increase in anabolic bone metabolism with an increased number of osteoblasts. (13)

RANKL however, which is also produced by osteoblasts but mainly by osteocytes (13), is the key factor in osteoclastogenesis and therefore in bone resorption. (15) In contrast to Osteoblasts, which are the main producers of OPG, the production of OPG by osteocytes exists, but is rather irrelevant in physiological context. (13)

Responding to endocrine signals is another characteristic of Osteocytes. If there is a shortage in oestrogen during the aging process, osteocytes undergo apoptosis, which leads to reduced bone turnover and reduced bone mass. (7)

1.1.6 Bone lining cell

Bone lining cells differentiate from osteoblasts. They remain on bone surfaces (trabecular, endosteal, endocortical) after the bone formation process is completed. (4) They mainly serve as a barrier between blood vessels and mineralized bone tissue, where ion flow is regulated. As cover cells, they also prevent contact between osteoclasts and the bone matrix, if no resorption is to take place. Nevertheless, bone lining cells can also differentiate back into osteoblasts, as soon as they are exposed to parathyroid hormone (PTH) or mechanical stress. (10)

1.2 Regulation of bone metabolism

According to Kenkre and Bassett, following messenger substances are relevant for the endocrine feedback loop of bone metabolism: Parathyroid hormone (PTH), calcitonin, vitamin D, thyroid hormone, growth hormone, glucocorticoids and sex hormones. (16)

PTH, formed in the parathyroid gland, controls the calcium and phosphate equilibrium in the blood via mobilization from the bones and via renal excretion of phosphate and reabsorption of calcium. Vitamin D is also produced to an increased extent, due to the influence of PTH. (17)
Long term exposure to PTH stimulates the OPG-RANKL-RANK signalling system and thus trabecular and - even more - cortical bone resorption by osteoclasts. PTH increases RANKL and decreases OPG. The opposite is the case with short term exposure to PTH. It modulates the Wnt signalling pathway by impeding Wnt-inhibitors. This circumstance leads to an altered expression of osteoblasts and increased new bone formation. (16)
Calcitonin, derived from thyroidal c-cells, (16) is considered to be the antagonist of PTH. (17) While its role in physiological conditions is described as unclear, it acts on osteoclast in the pharmacological context. (16) Furthermore calcitonin lowers blood calcium levels by inhibiting osteoclasts and reducing reuptake in the nephrons. (17)

The main function of $1,25(OH)_2D_3$ (vitamin D_3) is the regulation of intestinal calcium and phosphate absorption. (16) In addition, recent studies suggest the presence of a vitamin D receptor in osteocytes, although its exact function is still unclear. (4)

Thyroid hormones activate osteoblast differentiation and bone mineralisation. A deficiency leads to a longer lasting bone remodelling cycle. Subsequently, decreased bone turnover and an increase in bone mass can be determined. The exact opposite happens with exceedingly high thyroid hormone levels, leading to uncoupled osteoclast and osteoblast activity. A reduction in bone substance can be observed. (16) An increased risk of fractures is considered to be a consequence as well. (17)

*Growth hormon*e (GH) stimulates the production of *insulin like growth factor 1* (IGF-1) in the liver. One of many important target organs of IGF-1 is bone tissue. (18) A functioning

hypothalamic-pituitary-gonadal axis is essential for adequate secretion of GH and IGF-1. Hence, it ensures physiological growth of bones. (17) Patients with anorexia nervosa often show symptoms of an imbalanced hormone-axis with high GH and low IGF-1 levels, resulting in osteoporotic condition. (19) GH and IGF-1 stimulate both osteoblasts and osteoclasts, with a small increase in bone mass. If there is a GH deficiency, osteoclastic bone resorption predominates and osteoporosis occurs. (16)

Depending on the quantity, *glucocorticoids* can lead to different effects. While physiological doses have an anabolic effect on bone turnover, a higher level of glucocorticoids can lead to osteoporosis. In general, they cause an increase in RANKL and RANK expression and a reduced secretion of OPG, resulting in an increased activity of osteoclasts. (16)

Emmanuelle et al. categorise the effect of *oestrogen* on bone metabolism into three sections: Puberty, maintenance during adulthood and aging. During puberty high oestrogen levels cause a growth spurt via GH and IGF-1 and finally the closure of growth plates, leading to a stop of growth. (20) During the maintenance period in adulthood, the number of osteoclasts is reduced by apoptosis via the oestrogen receptor-alpha. At the same time, the number of osteoblasts remains the same, because of oestrogen preventing apoptosis of these cells. Additionally the differentiation of osteoblasts is promoted and the one of osteoclasts is hindered. (16) In the period of aging, reduced oestrogen levels in women and men lead to accelerated bone remodelling and lower bone density and therefore to an increase of the risk of fractures. (20)

Bone metabolism is also influenced by paracrine regulators. Growth factors, like TGF β1 and BMP induce expression of Runx2. This transcription factor initiates the differentiation of osteoblasts. Cytokines such as IL-1 and IL-6, as well as TNFα have a beneficial effect on the genesis of osteoclasts. IL-4, on the other hand, does the opposite.
Prostaglandins (PGE_2) influence both, formation and resorption, but their exact role in bone remodelling is still unclear. (16)
However, PGE_2 contributes to fracture healing. In the early stage after a fracture, it is produced by osteoblasts and mediates osteo- and angiogenesis, increase of bone strength and callus formation through different signalling pathways. (21)

1.3 Pathophysiological processes in various disorders of the bone

Diseases of various origins can affect bone metabolism. The spectrum ranges from inflammatory bone diseases (e.g. osteomyelitis) to generalized osteopathies (e.g. osteoporosis or hormonal imbalances) to neoplastic, tumorous bone diseases (e.g. metastases, osteosarcoma). (1) What they have in common is to change the integrity of the bone to such an extent that the risk of facing fractures increases. Of course, it is possible that patients with a history of cancer can also suffer osteoporotic fractures. Therefore, the background of both malignant bone diseases and osteoporosis will be examined in more detail.

In addition to this, drug therapies can change the bone tissue to such an extent that fractures may occur. (22) In the following chapters, an attempt is made to describe the difference between the most relevant bone disorders related to this thesis and to show their characteristic features in more detail.

1.3.1 Osteoporotic fractures and stress fractures

Osteoporosis is characterised by decreased bone mineral density (BMD), reduced bone strength and increased fragility. For these reasons, osteoporotic bones are more prone to fracture, especially in the area of the spine, hip, pelvis, proximal humerus or distal radius. Affected persons often only notice the disease after the first low-trauma fracture. (23)

There are two main groups of osteoporosis: primary and secondary. The primary form can be further divided into two subclasses. Postmenopausal osteoporosis describes type 1 primary osteoporosis and type 2 primary osteoporosis is called senile osteoporosis, affecting both genders. The causes of secondary osteoporosis are diverse and range from drug-associated osteoporosis (e.g. glucocorticoids) (23) to certain diseases affecting the endocrine system such as cushing's syndrome, anorexia nervosa or hypogonadal states. (24) Life style changes, like low calcium intake, or gastrointestinal disorders (malabsorption, gastric bypass) may also cause secondary osteoporosis. (24)

The common cause of these many different forms of osteoporosis is a general imbalance in the bone remodelling process, in which bone resorption predominates over bone formation. The major causes are old age and postmenopausal changes. (25)

Other relevant aspects that influence bone metabolism in terms of secondary osteoporosis are discussed in chapter 1.4.

Postmenopausal oestrogen deficiency directly affects bone cells. Oestrogen causes increased differentiation of mesenchymal stem cells and maturation of osteoblasts; bone formation is enhanced. At the same time, oestrogen leads to apoptosis of osteoclasts and prevents their development. Decreased oestrogen levels in the postmenopausal period cause a reduction in these effects and lead to progressive bone resorption. (26) This leads to destruction of the bone microarchitecture and bone loss. Thinning of the trabecular bone in the cancellous bone and reduced cortical thickness or increased porosity are characteristic in postmenopausal and senile osteoporosis. (25)

The pathogenesis of senile osteoporosis is associated with the general aging process. In this context, nine fundamental characteristics of aging have been defined, which are also valid in the aging skeleton. These include genomic instability, epigenetic changes, telomere degradation, loss of proteostasis, cellular senescence, mitochondrial dysfunction, dysregulated nutrient sensing, stem cell exhaustion, and altered intercellular communication. (27) This natural aging process leads to an accumulation of senescent, damaged bone cells, which in turn contribute to bone aging. They release senescence-associated factors, such as cytokines and chemokines, which drive unbalanced bone resorption. In addition, apoptosis of osteocytes and osteoblasts as well as bone marrow adiposity contribute to senile osteoporosis. (27)

1.3.2 Bone metastases

Around one fifth of deaths in Austria are due to malignant tumours, making them the second most common cause of death, after cardiovascular diseases. (28) In principle, bone filiae can develop from all hematogenous metastasising neoplasms. (29) However, among the most common cancers that lead to bone metastases breast cancer (70%), prostate cancer (85%) and lung cancer (40%) are included. Others worth mentioning are renal neoplasms (40%) and multiple myeloma, leading to lesions of the bone in 95%. (30)

Breast (29,7%) and prostate (26,7%) neoplasms are also by far the most common types of cancer in the Austrian population, taking gender into account. (31)

The site of metastasis reflects the distribution of red bone marrow, a very vascularized tissue with many HSC and a microenvironment favourable to cell growth. There is thus a

distribution with the highest frequency of metastases in the axial skeleton (spine, pelvis, skull, ribs) and the proximal humeri and femora. (32)

Depending on the predominant lysis or sclerosis in the bone metastases, a distinction is made between osteolytic and osteoblastic secondary lesions. In osteolytic metastases, characteristic of lung cancer and multiple myeloma, the work of osteoclasts predominates. Prostate cancer is more likely to cause osteoblastic filiae and mixed lesions are typical of breast cancer. In the mixed type, both, osteoblastic and osteoclastic processes are accelerated. (32)

This leads to severe bone pain and skeletal related events (SRE), including palliative radiation, palliative bone surgery, hypercalcaemia and the most common events, such as spinal cord compression and pathologic fracture. SREs reduce the quality of life of cancer patients and their chance of survival and increase medical costs. (33)

1.3.2.1 Bone colonisation by tumour cells and their influence on bone metabolism

The development of bone metastases is a lengthy process. Preclinical and clinical studies suggest the division of that process into several stages (34):

1. Formation of premetastatic niches

Via endocrine signalling of the primary tumour, this niche becomes receptive to tumour cells, circulating in the bloodstream. (29)

2. Extravasation of tumour cells and nidation into premetastatic niches

Osteoblasts and bone marrow stromal cells use special signalling proteins (e.g. VCAM1, nestin etc.) which cause HSCs to nest into the bone marrow. Tumour cells also express receptors that are receptive to such signalling proteins and thus compete with HSCs for nidation. They occupy the niche in the bone marrow, resulting in displacement of HSCs into the peripheral bloodstream. (29)

3. Evolution of premetastatic niche into a metastatic niche

In this phase, transmembrane proteins of tumour cells interact with the osteoid. In case of breast cancer, integrins bind to fibronectin, vitronectin and OPN, which ensures tumour cell invasion. A self- reinforcing sequence of events follows. (29)

Osteoblasts store growth factors (e.g. TGF β), which can also promote tumour growth. Growth factors are released by the metastases-related osteolytic processes. Tumour cells are able to secrete RANKL and interfere in that way with the RANKL-RANK-OPG-system. (29) The secretion of parathyroid hormone-related protein (PTHrP) by tumour cells again triggers the expression of RANKL. They thereby initiate increased activation of osteoclasts and thus start a vicious circle. TGF β again promotes metastatic growth, which leads to osteolysis and further release of growth factors. (35)

The formation of calcium-sensing receptors on cancer cells, act as an additional driver of this cycle. The calcium released during bone destruction thereby promotes further cell proliferation and PTHrP release.(35)

Osteoblastic metastases on the other hand, occur through tumour cells secreting cytokines and growth factors that have their greatest impact on osteoblasts. Consequently, there is an increase in bone mass of poor quality, which does not protect against pathological fractures. (29)

1.3.3 Primary malignant bone tumours

Primary malignant bone tumours largely occur in the young population and are the cause of about 6% of malignant diseases in childhood. The most common are osteosarcoma and Ewing's sarcoma. (36) Incidence of osteosarcoma peaks in the second decade of life and, with a lower peak, in elderly patients. (35) The sites of predilection are the distal femur, the proximal tibia and the proximal humerus. (36)

The second most common bone tumour is Ewing's sarcoma. t(11;22)(q24;q12) translocation is found in 95% of cases. This tumour occurs both in the axial skeleton and the limbs with the diaphysis being the preferred site in the long bones. (36)

Chondrosarcomas represent the third most common group of primary malignant bone tumours. Unlike the two other, chondrosarcomas are more common in older adults. Two groups are distinguished: primary chondrosarcomas, which arise de novo, and secondary ones, which develop from previously benign enchondromas or osteochondromas. (37)

1.3.3.1 Pathogenesis of malignant primary bone tumours

The process of bone remodelling creates very suitable framework conditions for both primary and, as already described in the previous chapter, secondary bone tumours, to promote their formation and progression. The pathophysiological circumstances about the viscous circle of cancer-associated, secondary bone degradation have already been studied

for years whereas the mechanism of bone degradation in osteosarcoma has not been studied as extensively. The lack of knowledge may be caused in the low incidence rates of osteosarcomas, although it is the most common primary malignant bone tumour.

Anyway, the same processes as in the pathogenesis of bone metastases have been suggested to take place in the formation of osteosarcomas. (35)

1.4 Other bone modifying factors

In contrast to the previous chapter, the following describes bone modifying factors that indirectly influence BMU. It is quite conceivable that, like primary bone diseases or bone tumours, they may be the cause of bone fractures without adequate trauma or at least promote them. These influencing factors were identified in a considerable proportion of the study population. For this reason, it was decided to take a closer look at their influence on bone structure.

1.4.1 Radiotherapy

Shortly after the discovery of x-rays almost 130 years ago, ionizing radiation was used for the first time as a treatment for malignant tumours. Since then, radiotherapy has been evolving to an indispensable part of cancer treatment, along with chemotherapy and surgery. (38) Ionizing radiation produces high energy ions. If the radiation encounters tissue, the energy is released, which leads to cell death. Malignant cells are particularly inhibited to proliferate by radiation energy causing the destruction of DNA. Although normal cells as well as cancer cells are damaged through radiation, healthy cells have the ability to regenerate more quickly, which leads to increased destruction of cancer cells. Furthermore, when radiotherapy is applied, the maximum of the radiation dose is concentrated in the area of abnormal cells, ensured by precise planning of the radiation target area. (39)

Cancers treated with radiotherapy are for example breast, prostate, cervix and lung carcinomas as well as lymphomas. (39) Therapy with ionizing radiation is also indicated for the treatment of bone metastases, although the effects of radiation on bone tissue are described contrary in the literature. Anyway, the objective of radiotherapy is to fight pain, facilitate bone reconstruction, minimize the risk of bone fracture and through that to improve quality of life and life expectancy. The mechanism of action of the analgesic effect of radiotherapy on bone metastases is not yet fully understood, but studies show an analgesic effect in approximately 70% of cases. It is also reported that radiation therapy should increase bone density in osteolytic bone metastases. (40)

These findings contrast with that from those of in vivo animal model findings. It is described that irradiation of rodents cause bone loss in form of demolition of trabecular bone at high and low (2Gy) doses because of higher activity of osteoclasts and lower activity of osteoblasts. According to Costa and Reagan, the results of these animal

experiments could be echoed in clinical studies. They cite a study in which 100 of 510 patients were said to suffer from insufficiency fractures of the sacrum or pelvis after radiation therapy for cervical cancer. (41) Another adverse effect of radiotherapy of pelvic cancers is the osteoradionecrosis of the femoral head. The irradiation induced bone loss is seen to be crucial in the pathogenesis of osteoradionecrosis of the femoral head among other factors negatively influenced by radiation (vascular injury, mesenchymal stem cell injury, radiation induced fibrosis, oxidative damage). (42)

1.4.2 Chemotherapeutics

Particularly those chemotherapeutic agents inhibiting the hormonal gonadal axis have significant influence on bone metabolism. These include aromatase inhibitors and androgen influencing drugs for breast cancer therapy, respectively prostate cancer therapy. Sex hormones, such as oestrogen, help to keep bone mineral density levels high. (43) This endocrinal therapy is associated with cancer treatment- induced bone loss and moreover a significant alteration in bone fractures. (44)

In addition, the cytotoxic drug cyclophosphamide, negatively influences bone mass both by suppressing the gonadal axis and directly by reducing the number of osteoblasts und osteoclasts. (43)

A review article attempts to summarize the effect of cytotoxic chemotherapy among breast cancer patients. Among other things, it is stated that methotrexate and doxorubicin are supposed to reduce osteoid synthesis. Also, doxorubicin is said to negatively influence osteoblast differentiation. Taxanes, in turn, interact with the cytoskeleton of osteoclasts, limiting their function and preventing pathological osteolysis. (45)

1.4.3 Renal insufficiency

The syndrome of chronic kidney disease and mineral and bone disorder is a well described phenomenon. Because of the continuous decrease of nephrons, phosphate cannot be excreted properly. As a result, FGF-23 secretion from bones rises, leading to a normalised elimination of phosphate. Simultaneously high levels of FGF-23 cause a decrease of calcitriol, resulting in hypocalcaemia, which is boosted through the inability of calcium reabsorption in chronic kidney disease patients. Hence, patients suffer from secondary hyperparathyroidism. (46)

As a consequence, increased bone remodelling would be expected. However, Austrian professional societies describe a shift towards reduced bone turnover in patients with

chronic kidney disease. Reasons given for this circumstance are the older age of patients, diabetes and excessive therapy with calcium and active vitamin D3 supplements.
Renal dystrophy resulting from renal insufficiency is characterised by a reduction in the width of the cortical bone. This leads to more fragile bones and an increased incidence of fractures, especially of long bones. (47)

1.4.4 Body-Mass-Index

In addition to the factors described so far influencing bone health and the possibility of bone fractures, being overweight or having a high percentage of body fat also has a certain impact. Obese individuals tend to show higher BMD levels than people with normal weight, because mechanical stress induces bone growth. Furthermore, the review by Rinonapoli et.al. summarized that a particularly high proportion of fatless mass is associated with high bone density. Another reason for high bone density in obese people is the large presence of aromatase, an important enzyme in oestrogen synthesis. Oestrogen, in turn, has positive effect on bone density. (48)
At the same time, the likelihood of suffering bone fractures is said to be higher among overweight people. On the one hand because of metabolic reasons, on the other hand because of the higher risk of falling. The low agility, postural instability, fatty infiltrations in the muscle, leading to dynapenic obesity should be mentioned as examples for reasons of the increased risk of falling and therefor the increased risk of traumatic fractures in obese patients. (48)
Looking more closely at the metabolic context, it is currently assumed that obesity leads to a state of low-level chronic inflammation. Adipose tissue should be understood as an endocrine organ that is able to produce different, biologically active substances. Substances seen as detrimental include leptin, adiponectin or cytokines such as TNF alpha or IL-6. (48)
The effect of leptin is mixed. In vitro studies showed that leptin promotes differentiation of osteoblasts, while inhibiting osteoclastogenesis. However, various animal studies on mice and rats showed the influence of leptin on the central nervous system. Here it is said to be a reduced release of serotonin. As a result, reduced bone formation or reduced femur bone mass and an increased bone marrow fat content are seen in the respective test animals. (48)
Adiponectin is considered to promote bone formation. In overweight people, adiponectin levels are usually lower than in normal weight people, which leads to reduced

osteoblastogenesis and increased osteoclastogenesis. The previously mentioned cytokines finally promote osteoclast-induced bone resorption at the end of their signalling cascade. (48)

But how should the fracture risk of overweight cancer patients be assessed? Scientists tried to answer this question by conducting a review article for breast cancer patients and concluded that obesity may correlate with an increased risk of skeletal fractures. (49)

Regarding AFF and obesity, Korean researchers were able to identify 17 fractures among 1362 patients as AFF and could define both bisphosphonates and elevated body mass index (BMI) as independent risk factors for AFF. (50)

1.4.5 Diabetes mellitus

Hyperglycaemia negatively affects mesenchymal bone marrow cells. It ultimately leads to fatty degeneration of the bone marrow, which in turn leads to a disruption in osteoblast differentiation through the secretion of cytokines and free fatty acids. In addition, cytokines have beneficial effects on the formation of osteoclasts. These processes described caused structural bone weakness in rats. (51)

Histological examination with special markers for bone formation and bone resorption showed that bone turnover in type 2 diabetes mellitus patients is lower than in the healthy population, but this does not necessarily lead to fragility fractures. Moreover, it is assumed that advanced glycation end products accumulate in bone tissue due to low bone turnover. There these end products interact with collagen fibres, which leads to microarchitectural weakening of the bone. In general, diabetes patients have a higher bone porosity and a lower density in the corticalis and are therefore more prone to fragility fractures. (51)

Similar to obese people, bone density is increased in patients with type 2 diabetes mellitus. However, this does not equate to a lower risk of fractures. Rather, type 2 diabetics with a T score that is a round 0.5 points higher have the same probability of fractures as non-diabetics. (51)

When it comes to AFF Muschitz et. al for example, were able to find out that patients with AFF were more likely to have comorbidities than the comparison group with typical subtrochanteric fractures. In addition to cardiovascular disease, chronic kidney disease, smoking and sarcopenia, these comorbidities also include type 2 diabetes mellitus. (52)

1.5 Atypical BMA associated fractures

BP have been an inherent part in the treatment of osteoporosis since the 1990s, as they inhibit bone loss. Since then, thousands of patients have been saved from suffering osteoporotic fractures. (53)

Since 2010 another important option in the treatment of postmenopausal osteoporosis has been available; denosumab, a human, monoclonal antibody that acts as a RANKL inhibitor. (54) The prescription of BP and denosumab is not entirely without risk. Especially the long-term use of BP can cause serious adverse effects, such as osteonecrosis of the jaw (ONJ), oesophageal cancer and AFF. (55)

Not only osteoporosis patients benefit from BMA therapy. In the guidelines for diagnosis and treatment of bone metastases the Japanese Society of Oncology recommends aggressive treatment with BMA for cancer patients (lung cancer, breast cancer, prostate cancer, multiple myeloma). This should treat or even prevent the occurrence of SRE caused by bone filiae of the primary tumour. (56)

1.5.1 Bisphosphonates

BP are administered either orally (alendronate, risedronate, ibandronate) or intravenously (zoledronate, ibandronate). Only about 1% of the orally administered dose is absorbed. About the half of this binds to bone mineral, where BP are taken up by osteoclasts. Here, BP inhibit the key enzyme farnesyl pyrophosphate synthase, which leads to the non-maintenance of the of osteoclast's cytoskeleton. The mode of action of clodronate and etidronate causes the accumulation of ATP analogues, leading to apoptosis of osteoclasts. (57)

This mechanism of action inhibits bone resorption within the BMU. There is an excess of osteoblast activity, which eventually leads to a 3-5% increase in bone mineral density (BMD). After a few months, osteoblast activity also ceases, since it is dependent on mutual communication with osteoclasts. The bone is preserved in this state and osteoprotective/ fracture-preventive effect was achieved by increasing bone mass and its mineralization. (8) However, BP may also lead to adverse effects, like AFF.

Ural reviewed current knowledge on the biomechanical mechanisms of AFF. He summarizes that BP therapy leads to increased levels of mineralization and maturation of collagen, due to the reduced bone remodelling. Together, this leads to more brittle bones and a loss of the ability to dissipate and absorb mechanical energy. In addition, the greater

homogeneity of the bone tissue means that microcracks on the cement lines are no longer stopped or dispersed. (58)

Reduced remodelling may impact the micro crack repair and as a consequence alter the microcrack density. Anyway, it is not clear, if a higher risk of AFF is related to a higher density of microcracks in the bone. It is also hypothesized that the progression of a single microcrack may lead to an AFF. (58)

Koeppen as well summarizes the effects of BP therapy to the bone in a table of her dissertation:

Table 1: Positive and negative effects of bisphosphonates according to Koeppen (8)

Bisphosphonates	**Positive effects**	**Negative effects**
Number of BMUs ↓	Bone density ↑ Bone mineralization ↑ Bone strength ↑	Homogeneity ↑ Bone primness ↑ Bone rigidity ↑
Remodelling ↓↓	Bone loss ↓ Structural decay ↓	Accumulation of microtraumas ↑ Recovery of microtraumas ↓
Collagen cross-linking and maturation ↑	Bone strength ↑	Bone rigidity ↑
Total effect	**Conservation of:** • **Bone mass** • **Functional architecture of the bone**	**Loss of:** • **Cyclic loading capacity** • **Ability to adapt**

1.5.2 Denosumab

Denosumab is a fully synthetic, monoclonal, neutralising humanised antibody, first approved by the FDA in 2010 for the treatment of postmenopausal osteoporosis and bone metastases from solid tumours. The drug is applied subcutaneously, reaches maximum serum concentration on day ten and is probably cleared via the reticuloendothelial system

after an elimination half-life of 28 days. The liver and kidneys are therefore unlikely to be involved in the metabolization of denosumab. (59)

Denosumab's mode of action prevents RANKL from binding to RANK on the osteoclasts. (60) By acting as a competitive antagonist, the drug inhibits the differentiation, survival and activity of osteoclasts which reduces bone resorption by them. (59)

Bone biopsies showed not only a reduction in bone resorption but also in bone formation. After approximately two to three years, the bone formation rate is zero. In contrast to BP, bone remodelling resumes quickly after denosumab is stopped. (22) A rise of vertebral fractures have been reported after discontinuation of denosumab. (61)

In general, denosumab increases BMD and bone strength, leading to a reduced risk of osteoporotic vertebra, hip and non-vertebral fractures. (61)

With regard to therapy for bone metastases, the following can be said about denosumab: It causes a delay in the formation of bone metastases when used prophylactically. Furthermore, it reduces the incidence of SRE and has pain-relieving effect on patients with bone metastases, which leads to an improvement in the quality of life. (59)

Typical side effects of denosumab include hypocalcaemia, hypersensitive reactions and theoretically increased risk of infection in immunocompromised individuals. In rare cases, ONJ or AFF may occur. (62) In the review paper by Starr et. al. the risk of AFF in osteoporosis patients on denosumab therapy is given as 0.8 per 10000 participant-years of a phase 3 trial. (63)

1.6 Atypical fractures in tumour patients

SRE as a result of bone metastases or multiple myeloma are serious sequelae of malignant pathologies. (64) As survival prognoses for cancer patients have continued to improve in recent years, there is concern about an increase in SRE. (65) Zoledronate has been used in Europe as agent against symptomatic SRE since it was approved for this particular indication in 2002 and denosumab since 2010. (64) Current guidelines recommend BP as an effective treatment for patients with skeletal metastases. Zoledronic acid reduces the risk of SRE by 36% compared to placebo and significantly increases the time free from SRE. (66) Denosumab, in turn, appears to be superior to zoledronate for the same indications. Denosumab extends the SRE-free time compared to zoledronic acid by approximately 8.2 months and reduces the risk of the first SRE by 17%. (64)

Nevertheless, studies on osteoporosis patients show that the use of BP and denosumab is associated with the occurrence of AFF. Moreover, long-term use of these drugs is associated with higher risk of AFF. (65) For example, the hazard ratio is approximately five times higher when BP is used for 8-10 years compared to 3-5 years. (67)

On the one hand, life expectancy of cancer patients is increasing and thus the potential duration of BMA administration is longer. On the other hand, the dosage of these drugs in the treatment of bone metastases is significantly higher than in the treatment of osteoporosis. This combination is expected to result in increased difficulties in dealing with and caring for AFF in cancer patients compared to osteoporosis patients. (65)

When it comes to AHF, the current situation of studies is not that clear. Yavropoulo et. al. analysed the connection between BP-use and AHF by conducting a case-control study. They were unable to find any association between BP use and AHF. (68)

1.7 Assessment of atypical fractures

The following chapter describes the characteristic properties that distinguish atypical fractures from other fractures. The diagnostic criteria for atypical fractures are discussed in more detail, as well as the typical clinical appearance and location of this particular type of fracture.

The ASBMR published a review in 2010 and an update in 2014 in which it summarised the current findings on atypical femur fractures. They define the following features, with which AFF typically can be distinguished from other fractures.

Table 2: Case definition according to the ASBMR (69)

Essential feature: Fracture localisation distal to the lesser trochanter and proximal to the supracondylar flare	
Major feature	Fracture associated with minimal or no trauma
	Fracture line: • originates at the lateral cortex • is orientated transversally • may become oblique after medial progression
	Fracture: • extends through both cortices • or is incomplete and involves only the lateral cortex • medial spike may be observed
	There is no comminuted or just minimal comminuted fracture
	Localised periosteal or endosteal thickening of lateral cortex at the fracture site

Minor feature	Increase of cortical thickness of femoral diaphysis
	Uni- or bilateral prodromal symptoms: • dull pain in thigh or groin
	Fracture may be bilateral
	Delayed fracture healing
Exclusion of: femoral neck fractures, intertrochanteric fractures with or without extensions to the diaphysis, periprosthetic fractures, pathological fractures connected with primary or metastatic bone tumours and bone diseases (Paget's disease, fibrous dysplasia)	

Beside this qualitative classification of AFF, Australian researchers made an attempt to use quantitative characteristics to develop a score indenting to identify AFF (Sydney AFF Score). The score is essentially based on geometric variables of female femur bones and demographic data. One point each is awarded if the patient is under 80 years of age, the width of the femoral neck is less than 37 mm and the lateral cortex of the trochanter minor is less than 5 mm. If two out of three points are met, the AFF could be identified with a sensitivity of approximately 73% and a specificity of around 70%. (70)

Anyway, the subtrochanteric or diaphyseal location of the fracture on the lateral corticalis is a main criterion of AFF. The reason for this could be the biomechanical properties of the femur in combination with the disturbed bone turnover and the consecutive basic problem of AFF, described in chapter 1.5, which are the unrepairable microcracks. (8) The highest tensile forces predominate at the lateral edge of the femur, with a maximum in the subtrochanteric region, decreasing slightly towards the middle of the shaft. (71) If this circumstance is combined with the described basic problem of AFF, the predilection points of these atypical fractures appear conclusive.

This fact may be worth mentioning when it comes to the assessment of AHF, as there is no official case definition of AHF available and AHF may as well occur in the area of greatest tensile stress of the humerus.

Nevertheless, Yavropoulou et al. attempted to investigate humeral shaft fractures associated with bisphosphonate administration. They defined AHF by applying the definition of AFF from ASBMR. (68)

Another possibility of identifying atypical fractures might be the histological examination of the fracture gap. Koeppen summarized these histological characteristics in her dissertation. There should be an amorphous material in the fracture gap that contains neither cells nor mineralised tissue. The gap is further characterised by the absence of remodelling processes, in contrast to the bone material surrounding the fracture gap. (8) Other sources (72) describe the presence of osteoclasts in the immediate vicinity of the gap, although some of them are morphologically conspicuous. (8)

In order to develop strategies for the best possible treatment of cancer patients suffering from atypical fractures affecting the femur or the humerus, is first of all to gain an overview of the case load and its specific characteristics. For this reason, this retrospective study was conducted.

2 Material and methods

2.1 Objectives

This retrospective, descriptive study was performed at the Department of Orthopaedics and Trauma at the Medical University of Graz.

The intention to initiate this analysis of fractures was, to investigate the proportion of non-tumorous fractures in cancer patients, in order to estimate the approximate number of AFF and AHF. This could lead to a broader understanding of the therapy of skeletal related events in cancer patients and therefore improve the treatment of patients with atypical fractures or even prevent them.

Identifying the location and the histological typing of the fracture were the primary endpoints of this study. Demographic and clinical data are to be given as secondary criteria.

The location was categorised in humeral and femoral fracture, as well as in proximal, diaphyseal or distal. Fracture's location points the way for further classification with regard to AFF. (69) Therefore, the diaphyseal area of the femur is defined as the area between below the lesser trochanter and the supracondylar extension. (8) As AHF in correlation with BMA application are a rare phenomenon, no fracture location can be associated with AHF. (68)

If there was more than one fracture in one patient, reference was made to the fracture that occurred earlier in patients' history.

We defined the fracture as tumorous, if histological evidence for malignant or cystic tissue could be found.

If a patient was diagnosed with more than one type of cancer, reference was made to the first cancer diagnosis of the patients' history.

Factors that could potentially influence the occurrence of a pathological fracture or an AFF/ AHF were included in the analysis, such as age, sex, body mass index, comedications (BMA, chemo-, immuno-, hormone therapeutics, synthetical glucocorticoids, vitamin D_3) and comorbidities (osteoporosis, diabetes, renal insufficiency, nicotine abuse).

2.2 Ethics

For the present study, an application was submitted to the local Institutional Ethical Review Board (Reference Number: EK-Nr.: 34-371 ex 21/22), which was approved.

2.3 Study population

Retrospective data of male and female patients admitted to the Level I Trauma Center from 2006 to 2020 because of suspected diagnosis of a pathological or atypical fracture was collected. Subsequently, these patients were hospitalised and underwent further treatment in the form of surgery or conservative treatment.

2.3.1 Inclusion criteria

To be included in the study, patients had to have a fracture of the humerus or the femur, with suspected malignancy as the cause or a history of malignant disease. This includes both groups of patients. Those with pathological fractures and the others who potentially suffered an atypical fracture as a complication of BMA therapy. At the time of admission to the hospital, all patients had to be older than 18 years of age.

2.3.2 Exclusion criteria

Consequently, patients under the age of 18 or fractures in bones not including humerus or femur were excluded from the study. As the strictly retrospective study was conducted after defining the study population's criteria, no patient had to be excluded. For reasons of simplifying statistical calculations and in order not to further increase the already complex inhomogeneity of the study population, patients with multiple neoplastic diagnoses were also excluded from statistical considerations.

2.4 Acquisition of data

The collection of patients' data was carried out via the hospital's internal data system MEDOCS. The Institute for Medical Informatics, Statistics and Documentation of the Medical University of Graz acquired the patient's data.

Demographic data, body mass index, admission date, location of the fracture and treatment of it as well as the presence of metastases, their location and their therapy with radiation, if there was any, were retrieved from discharge letters and nursing/ surgical reports. Just like the time of initial diagnosis of any malignant tumour diseases, their entity, as well as the time and manner of their treatment (chemotherapy, hormone therapy, immunotherapy, radiotherapy). An attempt was also made to ascertain any relevant comedications and comorbidities from the medical history of the patients. These would be BMA therapy,

synthetical glucocorticoids, vitamin D_3, osteoporosis, diabetes, renal insufficiency, nicotine abuse and COPD.

By evaluating histological findings obtained from preparations during the surgical treatment of the fracture, it was determined whether there was malignant or cystic tissue in the fracture area.

2.5 Statistical methods

In a further step, we prepared the data for statistical evaluation by using Excel® (Microsoft® Cooperation, Redmond, WA, USA). After the processing, data was analysed by applying IBM® SPSS® (Statistics 29.0, Armonk, North Castle, NY, USA).

In this retrospective analysis, descriptive statistics served as the primary method for statistical evaluation. Therefore, no hypotheses were generated and all other evaluations are to be regarded as exploratory.

For metric data, arithmetic means and standard deviations or medians and quartiles were calculated, depending on the distribution. To statistically represent categorical variables, medians and quartiles were determined. 95% confidence intervals were calculated for arithmetic means, medians and percentiles of each group.

Depending on scale level, bar charts, histograms and box plots were used to graphically present the results.

3 Results

3.1 Patients' characteristics

3.1.1 Distribution of gender and age

In the course of this study, a total of 362 patients were analysed, who were admitted to the Department of Orthopaedics and Trauma at the Medical University of Graz with suspected pathological or atypical fractures. Only one person's age at the time of the fracture could not be determined. The mean age at the time of the patients first fracture was 67.44 years (SD 12.85). The study population consisted of 57.18% (n=207) females and 42.81% (n=155) males.

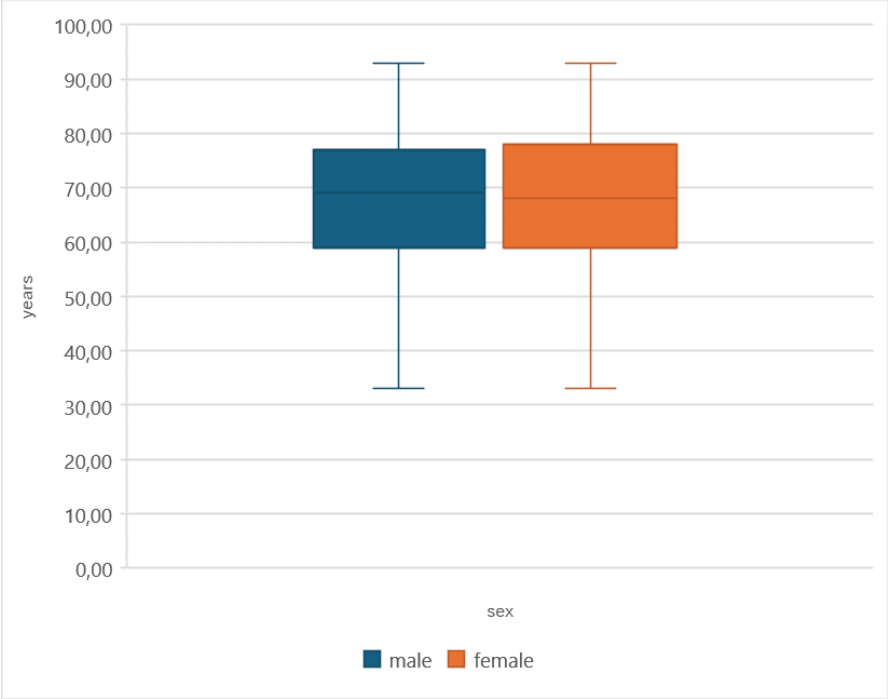

Figure 1: Distribution of age for each gender

If the patients are divided concerning their age into intervals of 10 years, the following age distribution is shown in figure 2. 0.83% (n=3) are matched in the group of the 15 to 25 years old. 1.10% (n=4) are between 25 and 35, 2.21% (n=8) between 35 and 45, 13.54% (n=49) are between 45 and 55, 24.03% (n=87) between 55 and 65, 30.11% (n=109) between 65 and 75, 20.99% (n=76) between 75 and 85 and 6.91% (n=25) between 85 and 95.

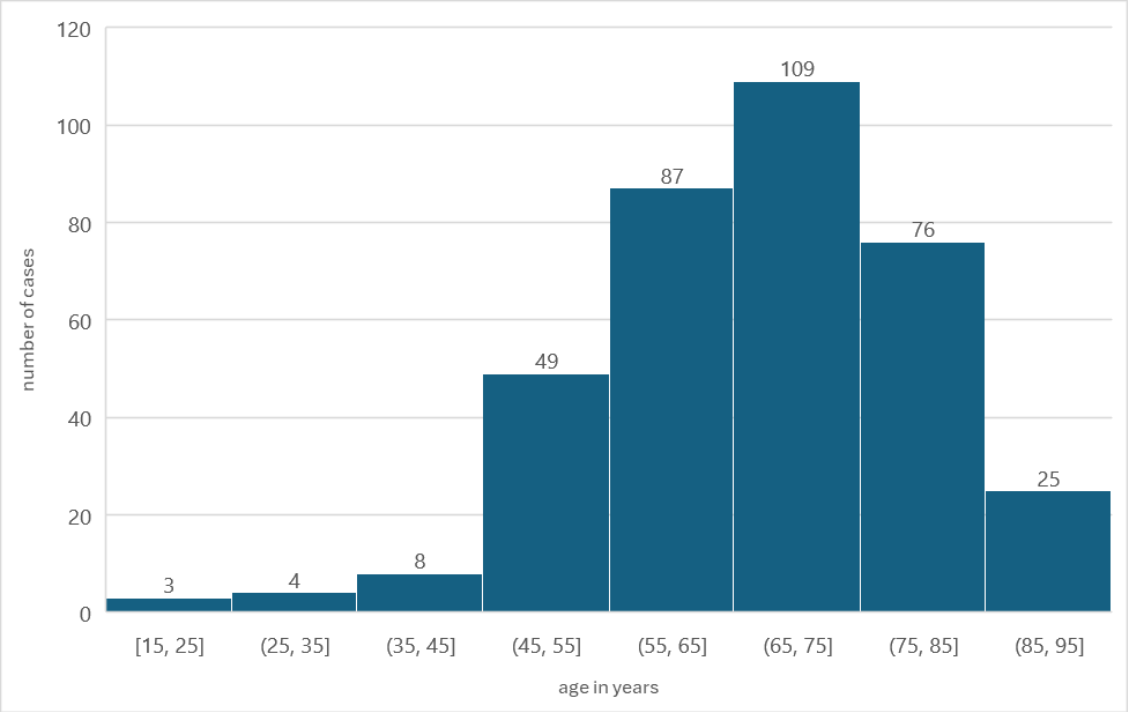

Figure 2: Distribution of the age at the time of the fracture, regardless of gender

3.1.2 Proportions of primary tumours

Of these 362 patients, 345 could be assigned a diagnosis of a primary tumour. Cancer entities were categorised into 13 different subgroups. The frequencies of these primary tumours were as follows: 17.68% (n=64) were diagnosed with breast cancer, 15.47% (n=56) with haematological neoplasms, 12.98% (n=47) with pulmonological neoplasms, 12.70% (n=46) with urological neoplasms, 7.73% (n=28) neoplasms of the bone and soft tissue, 7.46% (n=27) with nephrological neoplasms, 6.91% (n=25) with gastroenterological neoplasms, 4.14% (n=15) with non-tumorous lesions, such as osteomyelitis, osteonecrosis or osteopenia, 4.14% (n=15) with other neoplasms, such as CUP, thyroid carcinoma, synovial carcinoma, angiosarcoma, schwannoma etc., 2.21% (n=8) with dermatological neoplasms, 1.93% (n=7) with other gynaecological neoplasms, 1.66% (n=6) with otorhinolaryngological neoplasms and 0.28% (n=1) with neurological neoplasms.

3.2 Comparison of fractures regarding various parameters

3.2.1 Distribution of histological findings in the fracture gap

8.01% (n=29) out of 362 patients, suffered from more than one pathological or atypical fracture during the observation period. Histological findings of the fracture gaps were not available for 21.55% (n=78) of patients. Overall, 56.35% (n=204) of the examined fracture gaps of patients were positive for tumour or metastatic tissue and in 22.09% (n=80) no evidence of neoplastic changes could be detected histologically.

Taking the age into consideration, different values concerning the patients' mean age can be seen in relation to the findings of the histological fracture gap examination. The mean age of those patients without tumorous changes in the fracture gap is 70.85 years (SD=12.79) and that of the patients with evidence of a tumour in the fracture gap is 65.21 years (SD=12.90). The difference in the mean ages of the two groups is 5.64 years. This result is statistically significant ($p<0.001$), with the lower value of the 95% confidence interval being 2.30 and the upper value being 8.99.

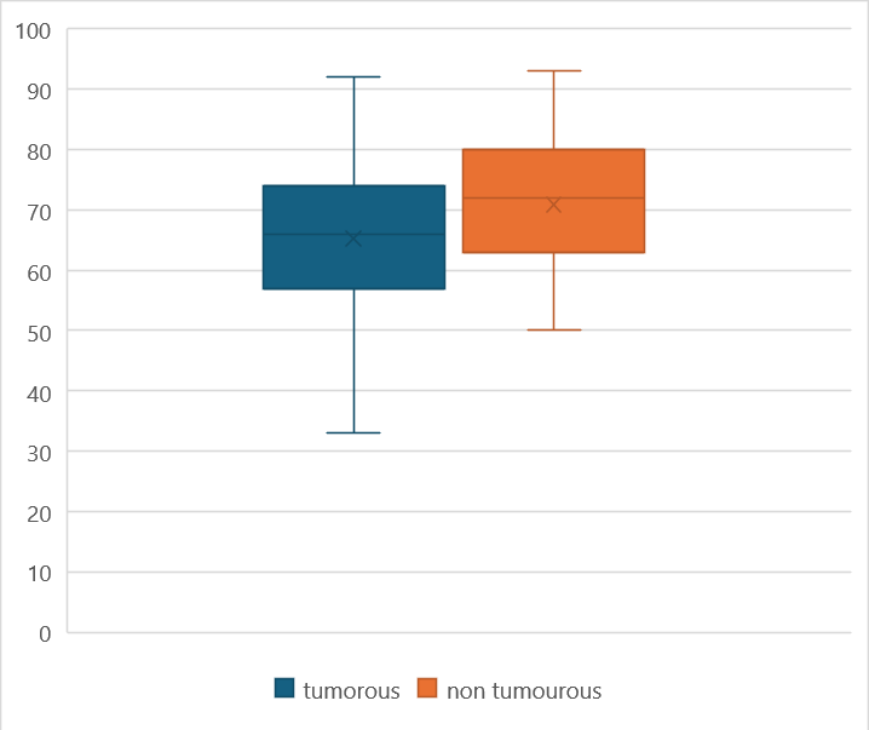

Figure 3: Distribution of age in years in relation to histological findings in the fracture gap

By disaggregating the absolute and relative proportion of the histological findings of the fracture gaps into the 13 different categories of primary tumours, the following results can be shown graphically in figure 4 and 5. What can be seen in these charts, is the dominance of tumorous, respectively metastatic, histological findings in most of the primary tumour categories. However, this does not apply to neurological neoplasms, to the category of other gynaecological neoplasms and of course not to the non-malignant category. Another point necessary to mention is the large amount of inconclusive histological findings, varying from one (6.67%) in the category of other neoplasms up to 17 (36.17%) in the category of pulmonological neoplasms.

The largest absolute proportion of fractures without histological evidence of tumorous tissue, apart from the "non-malignant" category, is found in the group of breast carcinomas (n=14), followed by the group haematological neoplasms (n=11) and the gastroenterological neoplasms (n=9).

Concerning the relative proportions of fractures without histological evidence of tumorous tissue, the largest one is found in the category of neurological neoplasms (100%), followed by other gynaecological neoplasms (71.43%) and gastroenterological neoplasms (36.00%).

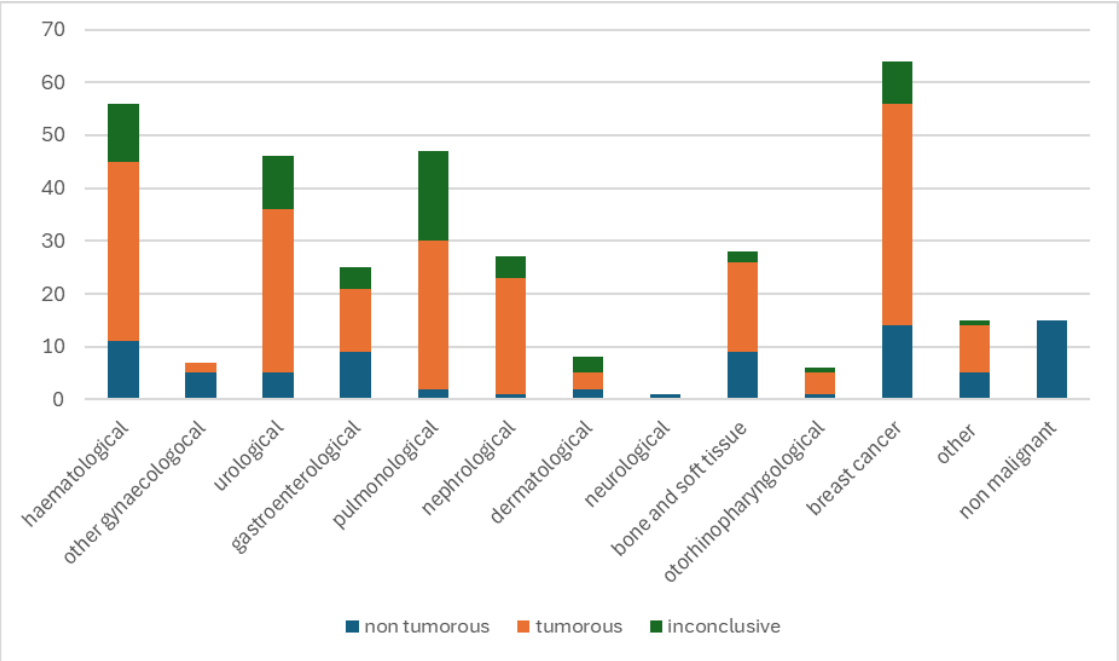

Figure 4: Absolute proportion of histological findings in relation to the categories of primary tumours

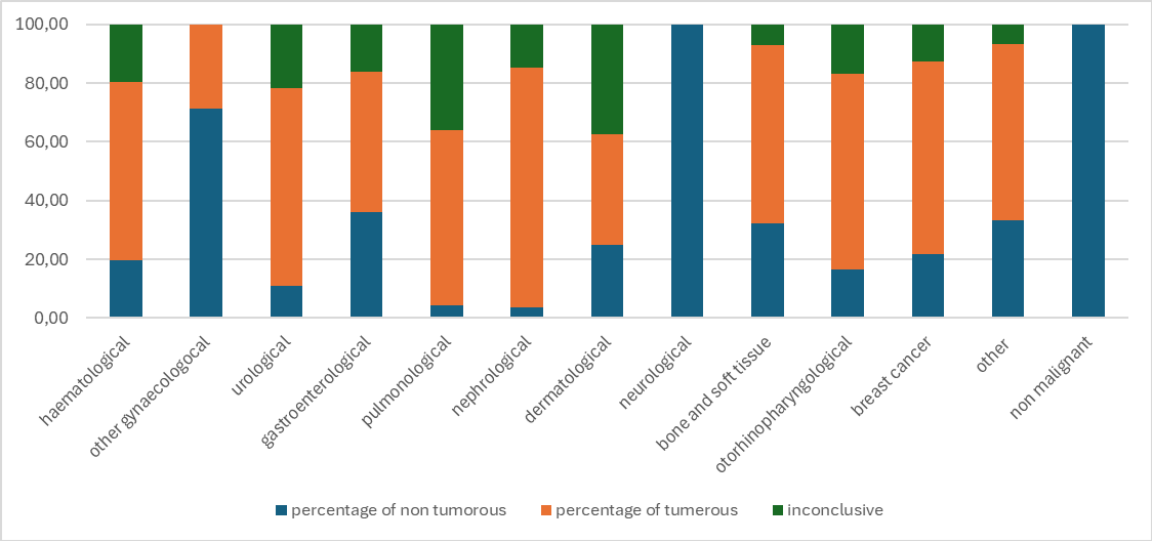

Figure 5: Relative proportion of histological findings in relation to the categories of primary tumours

We compared the two groups with regard to the mean BMI value, at which no significant difference could be observed. The mean in patients with tumorous tissue in the fracture gap was 26.08 kg/m², that in patients without tumorous evidence was 25.47 kg/m².

3.2.2 Anatomical location of the lesions

Of the 362 cases included, 350 (96.7%) fractures could be assigned to either the humerus or the femur. 108 (29.8%) fractures involved the humerus and 242 (66.9%) fractures the femoral bone. No anatomical assignment could be determined for 1.4%. 2% of the fractures were assigned to other anatomical regions and were incorrectly included in the data analysis. Of these, five fractures occurred in the spine and one each in the radius and pelvic bone.

In a further step, we were able to categorise 338 (93.4%) humeral or femoral fractures in the subcategories of proximal, diaphyseal or distal fractures (see figure 6). If we take a closer look at the fractures of the humerus, 42 out of 100 humeral fractures occurred in the proximal area. 50 out of 100 are on the diaphyseal part and eight out of 100 are distal humerus fracture. Taking the femoral fractures into account, it appears that proximal fractures are the vast majority (175 out of 238). The much smaller proportions of diaphyseal and distal femur fractures are distributed with 40 diaphyseal out of 238 femoral fractures and 23 distal out of 238 femoral fractures.

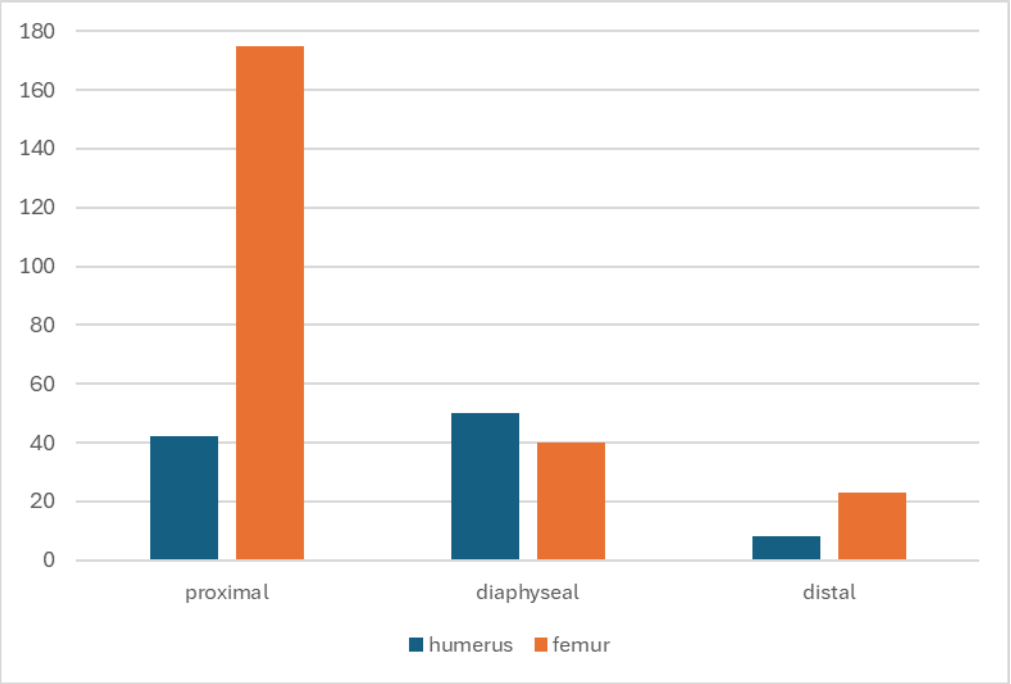

Figure 6: Anatomical distribution of the fractures

In a further step, the detailed results concerning the distribution of the fracture localisations were divided into the histological findings of the fracture gaps (figure 7). It is striking that in femoral fractures, the frequency of fractures decreases from proximal to distal. This is the case both in the group of tumorous fractures and in the group of non-tumorous fractures. At first glance, this also appears to be the case with humeral fractures. However, a closer look reveals a higher proportion of diaphyseal fractures, taking into account the high proportion of inconclusive histological results. Furthermore, it can be seen that in the majority of fractures, tumorous cells could be detected histologically, regardless of the exact location of the humerus or femur fracture. This would also be the case, if all inconclusive results were non tumorous for any reason. Only in the case of distal humerus fractures, the number of tumorous and non-tumorous fractures would be the same, assuming all inconclusive fractures as non-tumorous fractures.

Particular attention should be given to the groups of diaphyseal fractures, since in this group, according to the ASBMR criteria, atypical fractures are to be expected. There are six non-tumorous, diaphyseal femur fractures and seven non tumorous diaphyseal humerus fractures.

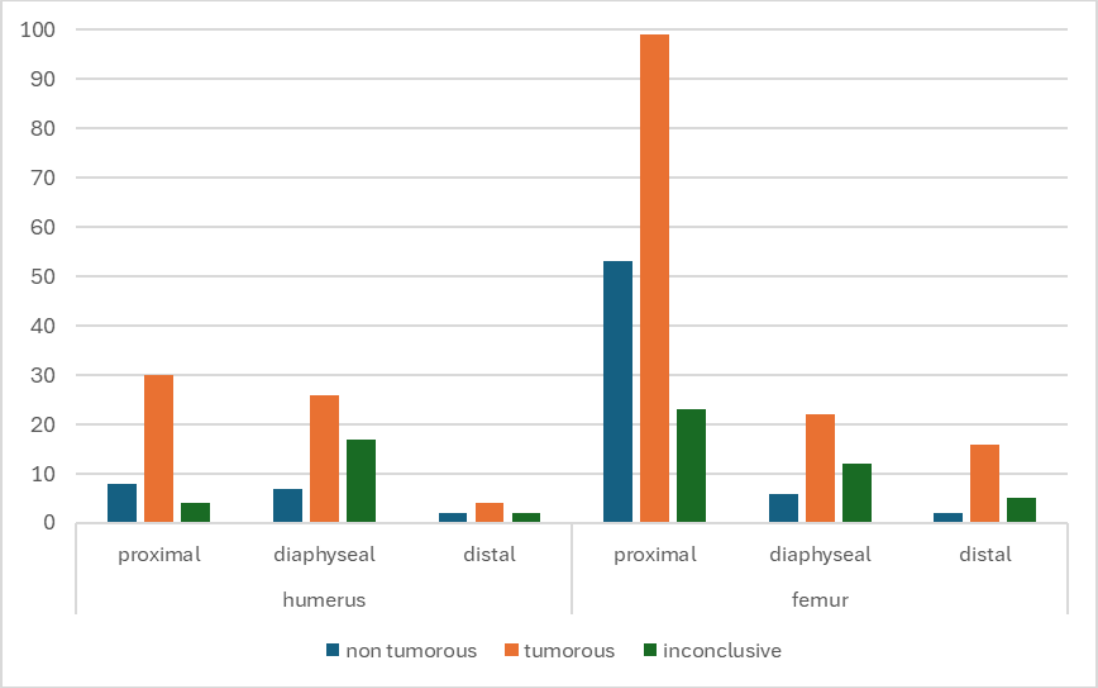

Figure 7: Distribution of the fracture in relation to the histological results

Table 3: Distribution of the fractures in relation to the histological results

	humerus			femur		
	proximal	**diaphyseal**	**distal**	**proximal**	**diaphyseal**	**distal**
non tumorous	8	7	2	53	6	2
tumorous	30	26	4	99	22	16
inconclusive	4	17	2	23	12	5

3.2.3 Time period from initial diagnosis of the primary tumour to fracture

We were able to collect data regarding the time of diagnosis of the primary tumour and the time of fracture for 240 (66.30%) included study participants. For 122 (33.70%) people, the data was incomplete or could not be obtained at all. These 240 People were again divided into 98 male and 142 female patients. The mean time until the fracture occurred was 47.90 months (SD 69.11) for all of the 240 patients, 39.52 (SD 61.15) months for the male and 53.69 (SD 73.76) months, approximately 14 months longer, for the female

patients (see figure 8). However, this difference is not statistically relevant. When a t-test is carried out, neither with a one-sided p (p=0.053) nor with a two- sided p (p=0.107) and a 95% confidence interval (-31.399; 3.060).

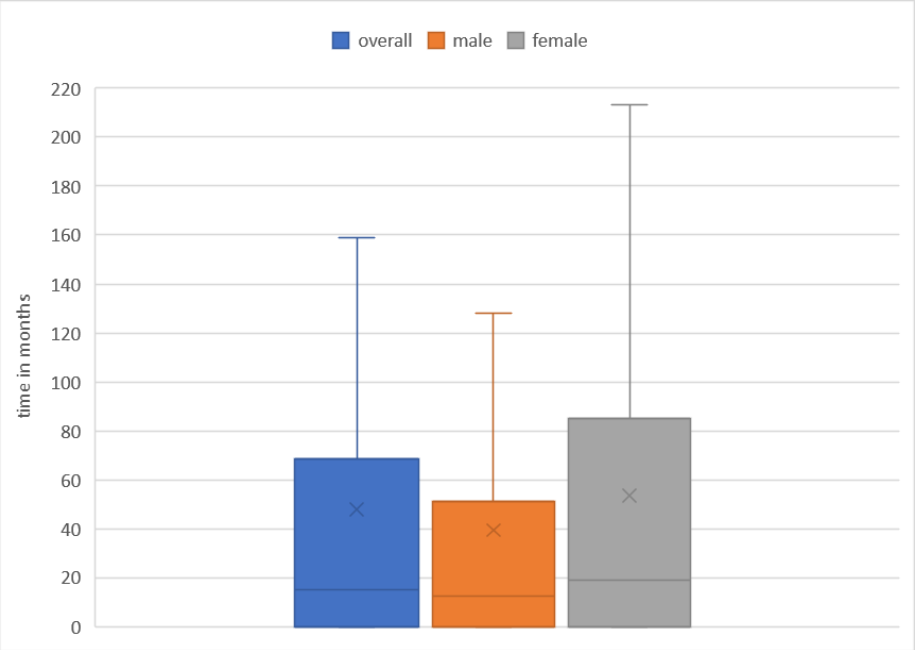

Figure 8: Time in months until fracture occurred overall and in relation to the gender

Dividing the group of 240 cases with regard to the histological findings (figure 9), the results are as followed: Humeral and femoral bones of 134 cancer patients in whose fracture gaps malignant tissue could be detected, fracture occurred after a mean time of 47.40 (SD 71.81) months. This is approximately 11 months earlier than in 64 cancer patients, in whose fracture gaps no tumorous tissue could be found. (58.45 months SD 76.89). In 42 cases, the histological circumstances could not be determined. The mean time until fracture in this subgroup is 33.45 (SD 40.50) months. As the high values of the standard deviation already might suggest, these results are not statistically significant.

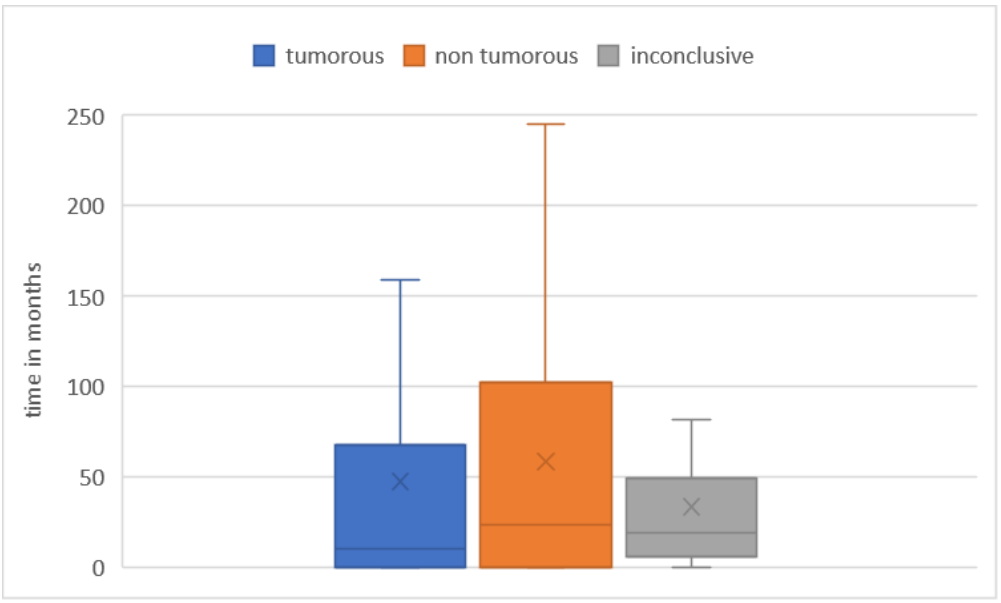

Figure 9: Time until the fracture occurred in months in relation to the histological findings in the fracture gap

Coming to the classification according to BMA administration (figure 10), there are again no statistically robust results. Our research has shown a difference of approximately 22 months of the mean time until a fracture occurs between the two subgroups, in which either BMA was administered or not. In 52 patients undergoing BMA therapy the mean time until fracture was 65.19 (SD 84.08) months and in 188 patients, for whom no evidence of therapy could be found, the mean time until fracture was 43.12 (SD 63.79) months.

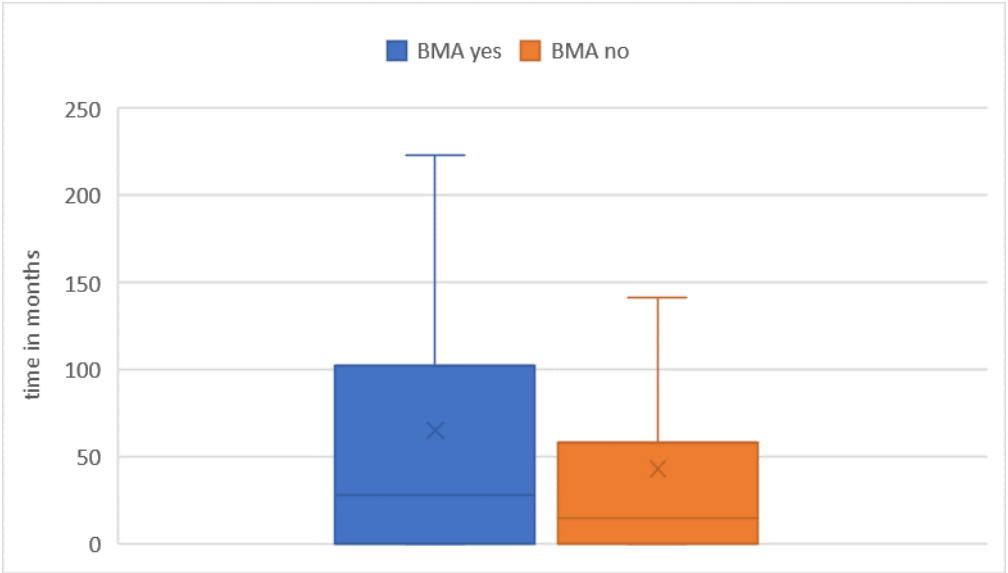

Figure 10: Mean time until fracture occurred in months in relation to BMA administration

The following table and figure give a brief overview of the mean time until fracture in relation to the histology of the primary tumour. It must be emphasized once again, that these results are purely descriptive. They show no statistical significance.

Table 4: Mean time until fracture occurred in relation to the several subgroups of primary tumours and their respective number of patients

	number of patients	mean time [months]	SD [months]
haematological	39	40,97	55,86
other gynaecological	5	27,20	37,15
urological	25	59,36	87,36
gastroenterological	19	40,21	45,21
pulmonological	25	18,80	46,54
nephrological	24	51,17	65,41
dermatological	5	29,60	14,77
neurological	1	242,00	
bone and soft tissue	24	24,83	52,48
otorhinolaryngological	4	76,75	139,53
breast cancer	48	89,31	81,10
other	6	39,50	50,52
non malignant	15	0,00	0,00
total	240		

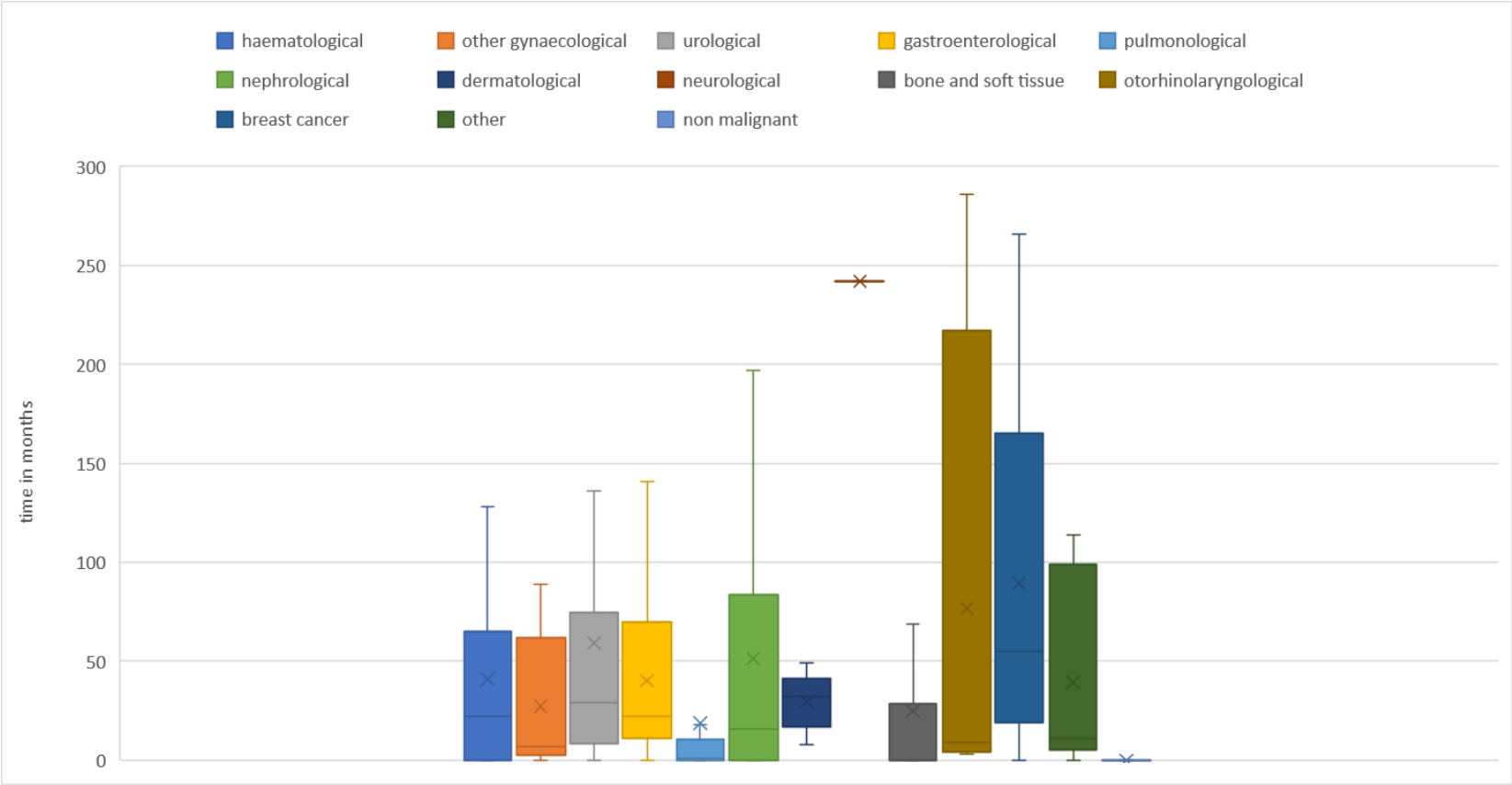

Figure 11: Mean time until fracture occurred in relation to the several subgroups of primary tumours

3.3 Administration of BMA

A prescription of BMA was identified in 70 cases (19.34%) of the study population. An attempt was made to determine the timing of the first administration of BMA. It was found, that for 68.57% (n=48) of the cases positive for BMA administration, determination of the date of first administration was not possible. In six (8.57%) patients, initiation of administration occurred within a six-month period before fracture. In sixteen (22.86%) patients, BMA were administered more than six months before the fracture or after the fracture.

With regard to the frequency of the different drug agents of BMA, the following results were determined (see figure 12). Denosumab was most commonly prescribed (n=32), followed by zoledronate (n=17) and ibandronate (n=4). A more precise determination of BMA could not be achieved in 17 patients.

Looking at the group of non-tumorous diaphyseal fractures of humerus and femur with regard to the possible administration of BMA, one case of BMA prescription was found in each group. To be more precise, the administration of BMA was detected in one of six cases of diaphyseal, non-tumorous femoral fracture and in one of seven cases of diaphyseal, non-tumorous humeral fractures. Regarding to the humeral fracture, the type of BMA was zoledronate and regarding the femoral fracture, no exact determination of BMA was possible.

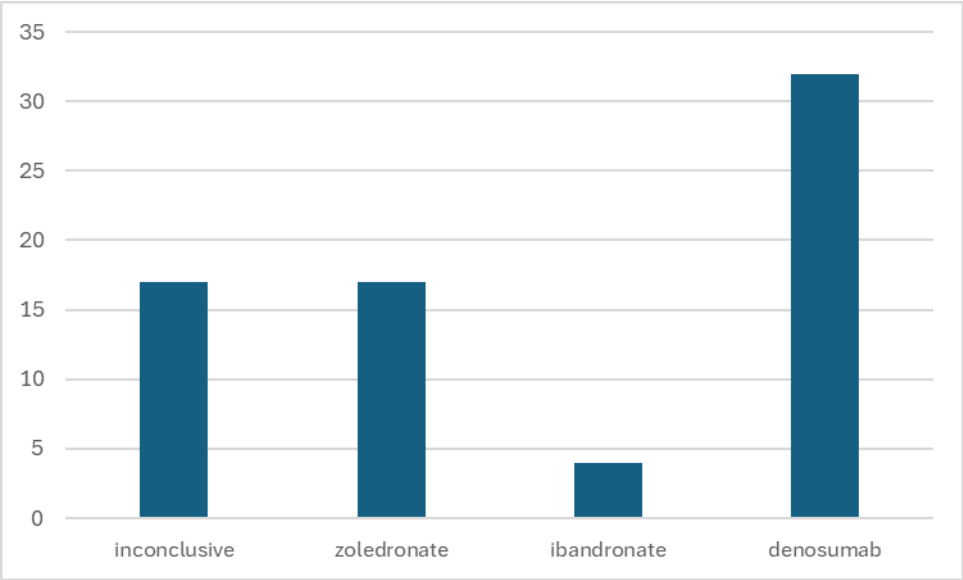

Figure 12: Respective frequencies of prescribed BMA

Considering the distribution of BMA administration in relation of the histology of the primary tumour, the following results emerge, as shown in figure 13. The largest proportion of BMA prescription occurs in the group of patients with breast cancer (32.81%; n=21), followed by those with haematological neoplasms (32.14%; n=18) and nephrological neoplasms (29.63%; n=8). The remaining proportions are 23.91% (n=11) for urological tumours, 14.29% (n=1) for other gynaecological tumours, 12.77% (n=6) for pulmonological tumours, 6.67% (n=1) for other tumours and 3.57% (n=1) for bone and soft tissue neoplasms. In three cases of BMA administration, the allocation to a primary tumour was not possible.

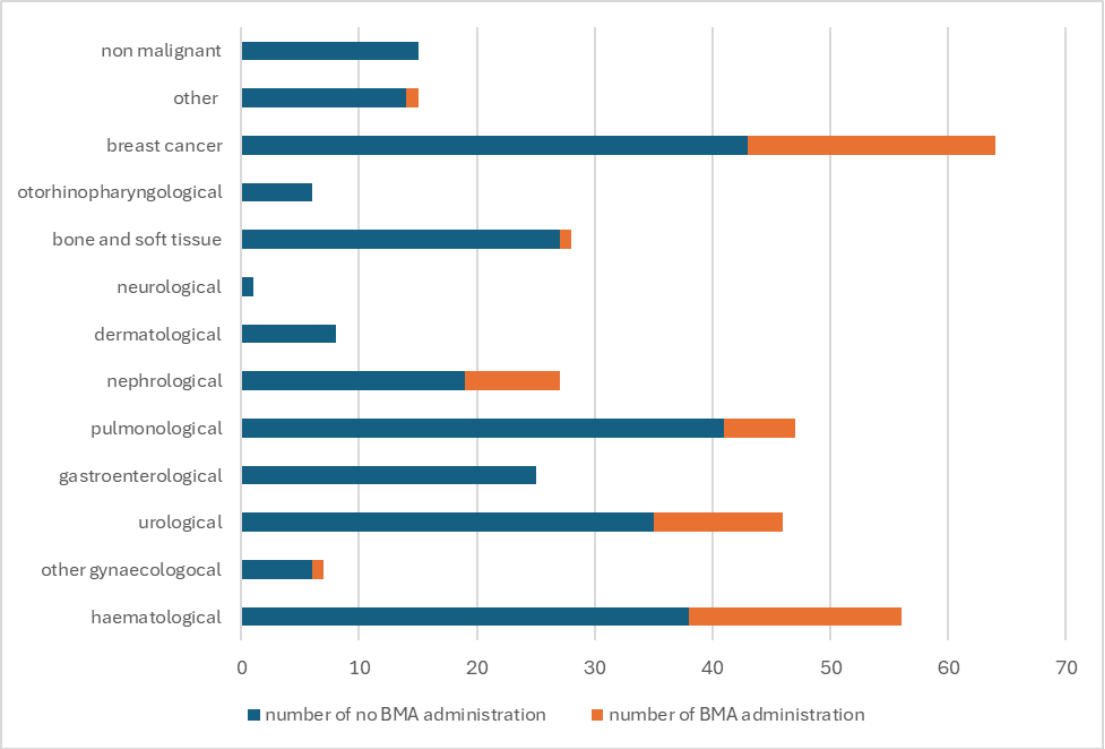

Figure 13: Number of BMA administrations in relation to the primary tumour diagnosis

3.4 Radiotherapy, chemotherapy, immunotherapy, hormone therapy

We examined the study population to see whether they had a history of therapy to treat the respective primary tumour or bone metastases. 154 (42.54%) cases were identified in which chemotherapy, immunotherapy or hormone therapy was definitely carried out. 10.22% (n=37) of the study population received such therapy within six months before the fracture. In 10.50% (n=38) of the patients analysed, such therapy was carried out or completed more than six months before the fracture or after the fracture. For 79 (21.82%) of the 154 people who were treated with certainty, no exact time of completion of therapy could be found.

The patients were analysed for radiotherapy according to the same scheme. In 107 (29.56%) patients, reliable evidence for radiation treatment of the primary tumour was found. In 14 (3.87%) of these, therapy took place within six months before the fracture. For 15 (4.14%) people there was no reliable indication of the exact moment of the last radiotherapy and 78 (21.55%) patients, stopped radiotherapy earlier than six months before the fracture or after the fracture.

Bone metastases were determined in 181 Patients (50.00%). Radiotherapy of bone metastases any time before the fracture occurred in 17.96% (n=65) of the study population. For one person the findings were inconclusive regarding the time of the radiotherapy of bone metastases. 296 (81.77%) persons either did not have a radiotherapy of their bone metastases or had the radiotherapy after the fracture.

3.5 Comorbidities and comedication

As a last step, we wanted to investigate, how many patients of the study population were positive for comedications and comorbidities that could potentially influence bone metabolism. For this reason, patients' history was scanned for the following diagnosis and medications: renal insufficiency, osteoporosis, nicotine abuse, diabetes, COPD, synthetical glucocorticoids and vitamin D3 substitution. The following table and bar chart show how many patients included, had reliable evidence of comedications or comorbidities at any time before the fracture.

Table 5: Number of patients with evidence for the respective comedication or comorbidity

	renal insufficiency	osteo-porosis	nicotine	diabetes	COPD	gluco-corticoids	vitamin D3
evidence	57	29	16	51	34	6	0
no evidence	305	333	346	311	328	356	362

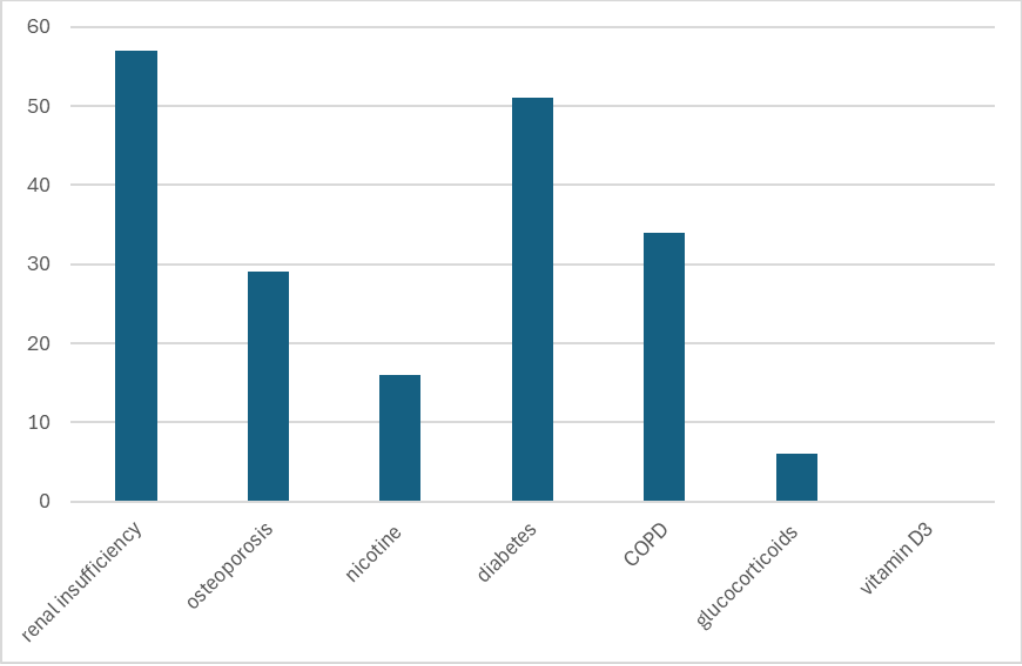

Figure 14: Number of patients with evidence for the respective comedication or comorbidity

4 Discussion

The primary goal of this study, determining the proportion of atypical fractures of the humerus and femur could not be fully achieved through the statistical analysis of the patients' parameters. In order to diagnose atypical fractures with a high degree of probability, the ASBMR criteria are necessary, which requires analysing x-rays. (69)

Nevertheless, we were able to determine the proportion of fractures in which no tumorous tissue could be detected. The probability of finding atypical fractures in that specific group of patients could be high.

In 14 years, 362 patients who met the aforementioned criteria, were treated at the Level 1 Trauma Centre for a suspected pathological fracture. The associated data was collected retrospectively. It was not possible to complete the data set entirely. Particularly with regard to the essential variables of BMA or histological findings, there are considerable gaps. There may be a variety of reasons for this; large amount of data, possible changes in the documentation and coding of diagnoses or non-standardised documentation should only be mentioned as hypothetical considerations.

This circumstance, in combination with the small study population, makes it difficult to generate statistically profound results. In addition, due to the numerous primary tumour entities and the various treatment regimens (radio-, chemo- and hormone therapy), the patient population studied was so inhomogeneous that meaningful groupings and filtering of possible bone-influencing risk factors were not possible in this study.

For these reasons, the focus was placed on a descriptive illustration of the patient group characteristics. In the following chapter, however, an attempt is made to categorise the results in the context of the current literature.

4.1 Patients' characteristics

4.1.1 Distribution of gender and age and the proportion of primary tumours

The gender distribution in this study was 57.2% women to 42.8% men. If you compare this result with the gender distribution of the incidence of all malignancies in Austria between 2017 and 2019, a different distribution can be seen. The incidence was 45.9% among women and 54.1% among men.(31) There are two striking differences in the characteristics of the two groups that could possibly explain the different results.

Firstly, the study population in our case consists of people who suffer to a large extent from malignancies that cause bone metastases. These are breast cancer, prostate cancer, multiple myeloma, and lung cancer.(30) These entities, also make up the majority of our study population, summarised as breast cancer, urological neoplasms, haematological neoplasms and pulmonological neoplasms (213 of 345; 61.74% of entities analysed). If one calculates the gender-dependent prevalence of these four cancer entities in the Austrian Cancer Report, this results in 90667 (52.89%) female cases and 80733 (47.10%) male cases. (31) A similar reversal of the gender ratio as in our population can be observed.

Secondly, the AFF could also be the cause of the higher proportion of women. Kharazmi et al give the RR for women to suffer an AFF as 4.31 compared to men. They hypothesise a lower biomechanical resilience of female femurs, as well as a higher bone micro damage and a greater trabecular and cortical thinning in women. (73)

In addition to the bone-spreading cancers already mentioned, our study also found a large proportion of neoplasms of the bone and soft tissue (n=28; 7.73%). Osteosarcoma, Ewing's sarcoma and chondrosarcoma should be mentioned here in particular. These entities normally have an extremely low incidence. In Germany for example, these tumours occur with less than one new case per 100000 person-years, or in other words, around 600 new cases per year. (74). In addition to a cancer diagnosis, a primary characteristic of our study participants is the occurrence of a bone fracture, that might explain the relative high number of patients with primary bone tumours. According to Christ et al. the rate of pathological fractures in 3083 patients with primary bone tumours is 78 (2.5%). (75)

A comparison of the age distribution at the time of fracture of our patients with the age distribution or the age-specific cancer incidence in the Austrian Cancer Report reveals a different curve. In our results, the number of patients in the category of 55-65 years of age is slightly higher than in the category of 75-85. In the Austrian Cancer Report, the opposite is the case. (31) In other words, our study population is younger overall. This could be explained by the low number of study participants or the high proportion of breast cancer patients. According to the report on cancer incidence in Germany, the average age at diagnosis is 64.3 years for breast cancer, 70.9 years for prostate cancer and 68.8 years for lung cancer. (76) An American study gives a mean age at diagnosis of breast cancer of even 59.7 years (SD 13.8) (77) and a Canadian study gives a mean age of diagnosis of multiple myeloma of 79 years (SD 12.1). (78) One could interpret that breast cancer affects comparatively young people, which could explain the age distribution in this study.

4.2 Comparison of fracture regarding various parameters

4.2.1 Distribution of histological findings in the fracture gap

In the case of this retrospective study, the results of this histological fracture gap analysis should be seen as the first step in filtering out possible atypical fractures of this study population. However, it should be noted once again that the diagnostic criteria of ASBMR should be respected as the standard of determining AFF or AHF. (69) The high proportion of unclassifiable histological findings of almost one fifth of fractures, which is therefore almost as high as the proportion of tumour-free fractures, has a further restrictive effect on interpreting the results.

Looking at the mean age of the two groups, there is a difference of 5.64 years, while the younger group is the one with the tumorous fracture gaps. The group of tumorous fractures includes not only pathological fractures due to bone metastases, but also a large proportion of the group of primary bone tumours. The peak age of occurrence of Ewing's sarcoma is around the second decade of life, as is that of osteosarcoma, while that of chondrosarcoma is around the eighth decade of life. (76) As the proportion of primary bone tumours is with 28 cases relatively high, this could be one of the reasons for the low mean age of patients with a tumorous fracture gap. In addition, the proportion of tumorous fractures from the group of breast cancer patients is quite high, which, as previously mentioned, are also of lower mean age.

Another reason for the age difference between the two groups could be the higher fracture risk in the older population. Especially when considering postmenopausal or senile osteoporosis, low energy trauma is often the cause of hip and humerus fractures. (23) Rupp et. al. analysed the incidence of adult fractures in Germany from the year 2009-2019 and found that the incidence of femoral and humeral fractures increases sharply as one gets older. The incidence of femoral neck fractures in the male and female 60–69-year-old German population is 68.7/100000 and 95.1/100000 respectively. The incidence increases in the 90+ age group for men and women to 1224.4/100000 and 1828.3/100000 respectively. The incidence of proximal humerus fractures also increases from 60.4 and 162.8/100000 to 247.6 and 666.7/100000 respectively. (79)

BMA are intended to prevent tumour patients from SRE. (56) This argument could also be used to justify the age difference between the malignant and non-malignant fracture group. It could be that the malignant group did not undergo BMA therapy. The patients in the

non-malignant group, on the other hand, could successfully prevent or protract a pathological fracture through BMA therapy, but suffered an AFF/ AHF, albeit later. However, looking at the figures of the second report of the ASBMR, a scenario in which 22.09% of cases suffered an atypical fracture seems extremely unrealistic. The absolute risk of bisphosphonate-associated AFF is between 3.2 and 50 cases or approximately 100 cases in long-term users per 100000 person-years. (69)

In addition to pathological fractures in tumour patients and atypical fractures, the data could also be interpreted to indicate the possible existence of a third major risk class for fractures in tumour patients. That would be older tumour patients with a higher risk of an osteoporotic fracture.

4.2.2 Anatomical location of the lesions

Different types of fractures can be expected in the patient population of our study: pathological fractures due to primary bone tumours or due to secondary bone tumours, osteoporotic fractures, fractures due to osteomyelitis or osteonecrosis and also AFF and AHF. As before, these fracture groups can be roughly divided into malignant and non-malignant fractures. In addition, the predilection sites of these fractures of different origins, can be helpful in interpreting the results of this subchapter.

Starting with the group of malignant fractures caused by primary bone tumours, we found a total of 28 potential primary bone tumours. Osteosarcoma is increasingly distributed over the distal femur, the proximal tibia and the proximal humerus. Ewing's sarcoma are often found in the diaphysis of long bones. (36) Chondrosarcomas, the most common primary bone tumour of patients over the age of 60, are increasingly found in the proximal humerus, femur and pelvis. (80) Following this logic, osteosarcomas should be found in the 17 tumorous distal femur fractures, as well as in the 30 proximal, tumorous humeral fractures. Ewing's sarcoma should be found in the tumorous diaphyseal humerus and femur fractures (n=26 and n=22). Chondrosarcomas in the group of tumorous proximal humerus and femur fractures (n=30 and n=99).

Assuming that the tumorous fractures in our study are mainly pathological fractures caused by bone metastases, the results would be similar to those of a Swedish research group. (81) They examined 1453 patients, with similar characteristics to the patients in this study, in terms of age, sex, and primary tumour, as well as localisation of pathological fractures caused by bone metastases. The descriptive results of the patient characteristics are similar

to our results. The ratio of pathological humerus and femur fractures is 1:2.08. Our ratio of tumorous humerus and femur fractures is with 1:2.28 in line. They found 721 femur fractures, 76.60% of which were in the proximal part, 19.14% in the diaphysis and 4.16% in the distal femur. The distribution of the 137 tumorous femur fractures of this study was 72.26% proximal fractures, 16.06% diaphyseal and 11.68% distal.

The Situation is similar with humerus fractures. In the study of Wänman et al. there are 346 pathological humerus fractures, 23.70% of which are in the proximal part of the bone, 70.81 in the diaphysis and 5.49% in the distal area. Of the 60 tumorous humerus fractures in our study, half of them are localised in the proximal part, 43.33% in the diaphysis and 6.66% distally. Here the distribution differs with regard to proximal and diaphyseal distribution. The reason for this difference could be the high proportion of inconclusive results (n=17) in the category of tumorous diaphyseal humerus fractures. (81)

When trying to interpret the results of non- tumorous fractures, two large groups of aetiologies should be considered.

Firstly, major osteoporotic fractures (hip, spine, wrist, or proximal humerus), as defined in the FRAX-tool. (82) The fact that major osteoporotic fractures increase with age was already illustrated in the previous chapter by the results of Rupp et al. This study showed a massive increase in in femoral neck fractures and proximal humerus fractures with increasing age. (79) This could be one of the reasons for the relatively high number of non-tumorous proximal fractures of the humerus (n=8) and femur (n=53). As we did not set the age in relation to the anatomical and histological distribution of the fractures, we are not able to go into more detail concerning this approach.

Secondly, AFF and AHF. As the case definition of the ASBMR already suggests, the AFF are to be expected subtrochanteric or in the shaft of the femur. (69) In this study, it is assumed that AHF are as well to be expected in the area of the shaft. Based on this, seven humeral and six femoral diaphyseal non-tumorous fractures were identified in our cohort. Atypical fractures can therefore be expected within these delineated groups. However, definitive proof can only be provided by examining the radiological features of these fractures. Anyway, how credible would an incidence rate of 1.66% for AFF and 1.93% for AHF in our case be? Considering the following study results in AFF in cancer patients, the proportion of AFF and AHF of our study is credible.

Lockwood et al. summarised the epidemiological statistics of AFF from BP in cancer patients in a review article. (83) Among others, they cited papers from following research groups:

Puhaindran et al. identified four (three with breast cancer, one with multiple myeloma) AFF out of 327 patients with skeletal malignant involvement with at least 24 doses of intravenous bisphosphonates. The calculated incidence in that retrospective study would be 1.2%. (84)

Edwards et al. found 23 AFF in a study population consisting of 10587 patients treated with BP against SRE. The estimated incidence of AFF in patients treated with BP was 0.05 per 100000 patient-years or differently calculated in percent: 0.22%. (85)

Yang et al. conducted a retrospective study of 253 patients treated with denosumab to prevent SRE. They concluded an incidence of 0.4% (95% CI: 0.1-2.2%) of AFF (1/253) in their study population. (86)

In 2020 Kaku et al. published a paper about the incidence of AFF in the treatment of bone metastasis. In their retrospective study they found 721 patients with bone metastases in their consultation system between 2011 and 2019. 529 of them were treated with BMA and five patients (four with breast cancer, one with prostate cancer) suffered eight AFF. The incidence of AFF was 0.9% and limited to breast cancer patients it was 6.6%. (87)

In 2023, another paper by Kaku et al. was published in which they investigated the prevalence of precursory signs of AFF in patients receiving BMA for bone metastases. In total they analysed 257 patients receiving either zoledronate for more than three years or denosumab for more than one year. They found 18 patients with a minimal or diffuse local thickening at the femur and 10 with an apparent local thickening; all of them were subclinical and without fractures. (88)

The data on AHF is notably limited. For example Odvina et al. describe 13 patients with unusual midshaft fractures of the long bones. Ten of these patients were treated with alendronate and three with risedronate. In addition to twelve unusual femoral shaft fractures, one humeral shaft fracture was described. Special attention was not paid to the treatment indication of bone metastases in this study. (89)

Another study by Yavropoulou, also not focusing on cancer patients with potential bone metastases, tried to analyse the connection of low energy fractures of the humeral shaft and the possible connection with the use of BP. They found 198 patients with low-energy trauma to the humerus, 20 of them had shaft fractures, of which only 4 were treated with

BP. Four of 20 humeral shaft fractures had atypical radiographic findings, but none of them have been prescribed BP. (68)

There are limited possibilities to compare our results with the results presented here, as they were designed differently. The main difference is the classification of AFF, which is based on radiological criteria. In our case, the study population was, sort of, preselected with the regard to fracture localisation and histology of the fracture gap, allowing us to narrow down a small group of patients who were likely to have atypical fractures.

4.2.3 Time period from initial diagnosis of the primary tumour to the fracture

First, the mean time span from diagnosis of the primary tumour until the fracture was compared between men and women. This showed that women are fracture-free for around 14 months longer than men. If one looks for the reason for the delay in the tumour entity, one could argue that women with breast cancer develop SRE (especially pathological fractures) later than men with prostate cancer. In 2009 Vestergaard et al. published a paper on the risk of fractures in patients with different types of cancer. It became apparent that women with breast cancer suffer a fracture after about 8.7 years. Men with prostate cancer, on the other hand, after about 4.7 years. (90) Compared with our results for breast cancer (7.4 years to fracture) and urological neoplasms (4.95 years to fracture), the results are quite similar. Though, Vestergaard does not refer purely to humerus and femur fractures, but to fractures in general.

A study by Svendsen et al. shows different results. They analysed the hospital stays of women in Denmark who were diagnosed with breast cancer and had SRE. The mean duration from cancer diagnosis to the occurrence of SRE was found to be approximately 13.1 months. Among 569 women examined, however, there were only about 38 pathological fractures. The remaining women suffered from different SRE. (91)

In the next step, the times to fracture were compared in the groups of tumorous and non-tumorous fractures. Patients with proven malignancy in the fracture gap suffered the fracture approximately 11 months earlier. The group of patients in which no tumorous tissue could be detected in the fracture gap and for which time data was available, consisted of 64 Patients. One could conclude that a pathologic fracture may have been prevented in these 64 patients and an atypical fracture may have occurred in these patients

due to an adverse effect of BMA. Nevertheless, this seems rather unrealistic, given the expected incidence of atypical fractures already discussed previously.

Comparing the time until fracture in relation to the BMA-administration, the results show an approximately 22 months longer period of fracture free time for patients administered with BMA (65.19 vs. 43.12). Unfortunately, it must be taken into account that BMA therapy could only be proven for 70 patients and time data could only be collected for 52 of these patients. This makes the results less reliable. In comparison, the early studies, summarised in a review article from Brown et al. (92), that tested the efficacy of BP compared to placebo show the following results: For example, Hortobagyi et al. demonstrated that SRE occurred approximately six months later in breast cancer patients treated with pamidronate than in the placebo group (7 vs. 13.1 months). (93) Theriault et al. reported similar results, in which the first SRE occurred approximately 3.5 months later (6.9 vs. 10.4 months). (94)

One of the few placebo-controlled studies of the efficacy of denosumab in breast cancer patients also shows a delay in the onset of SRE. Around 5% of the denosumab group suffered a fracture 36 months after randomisation, whereas 5% of the placebo group suffered a fracture around 18 months after randomisation. (95)

4.3 Administration of BMA

As already briefly mentioned before, administration of any BMA could be proven in 19.34% (n=70) of the included study participants. The most commonly used BMA was denosumab (n=32), followed by zoledronate (n=17) and ibandronate (n=4) In 17 cases the exact type of BMA could not be determined. Compared to other study populations, there is an enormous undertreatment with BMA in our study population analysed.

For example, the rate of Dutch castration-resistant prostate cancer patients treated with BMA between 2010 and 2015 is 60.22% of 1923 participants. In that study, zoledronate (n=626) and denosumab (n=276), were the most commonly used BMA. (96)

Compared to a paper by Hechmati et al., the undertreatment is clearly evident as well. The participants from France, Germany and the UK, of the survey included to the study, suffered from the following primary tumour types, in descending order: breast, lung, prostate, kidney, thyroid and melanoma. 68.4% of the 150 French, 75.8% of the 166 German and 70.9% of the 159 UK participants were treated with bone metastasis-delaying agents. (97)

In a German study, 89% of 1094 breast cancer patients with bone metastases received BMA therapy. 37% of patients received zoledronate and 36% received denosumab during the observation period of 2014-2015. (98)

Given the different rates of tumour patients treated with BMA, the question arises as to which tumour patients should be treated with BMA.

After extensive education of patients, the authors of the *"Bone health in cancer: ESMO Clinical Practice Guidelines"* recommend starting BMA therapy as soon as bone metastases have been diagnosed. Although the results of many animal model systems and clinical trials are promising, the authors recommend the use of adjuvant BMA-therapy for the prevention of bone metastases only for postmenopausal women or premenopausal women treated with GnRH-analogues with early breast cancer. Treatment for prevention of bone metastases of other women or women and men with other solid tumours is not recommended, as is treatment with denosumab. (30)

4.4 Radiotherapy, chemotherapy, immunotherapy, hormone therapy

Not quite half of the participating patients (42.54%) were found to be undergoing chemo-, immune-, or hormone therapy. Of these, it could not be determined in over half of the cases, at which time they had undergone this therapy. The lack of data makes it difficult to categorise and interpret the results. In order to contextualise the results of this study, however, it is worth taking another look at the studies by Hechmati et al. and Kuppen et al.

In the study by Hechmati et al. described above, 73.0% of the French participants, 68.5% of the German and 53.5% of the English participants were undergoing chemotherapy at the time of the survey. (97) In Kuppen et al. 63% of the 3616 patients with metastatic castration-resistant prostate cancer receives life-prolonging drugs (docetaxel, cabazitaxel, abiraterone acetate, enzalutamide, radium-223). (96)

With regard to radiotherapy, a certain degree of underuse can be noticed as well in this study cohort. A review article from 2012 states that around 50% of all cancer patients undergo radiotherapy during their illness. (39)

As in the chapter on BMA administration, the patients in our study were clearly undertreated concerning the primary tumour and bone metastases. This apparent underuse of life prolonging therapies certainly does not reflect the real circumstances of patients care at the trauma centre analysed. Rather, these figures are indicative of incomplete data collection. Considering the lack of central medication or patients registers, the data collection was carried out in the best possible quality by searching patients documents for relevant medications or diagnoses.

4.5 Comorbidities and comedication

In the last point of this thesis, an attempt was made to identify possible bone-influencing comorbidities and comedications in this study cohort. The negative influence of these factors on bone health and a possible associated higher risk of fracture was already discussed in the introduction. Exact figures on whether and how the listed comedications and comorbidities affect the risk of pathological or atypical fractures in cancer patients require further research.

However, Rasmussen et al. published a paper in which they compared the risk of subtrochanteric femur fractures femoral shaft fractures in diabetic patients with healthy controls. They also determined the HR for patients with BP therapy, alcohol abuse, osteoporosis and systemic or oral glucocorticoids. The HR for subtrochanteric fracture or femoral shaft fracture in type 1 diabetes was 2.07, for BP use 1.72, for alcohol abuse 4.0 and for osteoporosis 1.3. The HR for patients with glucocorticoid therapy was not significant at 1.05, nor was that for type 2 diabetes patients at 0.99. (99)

A recent Danish case-cohort study, with blinded radiological examinations analysed various risk factors for the development of AFF. Diabetes and COPD were not associated with increased risk of AFF. Contrary to the previous study, they found an association of increased AFF with the use of proton pump inhibitors and systematic oral glucocorticoids. (100)

The example of these two studies with different results demonstrates the necessity of large-scale studies, to identify possible risk factors associated with AFF or AHF in cancer patients treated with BMA.

Limitations

Self-reflection on own scientific work and reference to any limitations of a study is essential in order to be able to interpret the results and discussions in an appropriate manner.

Firstly, any methodological limitations must be pointed out. The patient population in this study is difficult to characterise and describe in many respects. The diversity of the various cancer diagnoses alone, with the different histological subcategories, represents a major inhomogeneity. Added to this are the different treatment regimens of radio-, hormone-, immune- and chemotherapy, all of which have different effects on the human organism. This makes it difficult to contextualise the results of this study in everyday clinical practice and the care of individual cancer patients. Large-scale, multicentre studies, in which fractures of individual tumour entities are investigated, would certainly provide more profound information about characteristics of tumour patients who have suffered a fracture. An attempt was made to homogenise the population by concentrating on only one tumour entity or fracture locations when collecting data, even though several different tumour diagnoses and fractures have occurred during the patient's history. This arbitrary simplification naturally limits the validity of the results to a certain extent.

Histological evidence in the fracture gap is certainly a good method for determining the proportion of non-tumorous fractures. This may reduce the number of fractures in which atypical fractures are to be expected. However, precise proof of this can only be obtained if the radiological findings of the fractures are analysed.

The process of data collection is certainly very limiting. Unfortunately, a national patient register with diagnoses and medications had not been available at that time. Instead, we had to rely on the hospital’s internal digital archives. In this context, one is heavily dependent on the accuracy of the patient records. In many cases, such as the collection of histological findings in the fracture gap, the BMA administration or the data relating to radiotherapy and life-prolonging therapies, we had to face a relatively high amount of missing data.

Another point worth keeping in mind, is that the age of our study population was calculated at the time of the fracture. This means that the mean age in this population is likely to be higher than in the studies mentioned before.

Conclusion

It is feared that the incidence of SRE due to bone metastases or multiple myeloma will increase in the future due to increased life expectancy of tumour patients. The administration of BP and denosumab is currently recommended as treatment of SRE, the use of which is associated with an increased incidence of AFF. In addition to a long duration of use of BP and denosumab, the higher dosage in tumour patients is also feared to be a risk factor for AFF. The data situation regarding AHF in this context is unsatisfactorily low.

The aim of this study was to determine the proportion of non-tumorous fractures of the humerus and femur in an inhomogeneous group of tumour patients and thus estimate the possible proportion of AFF and AHF.

Of the 362 patients no evidence of tumorous tissue in the fracture gap could be found in 22.09% of cases (n=80). In 21.55% (n=78) of cases the histological results were inconclusive. A prescription of BMA could be proven in 19.34% (n=70) of cases, with denosumab being prescribed most frequently (n=32). To approximate a rough estimation of AFF and AHF, the non-tumorous diaphyseal fractures of the humerus and femur were determined. There were six femur and seven humerus fractures of this type.

Nevertheless, the results of this study should be viewed with limitations, due to missing data. The estimate of AFF and AHF, in this connection, should only serve as a possible preselection for the definitive future radiological confirmation of AFF and AHF. However, validation of such a preselection should be carried out in future studies.

As conclusion, this thesis could serve as a basis for future large-scale studies. These could be used to create personalised risk profiles for tumour patients, in order to prevent fractures, regardless of entity, which would reduce the burden on our health care system, health care professionals and, most importantly, enormously increase patients' quality of life.

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