Overview and comparison of the outcome of different treatments modalities of bone cysts and fibrous dysplasia of the proximal femur in children and adolescents, a multicentre experience

Local Research protocol Bone cysts

EPOS + ISOLS

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1. Introduction and rationale

Unicameral bone cysts (UBC), also called simple bone cysts, Aneurysmal bone cysts (ABC) (and Fibrous Dysplasia (FD) lesions) can present as benign fluid filled cavities that can enlarge over time, leading to thinning and with that weakening of the bone. Both bone cysts and FD predominantly occur in children and adolescents, with a peak age between 3 and 14 years [1-3]. The annual prevalence and incidence are both estimated at ±0.3 per 100.000 people for UBC [4, 5]. For ABC, the annual prevalence is estimated at ±0.3, with an annual incidence ranging from 0.14 to 0.54 per 100.000 people [1, 4-6]. However, the true prevalence and incidence is difficult to estimate due to clinically silent cases and spontaneous regression. For the same reason the incidence and prevalence of FD is unknown and no estimation is given in literature.

Unicameral bone cysts represent about 3% of all benign bone tumours [2, 7]. These cysts are unicameral or partially separated lesions and usually solitary. UBCs are more commonly seen in males (2:1) [1, 2, 5]. The exact aetiology remains elusive, although many theories have been proposed such as blockage of the drainage system of interstitial fluid and venous obstruction within the bone [2]. UBC mainly involves the long bones; the proximal femur, together with the proximal humerus, account for more than 80% of the cases. UBCs are rare in adults, and therefore believed to spontaneously resolve with skeletal maturity [1, 2]. UBC on its own is often without clinical impact, the most common context of revelation is by (pathological) fractures, pain due to fissuring of the cyst lining or sometimes serendipitously on plain X-ray taken for other reasons. A UBC may be complicated by a secondary aneurysmal cyst.

Aneurysmal bone cysts represent about 1-6% of all bone tumours [5, 8, 9]. These cysts are expansive, osteolytic, haemorrhagic lesions, often multi-cameral. They are usually solitary lesions. The exact gender distribution is unknown, as the current literature is divided; some state it is more

common in males (1.8:1) [4-6], whereas others state there is a slight predominance in females [1, 3, 7]. A primary ABC arises without evidence of another underlying lesion. Cytogenic analysis has revealed a characteristic genetic translocation of the USP6 oncogene in primary ABCs, leading to upregulation of USP6 transcription [10]. An estimated thirty percent of ABCs are secondary to an underlying lesion, such as chondroblastoma, giant cell tumour, osteosarcoma, fibrous dysplasia or non-ossifying fibroma [1, 3, 6]. These secondary ABCs lack the aforementioned cytogenetic aberration [1, 10]. In case of a secondary aneurysmal cyst, a predominate aspect of the ABC might mask the causal lesion, which has to explored for. ABC can occur in any part of the skeleton, but especially in the long bones (femur, tibia, humerus and fibula), spine or pelvis [1, 11]. Whereas the UBC is often without clinical impact of its own, the ABC is often revealed by pain or swelling and sometimes, but more rarely, by fracture. Although uncommon, ABCs may sometimes also resolve spontaneously [1, 9], however, often treatment is needed to prevent complications like fracture or decrease in quality of life.

Bone cysts usually develop in the metaphysis of the long bones, and may cross the growth plate extending into to epiphysis. The cyst crossing the growth plate may induce growth disorder and with that limb length discrepancy or axial deviation, either spontaneously or as a complication of treatment. This is more often seen in ABC than in UBC [1, 3]. As unicameral and aneurysmal bone cysts affect similar populations, occur at similar locations and might show similar clinical and radiological aspects, differentiation can be difficult but is necessary for adequate treatment and follow-up. Biopsy of the lesion may help differentiating between UBC and ABC and can either reveal or rule out an underlying disease in case of secondary ABC. Next to the comparison clinical and radiologic findings, the aspect of the aspiration fluid can help differentiate, although this is non-specific [1].

Fibrous dysplasia (FD) represent about 5% of all benign bone tumours. It is a genetic, non-inheritable, rare bone disorder that was first described in the late nineteen thirties [12]. The disorder is due to a post-zygotic activating mutation of the GNAS-gene, which decreases GTPase activity of the stimulatory G-protein (Gsα) [13, 14]. This results in increased intracellular levels of cAMP in bone forming cells, leading to local replacement of lamellar bone with ill-woven, under mineralized (fibrous) tissue of poor quality in affected parts of the skeleton, associated with clinical manifestations of pain, deformity and pathological fractures. The clinical spectrum of fibrous dysplasia varies widely, including single bony lesions (mono-ostotic fibrous dysplasia) and multiple skeletal lesions (poly-ostotic fibrous dysplasia). The bony lesions are predominantly localized in the proximal femur and craniofacial bones [15]. Often these lesions contain cystic parts and are in the differential diagnosis of Bone cysts. The surgical management of fibrous dysplasia of the proximal

femur has been particularly challenging due to the high load of mechanical forces acting at this skeletal site [16]. A number of surgical options have been originally proposed, including different types of bone grafting, various osteosyntheses, with or without additional osteotomies or a combination of these modalities.

Although healing spontaneously, after fracture or after biopsy (in case of ABC) has been described for both types of bone cysts [1, 17-20], treatment is often necessary to prevent progression of disease, (re-)fracture and long-term impairments in quality of life.

When determining a treatment plan for a specific patient, the surgeon has to take the morbidity of disease and treatment, the average number of treatments and the success and complications rates of the treatment methods into consideration. The goals of treatment is to decrease the risk of fracture, restore functional activity to pre-existent level, enhance cyst healing and resolve symptoms like pain. Currently, treatment modalities include injection with steroids, bone marrow, demineralized bone matrix or bone substitutes, cementation, sclerotherapy, cryotherapy, argon beam coagulation, curettage with or without bone grafting and/or adjuvant high speed burring, (continuous) decompression, osteosynthesis, resection, or a combination of treatments. All of which have a great variety of success rates in the currently available literature [2, 3, 6]. Despite the numerous treatment methods, there is no consensus among orthopaedic specialist on the best treatment for both UBC and ABC.

For this reason, the aim of this research is to evaluate the outcome of treatment of bone cysts in the proximal femur at the LUMC and other collaboration centers from EMSOS and EPOS community. Special focus will be on the duration of partial weight bearing and functional restrictions, radiographic healing of the bone cyst after treatment and complications of the treatment, like (re-)fracture, infection and recurrence. This international, retrospective, multi-centre trial, with the aim to give an overview and comparison of all the different treatment modalities used in treating unicameral and aneurysmal bone cysts in children.

2. Objective

Overview and comparison of (clinical)outcome of different treatment modalities of bone cysts of the proximal femur in children and adolescents.

Primary study outcome:

- Number of (re-)Fractures

Secondary study outcome:

- Time to (partial) weight bearing from diagnosis (divided into 5 subgroups: cast immobilization, no-15% weight baring, partial weight bearing with crutches, full weight bearing, return to sports)
- Number of treatments

Tertiary study outcome:

- Treatment success / Bone cyst resolution (healing of cyst on x-ray). In case of UBC and ABC, healing is described according to modified Neer classification [21]:
    - Grade I Clearly visible cyst
    - Grade II Visible but (multi-)locular and opaque / translucent / radiolucent
    - Grade III Sclerosis around or within the partially visible cyst
    - Grade IV Complete healing with obliteration of the cyst
        - Cyst healing grade III and IV are considered satisfactory healed cysts
- Monitoring complication rates (infection, recurrence of cyst, growth of cyst)
- In case of FD cortical thickening and size of the cyst will be measured as a proxy of response.

3. Design

A retrospective multicentre international observational cohort study design will be used.

4. Materials and methods

EPOS and EMSOS members and other possible collaborators will receive a maximum of 3 emails, with an interval of 1-2 weeks, regarding information about this study and inviting centres/investigators to participate.

Each collaborating centre will be assigned a number, this is done coordinate study case-numbers and prevent double study case-numbers in the final database. The study case-numbers will consist of 'BC', followed by the assigned number of the centre, followed by the number of the amount of cases. For example: LUMC is assigned number 1. The first inclusion of the LUMC will be named BC + 1 + 01 ('BC101'), case 25 of the LUMC will be named 'BC125'. A collaborating centre is assigned number 3, so their 15th inclusion will be numbered 'BC315'.

Data from 2002 till 2017 will be collected. All <u>consecutive</u> cases meeting the inclusion criteria are to be included, with a minimum of 20 consecutive complete cases per collaborating centre.

Inclusion criteria:

- Patients age ≤ 16 years
- Bone cysts: simple (unicameral) and aneurysmal and mono-ostotic Fibrous dysplasia.
- Location: proximal femur; meta-diaphysial or inter-trochantaric area.
- Treatments: wait-and-see, different types of injection (depomedrol, etoxysclerol, steroids, Ethibloc, platelets of bone marrow), Cement injections (HA cement, bone cement PMMA), insertion of cannulated screw, osteosynthesis (paediatric hip plate, dynamic hip screw, intramedullary nail, titanium elastic nail, cortical allograft, other).
- Inclusion after Central review of X-ray/MRI image to discriminate SBC, ABC from FD.
    - ABC diagnosis should be made on MRI
    - Solitary FD diagnosis on histology or X-ray

Exclusion criteria:

- Involvement distal to the isthmus of the femur
- Polyostotic Fibrous Dysplasia / McCune Albright syndrome
- Comorbidities also increasing the risk of fracture, for example, Rickets, Osteogenesis Imperfecta or Olliers' disease.
- Insufficient Follow-up due to lost-to-follow-up or historical data.

5. Collection of data

Data will be collected in an Excel or SPSS database by each collaborating centre individually. Once sufficient data is gathered, it will be send to the LUMC main investigator via secure email, via secure attachment (passcode encrypted) or via secure data sharing like share file. All data of collaborating centres will be stored only in a private map on the secured hard drive of the LUMC. The map is only accessible by the local researcher and supervisor (M.A.J. van de Sande). The data will be pseudo-anonymised and coded, so no patient specific data like name or date of birth will be used in the database. Coding will be done by assigning a research-number to each patient. This key file will be stored separately from the database on the same secured hard drive of the LUMC. Patient will be pseudo-anonymised. Data will not be shared with all collaborators as this is not allowed in GCP/GCR, though contributing centres will remain ownership of their own data.

Parameters included in database (see appendix A):

Gender, age at diagnosis, size of lesion, minimal cortical thickness, cortical thickness (at calcar), involvement of growth plate/apophysis of trochanter, involvement of calcar, diaphyseal extension,

primary/recurrent lesion, fracture yes/no, treatment (as stated in inclusion criteria), number of treatments/surgeries/general anesthetic, (time of) cast immobilization, time of (partial) weight bearing, complications; infection, (re-)fracture, recurrence, growth of cyst.

6. Bias and confounding

Loss to follow-up bias; high loss to follow-up is not expected as this research is conducted children with primarily a non-life threatening disease. Monitoring loss to follow-up, rule-of-thumb:
<5% loss leads to little bias.
Some confounding is to be expected in this study design, as specific treatments differ not only per centre but also per surgeon and even per patient. Therefore only the outcome of specific treatments can be described but not compared to causative detail. Indication bias will be addressed by weighted or multivariable cox regression analyses, or propensity scoring.

7. Analysis of data

A database of each included centre is to be created in Excel or SPSS. To investigate the effect of risk factors associated with fracture or treatment failure, we did univariate and multivariable analyses on pre-specified risk factors: Gender, age at diagnosis, size of lesion, minimal cortical thickness, cortical thickness (at calcar), involvement of growth plate/apophysis of trochanter, involvement of calcar, diaphyseal extension, primary/recurrent lesion, fracture yes/no. Using a Kaplan-Meier method for interval censored data, we calculated all time-to-event endpoints. We will estimated the effect of risk factors with a multivariable Cox regression model on the subset of data with complete covariate information. We reported the results as hazard ratios (HR) and 95% CIs.

8. Ethics

No ethical dilemmas arise in this study design. Since this is a retrospective design, no direct patient contact is necessary during this research and no interventions or behavioural codes will be applied. No patient-specific data will be shared among the different centres. Additional WMO approval is not necessary. A waiver will be generated at the LUMC ethical committee.

9. Time schedule

Starting phase in April 2019:

- April-may 2019: literature search, writing and submitting research protocol to Ethical committee EPOS and EMOS, create basis and outline for database in SPSS and Excel.

- May: Building database
- Centre collaboration from EMSOS and EPOS
- Deadline to close the study is six months after opening the study.
    - Aim: July – Dec 2019 Data collection.
- Generate papers discussing results for UBC, ABC and FD
- Paper ready before EPOS and EMSOS 2020 deadline.

10. Literature

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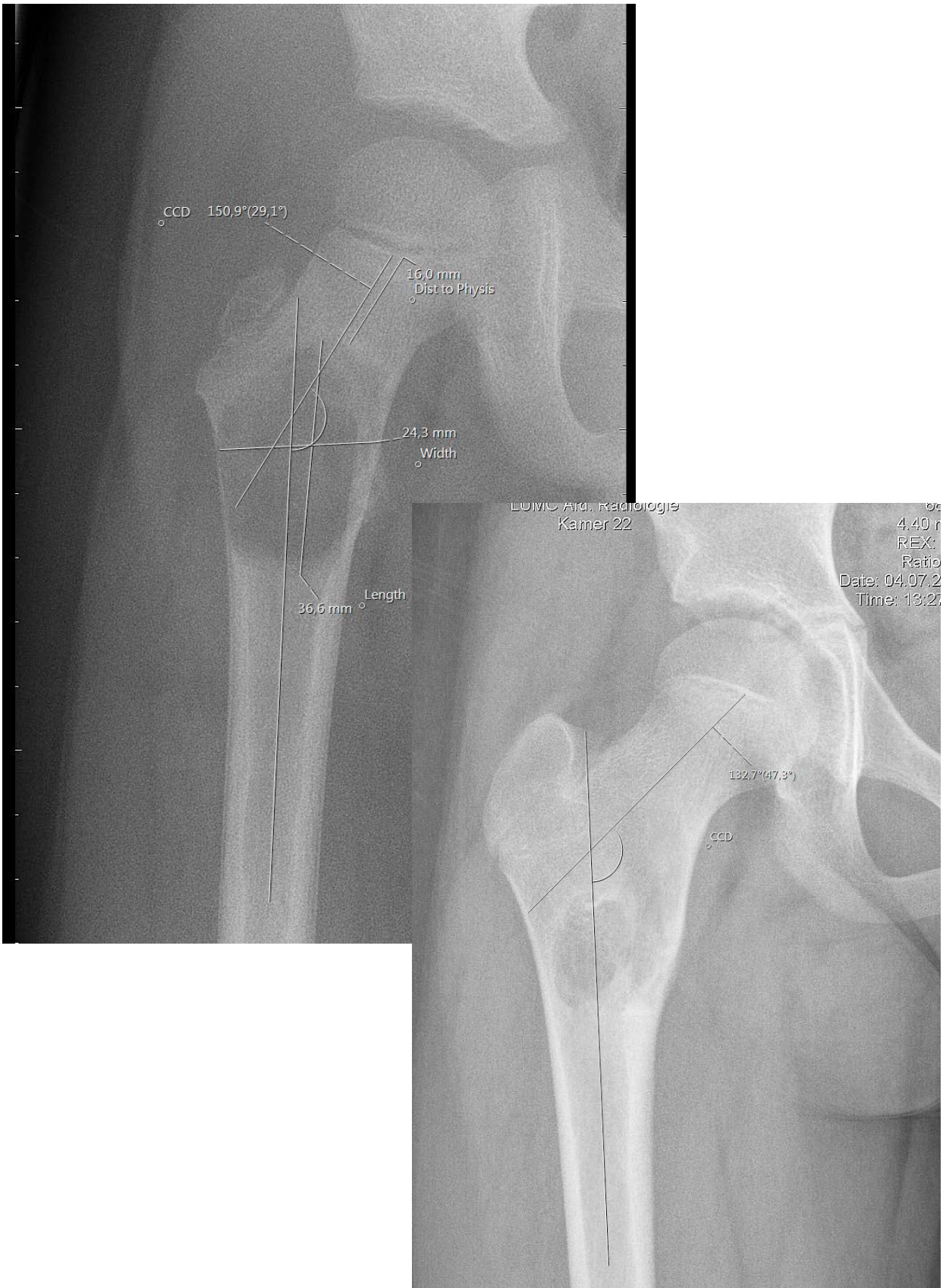
Appendix A

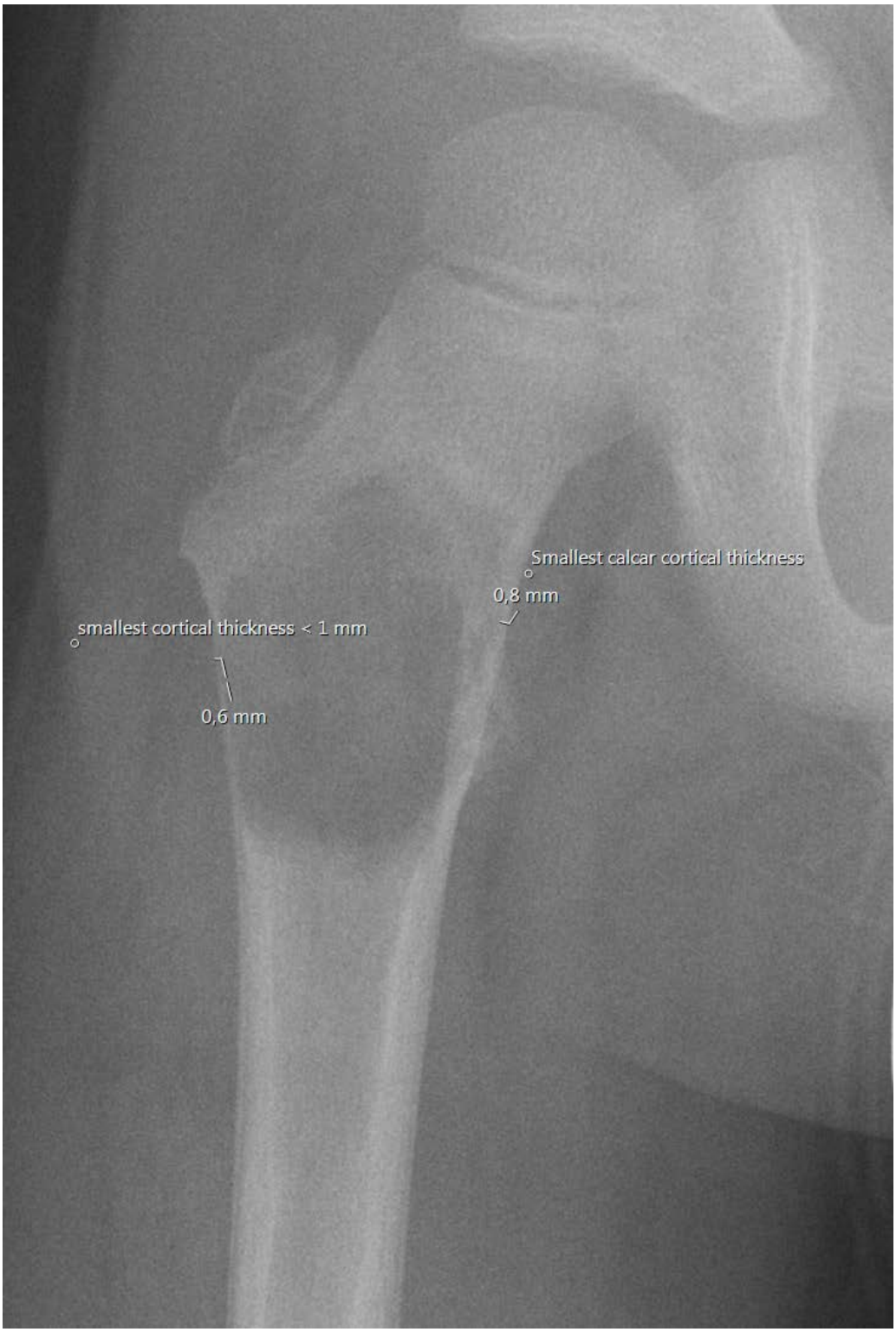
Measuring CCD angle:

- Longitudinal angle of the neck is obtained by joining two midpoints of the diameter of the caput and collum of the femur
- Longitudinal angle of the shaft is obtained by joining a point at the trochanteric fossa and a midpoint of the diameter of the of the lowest part of the shaft on AP plain film radiograph



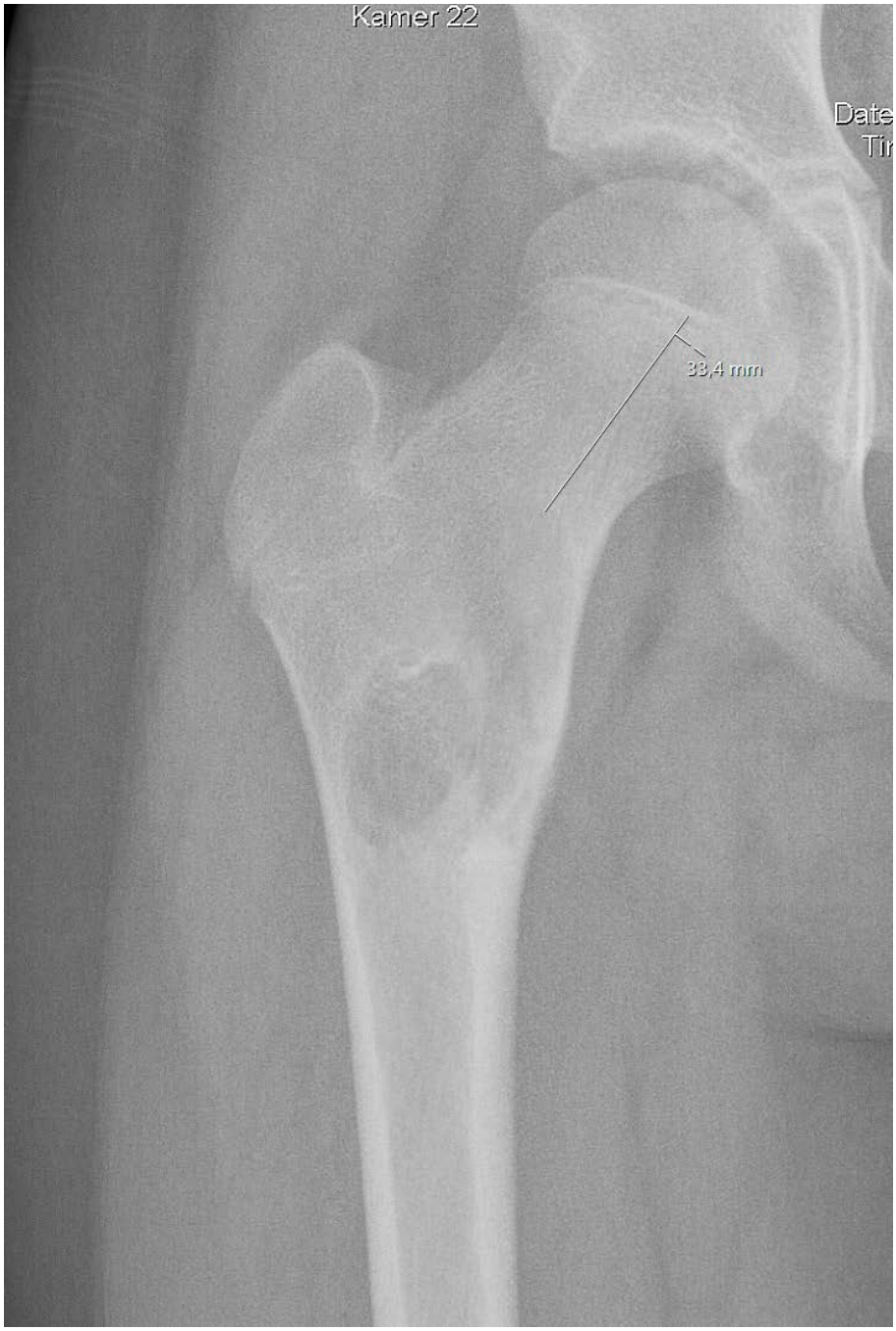
Smallest cortical thickness and smallest cortical thickness at calcar:

- Smallast cortical thickness measured on the AP/PA or lateral plain film.
- Smallest cortical thickness measured on the AP/PA plain film at side of the calcar
- If the cortical thickness at the calcar is also the smallast cortical thickness of the cyst, the two above mentioned measurements are equal



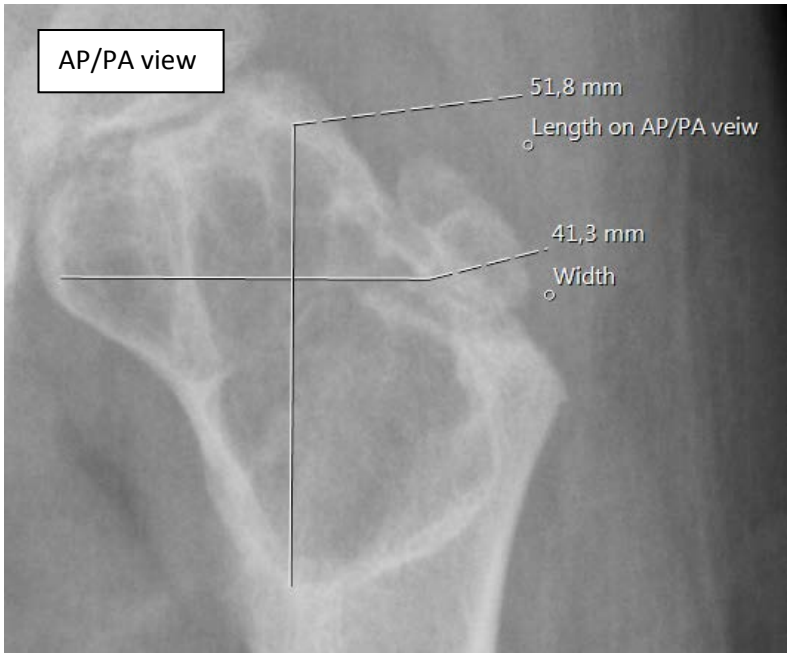
Distance to physis:

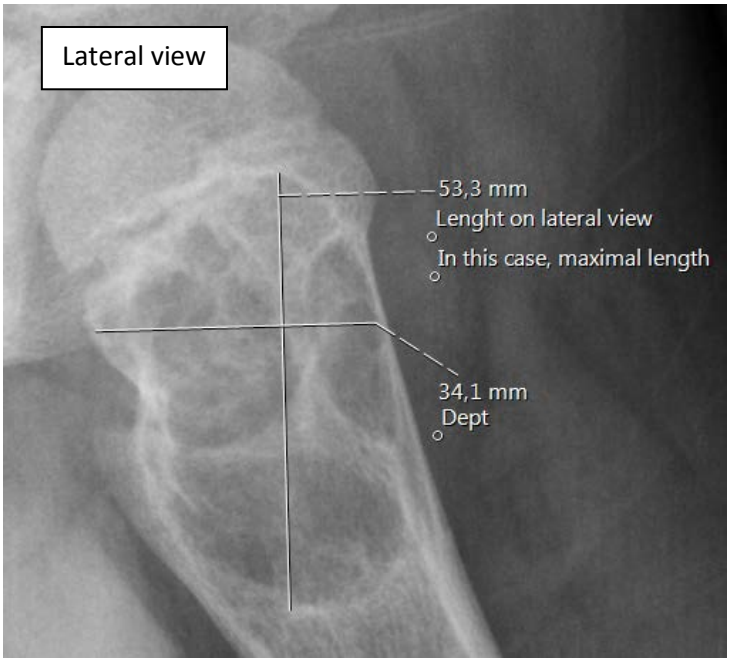
- Measured from the most proximal ending of the cyst to the physis, on AP/PA plain film



Measuring size of cyst:

- Length: maximal length measured from the most proximal to the most distal side of the cyst in a vertical line (not diagonal). Measured on both AP/PA and lateral view, largest measurement is used in database.
- Width: maximal width measured from the most lateral points of the cyst in a horizontal line (not diagonal), measured on AP/PA plain film
- Dept: maximal dept measured from the most lateral points of the cyst in a horizontal line (not diagonal), measured on lateral view of plain film





In the example above, the maximum length of the cyst used for the database is the length measured in the lateral view.