Minimally invasive CT-guided excision of benign bone tumours

by

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PART C: ADDENDA

Declaration

I, Timothy Richard Sluis Cremer, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I authorise the University to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever. I further declare the following:

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This work was inspired by Dr. Hosking whose knowledge and passion on the subject led to the development of the treatment protocol described in this paper that is now used in the Princes Alice Orthopaedic Unit and Life Vincent Pallotti Orthopeadic Hospital.

List of Tables and Figures

Abbreviations

ABC - Aneurysmal Bone Cyst

AP - Antero-posterior

CT - Computed tomography

DBM - Demineralised bone matrix

K-wire - Kirschner wire

MRgFUS - Magnetic resonance-guided focused ultrasound

MRI - magnetic resonance imaging

NSAID's - Non-steroidal anti-inflammatory drugs

OO - Osteoid osteoma

OB - Osteoblastoma

PET - Positron Emission Tomography

PMMA - Polymethylmethacrolate

PET/CT - Positron Emission Tomography/Computed Tomography

PRP - Platelet rich plasma

RF - Radiofrequency

SPECT - Single-photon Emission Computed Tomography

US - Ultra sound

XR - X-ray

Abstract

Background: The management of osteoid osteoma (OO) and other small primary benign lesions of bone has evolved over the past 50 years from open surgery with wide resection margins to less invasive surgical techniques such as image guided intralesional excision and percutaneous radiofrequency ablation. We aim to evaluate the outcomes of patients treated with computerised tomography (CT guided) intra-lesional excision and bone grafting of small benign lesions of bone. We surmise that this is the optimal method of treatment for these lesions as it provides high success rates and a histological diagnosis.

Method: A retrospective folder review of patients treated between March 2012 and May 2016 was performed. Patient demographics, details of presentation, clinical information and outcome following treatment were analysed. Pre-operative diagnosis based on radiological examination was compared with histological diagnosis.

Result: Eleven patients met the inclusion criteria, 5 male and 6 female, with a median age of 16 years (range 5-33). Pain was the most common presenting feature. A histological diagnosis of OO was confirmed in 5 of the 9 patients with a suspected diagnosis of OO preoperatively. Of the 4 patients whose diagnosis changed after the procedure the diagnoses included a benign spindle cell lesion (1), a benign fibrous histiocytoma (1), subacute osteitis and an osteochondral defect with geode cyst formation (1). Of the 2 patients where OO was not suspected preoperatively, chondroblastoma was confirmed in one while a benign spindle cell lesion was reported in the other. Overall histological yield was thus 100%. There were no complications or repeat procedures at a median follow up of 42 months (range 30-52 months).

Conclusion: CT guided intralesional curettage is a safe procedure that has the advantages of providing a histological diagnosis and definitive treatment through a minimally invasive approach. This is especially useful in less accessible regions of the skeleton as it provides a way of swiftly and accurately locating the lesion with minimal risk of complications and morbidity to the patient.

Key words:

CT guidance, osteoid osteoma, percutaneous treatment, benign bone tumours, intralesional curettage, radiofrequency ablation.

Level of evidence:

IV – Case Series

Part A: LITERATURE REVIEW

A: Literature Review

This chapter was structured according to the following points:

a. Objectives

b. Methods

c. Background to research question

d. Introduction

e. Clinical presentation, diagnosis and natural history

f. Summary of the literature & available treatment options

1. Medical Management

2. Surgical Management

3. Novel treatment strategies

g. Cost implications: An area for further research

i. References

a. Objectives

The objectives of this literature review are to:

- Clarify the definition, classification, epidemiology, etiology, pathology, differential diagnosis, clinical and radiographic features and natural history of Osteoid Osteoma as well as other small benign lesions of bone.
- To research treatment options, both medical and surgical, and critically analyse the literature regarding outcomes and complications of these described methods.
- To identify and discuss novel treatment approaches to these lesions
- To identify areas of potential future research

b. Methods

Google Scholar and Pubmed Internet search engines were used to search online databases. The key strings 'osteoid osteoma', 'benign bone tumour treatment', 'CT-guided percutaneous treatment bone tumour' were used to search for articles. All articles not relevant to percutaneous treatment of benign bone tumours and osteoid osteoma were excluded. Articles not originally written in English were excluded if an English translation was not available. A total of 107 articles were selected.

The reference text Differential Diagnosis of Orthopedic Oncology, 2nd Edition by Greenspan et al. was reviewed and the relevant references from chapter 2, Bone-Forming (Osteogenic) Lesions, were researched. An additional search was done for 'cost effective health care'.

Quality of evidence

The evidence on the topic is limited to case studies, case series and case control studies due to the rarity of this condition. No prospective randomized trials have been performed. All the studies are classified as levels III and IV evidence.

c. Background to research question

Benign lesions of bone, of which osteoid osteoma is considered one of the most important, are rare conditions and seldom encountered in general orthopaedic practice. The management of these lesions has evolved over the past 50 years from open surgery with wide resection margins to less invasive surgical techniques such as image guided intralesional excision and percutaneous radiofrequency ablation. Novel treatments are also being evaluated. The trend in the international literature has been towards expensive, technology dependant techniques, such as RFA and Laser Photocoagulation. We perform

percutaneous CT-guided intralesional curettage and bone grafting. We believe this to be more cost effective method than RFA and certainly more available while still being a safe, effective procedure. It also has the advantages of providing a histological diagnosis that RFA does not.

d. Introduction

Bergstrand, in 1930, first described 2 cases of a small painful bony lesion in adolescent patients. These were initially suspected to be malignant lesions and were excised en-bloc. However the histological findings were noted to be of a "bony new growth, neither a tumour nor inflammatory process".[1] It was Jaffe in 1935 that described a case series of five patients with small painful benign osteogenic lesions and defined the condition. He termed this lesion "Osteoid-osteoma" and described the following clinical features

1. All patients were adolescent, age range of 11-22years.
2. The principle complaint was local pain, severe enough to interfere with sleep.
3. Lesion is always subperiosteal and usually metaphyseal.
4. Radiographically the lesion is round, well circumscribed and confined to bone.
5. All lesions were small, none larger than 2cm in diameter.
6. No sign of infection was found at the site of the lesion.
7. Surgical resection resulted in immediate and dramatic resolution of pain.[2]

A follow up study in 1940 by Jaffe and Lichtenstein describe a further 33 patients with this condition and found that in half of these cases the lesions were intra-cortical.[3] They recommended en-block surgical excision of the lesion.

Osteoid osteoma (OO) is a small benign lesion of bone which has a central nidus circumscribed by an area of dense sclerotic bone. It is the most common primary lesion of bone in young patients, accounting for 3% of all bone tumours and 12% of primary benign bone tumours.[4]

Macroscopically the nidus has a discrete, round, central area of 5-15 mm that appears similar to cancellous bone and is richly vascularized. It is usually a solitary lesion but there can be a second nidus elsewhere in the body. Surrounding the nidus is an area of dense sclerotic bone. Microscopically the nidus is a discrete well-marginated area of mineralized

immature woven bone, termed osteoid. This osteoid is irregular and is on a background of a well-vascularized fibrous stroma. Adjacent to the vascular areas are regions rich in unmyelinated nerve fibres. Osteoclastic activity predominates at the periphery of the lesion and this gives rise to an area of lucency around the nidus. [5, 6] The expression of cyclo-oxygenase type 1 (COX1) and cyclo-oxygenase type 2 (COX2) results in the local production of prostaglandins, in particular prostaglandin E2 and prostacyclin.[5, 7] The presence of these inflammatory mediators and rich innervation is thought to account for the significant pain experienced by the patient and the marked relief noted with the use of NSAID's.

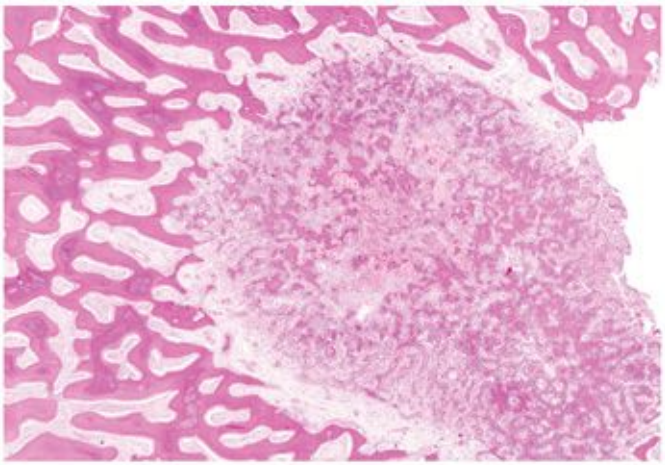

Figure 1: Low power magnification of a histological slide showing an osteoid osteoma. Note the central nidus of woven bone. Reproduced from (https://basicmedicalkey.com/bone-tumors-5/> accessed 10/11/2017)

Classified by Eidekin in 1966 by location into 3 groups:

1. Cortical OO is the most common presentation. The sclerotic margin is usually fusiform in shape and the nidus is located centrally within the lesion. The location of this type of OO is usually within the cortex of long bones such as the tibia and femur.
2. Cancellous or medullary OO has less sclerotic bone surrounding the nidus, which is not always centrally located. Located within the metaphyseal region of long bones, often around the hip and knee. Surgically these OO may be more difficult to address and have a higher recurrence rate.
3. Subperiosteal OO are the least common presentation. The classic radiological feature of a sclerotic margin surrounding a lucent nidus as seen with cortical OO is not always present, and there may be an associated soft tissue mass. These OO are

located within the small bones of the hands and feet particularly the neck of the talus and the medial neck of femur.[4]

e. Clinical Presentation, Diagnosis and Natural History

Localised pain is the most common primary presenting complaint and is classically described as being worse at night, severe enough to wake the patient from sleep, and is usually relieved by the use of non-steroidal anti-inflammatories (NSAID's). Alcohol ingestion may also precipitate the onset of pain.[8] Other clinical manifestations are dependent on the location of the lesion and age of the patient. Growth disturbance including altered mechanical alignment and leg length discrepancy may occur in skeletally immature patients. Peri-articular OO may result in a decreased range of motion in the affected joint, muscle wasting and gait abnormalities.[9] Localised swelling and tenderness in subcutaneous lesions may also be noted.[10] OO of the spine commonly results in painful, correctable muscle spasm that in turn results in lumbar scoliosis with a concave deformity on the same side as the lesion. [11] Thoracic spine lesions are significantly less common but can also result in painful scoliosis.[12, 13]

OO has been described in almost every bone of the body but is markedly more common in the long bones of the lower limbs with 53% occurring in the metaphyseal regions of the femur and tibia. The spine accounts for 10% of sites with the posterior elements of the lumbar spine being most commonly involved. Other common areas of involvement included the upper limb, ribs, scapula, pelvis, small bones of the hands and feet, pelvis and sacrum. Lesions can be located within the cortex or metaphysis. Peri-articular lesions may have intra-articular extension. A multifocal OO is a single lesion with more than one nidus (double or triple nidus) while a second discrete OO in a different site is termed a multicentric OO. Multifocal and multicentric lesions are extremely rare and are difficult to diagnose.[14] OO is more common in males, with a male-to-female ratio of 2-4:1.[4, 8] Although OO's can occur at any age, the most common age at presentation is in the second and third decade with 80% of patients being under 30 years at presentation. [4, 15]

Diagnosis and Imaging studies

The diagnosis is usually made on clinical grounds. The classic symptom of localized night pain relieved by NSAID's is present in up to 85% of patients but due to the rarity of the condition and wide differential for limb pain in an active young patient,

there is often a delay in reaching a diagnosis. The mean time from the onset of symptoms to surgical treatment being 16 months.[16, 17] Richardson describes a missed case of intra-articular OO in the hip of an 18 year old patient where the diagnostic delay was 2 ½ years due to inadequate imaging.[18] Imaging plays a major role in the diagnosis of OO. Plain x-rays are the initial modality of choice if OO is suspected. Axial scanning, including CT and MRI, are excellent adjunctive imaging methods that aid in the diagnosis if clinical examination and plain film x-rays are insufficient in making the diagnosis. The location of the lesion is important in this regard. The radiological features of a cortical OO are a lesion that is small (less than 15 mm) and has a radiolucent nidus circumscribed by an area of a densely sclerotic reactive bone. Metaphyseal OO do not exhibit the same degree of surrounding sclerosis while intra-capsular lesions are characterized by periarticular osteopenia and may even show signs of joint destruction. The nidus may be calcified or sclerotic.[19] The role of conventional tomography has largely been superseded by computerized tomography (CT) scan.

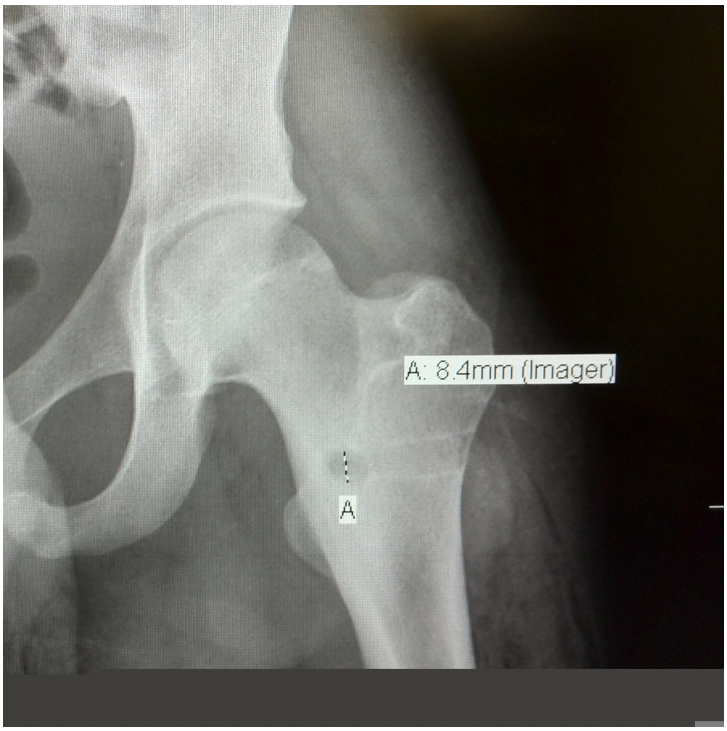

Figure 2: XR of an OO in left proximal femur. Note the lytic, central nidus and surrounding sclerosis.

The features of OO on CT are of lucent nidus surrounded by varying degrees of sclerosis. The nidus may show features of calcification. CT is often more useful than XR in making the diagnosis.[20-22]

The role of MRI in the diagnosis and treatment of OO has been the subject of much debate in the recent literature. The advantage of MRI over CT is decreased radiation exposure, particularly important in the paediatric patient. However, its diagnostic accuracy has been shown to be inferior.[23, 24] Conventional MRI tends to over estimate the aggressiveness of a lesion due to the surrounding bone oedema, which is a result of the localized inflammatory reaction. The nidus is also not clearly demonstrated as a circumscribed sclerotic lesion as seen on CT and XR.[25, 26] In one study by Hosalker and colleagues in 2005 MRI was successful in diagnosing an OO in only 19% of cases (7/36). A number of lesions were misdiagnosed as either infection or a malignant lesion such as Ewing sarcoma or osteosarcoma. All lesions in this series were accurately diagnosed on fine cut CT imaging.[27] The use of gadolinium enhanced MRI may yield higher accuracy in diagnosing OO, but this is may increase the cost of the imaging study and it has not been shown to outperform CT in terms of diagnostic accuracy.[28]

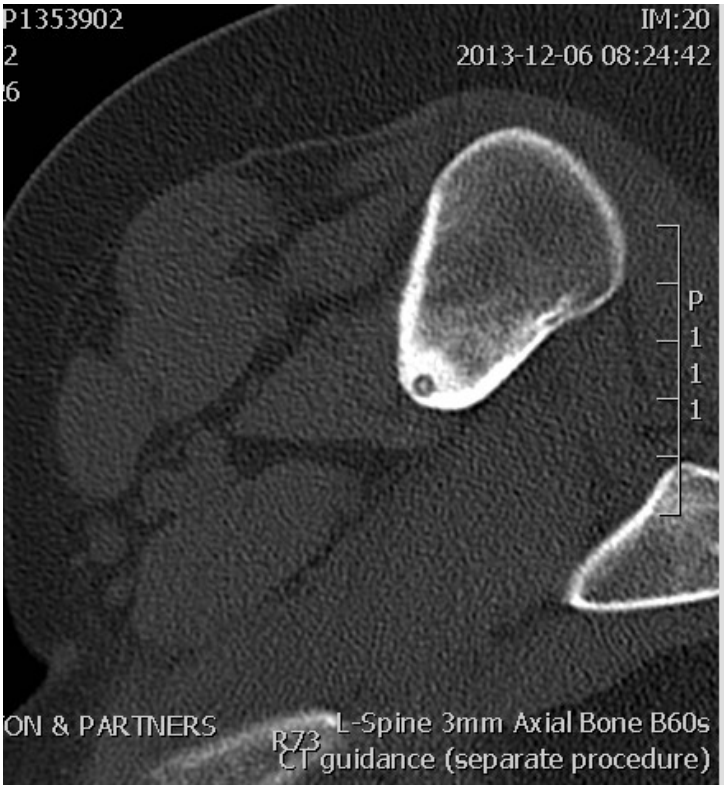

Figure 3: Axial slice CT of the left proximal femur clearly shows a lytic nidus and surrounding sclerosis of an OO.

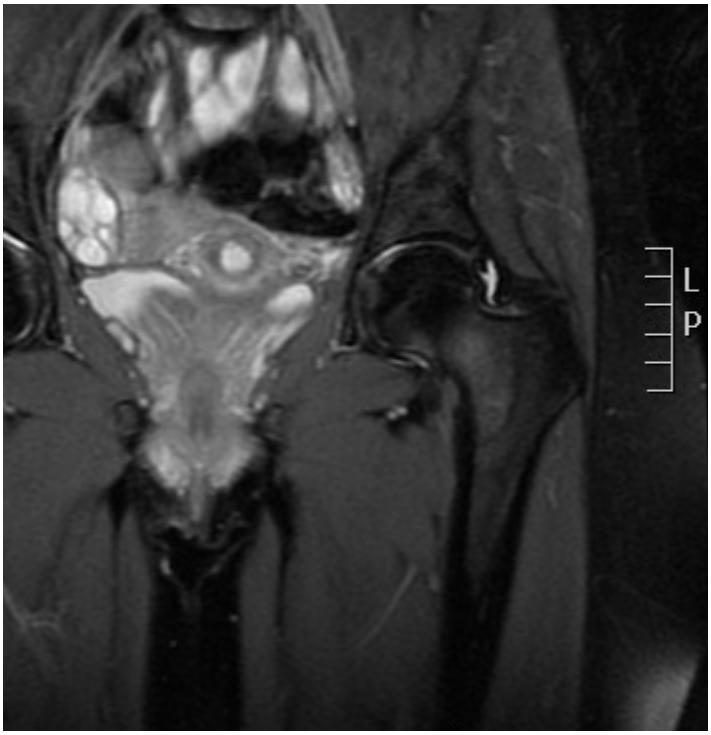

Figure 4: Proton Density Fat Saturation MRI of the same patient. Note poor visualisation of the nidus and marked surrounding bony oedema.

Scintography or nuclear bone scanning is a highly sensitive imaging modality for the detection of OO and is particularly useful when X-ray features are atypical. A three phase radionuclide scan with technetium-99 labelled methylene diphosphonate (tech-99 MDP) has been shown by Wells to have 100% sensitivity for the diagnosis of OO.[29] Park and colleagues found that 28% of the OO's in their series of 18 were not initially detected on conventional radiography but were all accurately diagnosed on tech-99 bone scan.[30] The classic feature of OO on bone scan is the double density sign, whereby the nidus has markedly increased tracer uptake, due to the vascularity of the lesion, this is surrounded by a region of slightly less intense activity.[19, 25]

Another advantage of scintography is the ability to confirm the solitary nature of the lesion.[29, 31]

Single-Photon Emission Computed Tomography (SPECT) has excellent spatial resolution and has been shown to accurately diagnose and locate even the smallest of lesions, with some authors advocating SPECT as the investigation of choice in OO.[32-34] The disadvantages are of increased cost and radiation dose. Positron Emission Tomography (PET) with F-18

fluorodeoxyglucose (FDG) tracer has also been used in the diagnosis of OO and other bone lesions. The sensitivity and specificity has not yet been quantified and its role is still under evaluation. The use of PET exposes the patient to ionizing radiation and it is an expensive investigation.[35, 36] Ultrasound and angiographic features of OO are described in the literature but are not considered as primary investigative tools.[37, 38]

Natural History

The natural history of OO is thought to be spontaneous resolution over a time period ranging from a few months to many years.[39, 40] Malignant transformation has never been described but there is some debate as to whether OO can become osteoblastoma (OB). There are a number of published cases of lesions, initially believed to be OO, continuing to grow while under surveillance and later being labelled as an OB. It remains possible that these lesions were OB's all along and were misdiagnosed as OO due to their small size.[9, 39] It has been proposed that because OO and OB exhibit a similar histology, they represent the same lesion but with different behaviours. [42,43] Chotel et al. point out that OO and OB have different immunohistochemistry, differing natural history and a different clinical presentation. For these reasons the authors advocate OO and OB should be considered different entities. In fact, it is only the similarity on conventional radiography and the tissue of origin that these two lesions have in common. They recommend against using a radiological size limit of 20mm distinguish the 2. [41]

Differential diagnosis of a small benign bone lesion

Table 1: Differential diagnosis of Osteoid Osteoma	
Traumatic	*Cortical stress fracture* *Osteochondral defect (OCD)*
Infective	*Brodie's' abscess*
Benign	*Osteoblastoma* *Chondroblastoma* *Cortical desmoid* *Enostosis* *Osteochondroma*
Malignant	*Osteosarcoma*
Other	*Geode cyst*

There are many causes of bone pain in the young patient and the differential diagnosis should include trauma, either acute or chronic (cortical stress fracture), overuse injuries in the active patient, infection and other types of bone lesions, such as osteoblastoma or osteosarcoma.

Radiological differential diagnosis

Even when the radiological features are typical of osteoid osteoma the differential diagnosis should include osteoblastoma, a cortical stress fracture, an infective process and osteosarcoma. Very rarely osteocartilagenous exostosis may simulate OO.[10] OO is usually differentiated from OB based on size (less than 20 mm diameter) alone, but immunohistochemical and genetic studies have shown these to be different lesions.[41] The radiologically lucent region of a cortical stress fracture is usually linear and runs perpendicular to the cortex but this is not always easily elucidated on X-ray and the cortical sclerosis may be equally as pronounced as OO.[42] Intra-cortical Osteosarcoma is usually much larger than 2 cm at presentation but it is possible that early lesions may be small and have features of a lucent nidus within a sclerotic margin, but these are usually not smooth and round as a typical OO. Cortical bone abscess usually has a serpentine tract leading away from the lucent abscess cavity. Medullary lesions mimicking OO include medullary osteosarcoma, Brodie's' abscess, OB and in the case of a calcified nidus, bone island. OB's are larger lesions (more than 20 mm) and in the medulla exhibit less perilesional sclerosis. Brodie's' abscess, as in cortical bone abscess, exhibits a serpentine tract leading away from the lesion toward the growth plate. The margin of osteosarcoma is more permiative and poorly defined with variable lysis and sclerosis. These lesions are also rapidly progressive and tend to present significantly larger than OO.

Histological differential diagnosis

Histologically it is relatively easy to differentiate OO from infection. Sarcomas present a more cellular lesion with chromosomal aneuploidy, a high nucleus to cytoplasm ratio, cellular pleomorphism and high mitotic rate. There is also an abundance of lacy osteoid. The histologic features of OB are similar to OO, with a nidus of immature
osteoid and osteoblasts with abundant cytoplasm and normal nuclei, giant cells may also be present but the amount of osteoid tissue is significantly greater in OB with an increased amount of vascular stroma[43]. Intra-articular OO may be difficult to differentiate from osteochondral lesions, particularly those associated with geode (subchondral) cyst

formation. Laffenêtre and colleagues describe the fractures, osteonecrosis, geodes (FOG) radiological classification for osteochondral lesions of the talus.[44] Type G lesions, geode cysts, have features similar to OO on plain XR including a lytic centre surrounded by sclerotic margins. There is minimal reactive sclerosis but this is similar to subperiosteal OO.

f. Summary of the literature on available treatment options

While medical management alone may suffice, many patients benefit from surgical excision as pain can be severe and sleep patterns greatly interrupted.[40, 45-47] This may be performed either by open marginal excision of the lesion and surrounding bone or through a less invasive percutaneous technique under image guidance. Direct curettage, laser photocoagulation and radiofrequency ablation with or without biopsy have been described.

1. Medical Management

Symptomatic relief can be gained with the regular use of NSAID's but side effects, particularly gastric irritation, may hamper this strategy.[40, 46, 47] Feletar and Hall in a 2002 review make a compelling case for medical management of OO. They highlight the risk of complication with surgical treatment as well as the prolonged recovery time before return to full activity post operatively. They argue that in the case of active young patients, who have good symptomatic relief with NSAID use, surgical resection should be avoided in favour of medical management.[46] Kneisl and Simon compared medical and operative treatment in a group of 24 patients where 9 received NSAID's only. They found all patients in the non-surgical group had complete symptomatic relief after a mean treatment period of 33 months (range 30-40 months).[45]

2. Surgical Management

Indications for surgical management include the need for histological confirmation of the diagnosis, failure of medical management to control symptoms and rarely to prevent permanent skeletal injury in the case of lesions adjacent to the physis, in the spine or within a joint. Recurrence is rare unless incomplete resection has occurred. Symptomatic relief is drastic and immediate. As the lesion is benign in nature, intralesional resection is all that is necessary and a wide resection adds no additional benefit but increases the surgical morbidity. For this reason there has been an evolution of the surgical technique from open surgical approaches with wide resection margins to less invasive, percutaneous intralesional resection or thermal destruction by radiofrequency or laser photocoagulation.[48] Intra-

articular OO may also be approached by arthroscopic means and lesions can be excised by curettage or using a high-speed bur. The use of this technique has been described in the hip, knee and ankle.[18, 49]

Table 2: Interventional treatment options for OO and other benign lesions of bone

Wide Margin resection ("En bloc")	**Open procedure, large dissection, moderate bone defect. Nidus excised with margin of surrounding bone. Longer recovery time.**
Open intralesional resection ("Burr-down")	**Open procedure, less soft tissue dissection and minimal bone excised. Difficulty in locating lesion may require the use of adjuncts. Nidus directly removed without any margin of bone.**
Percutaneous CT Guided intralesional curettage	**Percutaneous procedure, minimal soft tissue trauma. Requires radiology services to place guide wire. Nidus is removed by indirect means under fluoroscopic guidance.**
Percutaneous CT Guided RF ablation	**Percutaneous procedure, minimal soft tissue trauma. Requires radiology services to place guide wire. Nidus ablated by thermal necrosis.**
Percutaneous CT Guided Laser Photocoagulation	**As for RF ablation but uses Laser to ablate lesion.**
Arthroscopic excision	**A minimally invasive technique that may be useful for intra-articular lesions. Requires specialised skill and surgical equipment.**
Magnetic resonance-guided focused ultrasound	**A non-invasive, transcutaneous technique whereby MRI guided focussed US causes heat necrosis of the lesion. Requires specialised equipment that is not readily available in most centres. As for surgical procedures regional or general anaesthesia is required.**

US - ultrasound, RF - Radiofrequency, CT - Computed tomography, MRI - Magnetic resonance imaging

En bloc Resection

Open surgical resection with a wide margin has been considered the standard of care for many years. From the earliest reports of OO the prescribed management was open surgical resection.[3] Proposed advantages of this technique include the low recurrence rate because the entire nidus as well as surrounding sclerotic bone is excised with a margin of normal surrounding bone. Following open resection the excised tissue can be X-Rayed to confirm that the tissue excised contains the OO. Difficulty with localizing the tumour within the affected bone has been reported, resulting in increased surgical time, local morbidity and large bone defects as more bone is excised in order to identify the offending OO. This also increases the risk of fracture, which has been reported to occur in up to 4.5% of cases.[50] With a larger margin of resection the expectation would be for lower recurrence rate, but this has not been shown to be the case. While some authors reported no recurrences [25] others have reported significant failures. Rosenthal et al. reported 6 of their 68 patients (9%) presenting with recurrent OO [51] and Sluga et al. had a recurrence rate of 4.5% [50] following open surgical resection.

In an attempt to decrease the surgical site morbidity, length of surgery and hospital stay and lower the risk of fracture less invasive surgical techniques have become more commonly preferred.

Open Burr-down and the use of adjuncts

Intralesional excision involves removing just the nidus of the OO without excising the sclerotic margin. This can be performed via a smaller incision than “En bloc” resection and requires removal of significantly less structural bone. The cortical bone overlying the lesion is removed with a high-speed burr until the nidus is located which is then removed with a curette or trephine.[25, 50, 51] Pre-operative planning can be performed using X-rays, tomography or CT imagery. Intra-operative imaging is mandatory for this technique in order to localize the nidus accurately. Fluoroscopic imaging is most commonly used, but may not always allow accurate localisation of the lesion. Novel techniques have been described to augment fluoroscopy including tetracycline labelling and intra-operative scintography. Tetracycline 4mg/kg in divided doses is given to the patient 1-2 days prior to surgery. There is significant uptake of tetracycline in the metabolically active region of the nidus which exhibits gold/orange fluorescence under Woods lamp.[19] Intra-operative scintography involves the use of radioisotope labelled bisphosphonate that can be localized using a sterile probe.[4, 51, 52] Both of these techniques are rarely used, as CT guidance has become the

norm. Following the removal of the nidus adjuncts such as liquid nitrogen cryosurgery, polymethylmethacrylate (PMMA) cement [53] and intralesional ethanol injection [54] have been described. There is no consensus on the benefit of adjuncts and there is ample evidence that simply removing the nidus is sufficient to bring about symptomatic relief.[4, 55]

Percutaneous CT Guided intralesional excision

The use of CT to accurately localise the nidus allows for a minimally invasive percutaneous surgical approach, various techniques have been described but all revolve around the principle of placing a guide wire into the centre of the nidus under CT guidance and following this wire with either a drill or curette and excising the nidus.[20-22, 26, 48, 54, 56-63] The advantages of this approach are the ability to accurately locate the nidus with axial imaging, a small (stab) skin incision, limited soft tissue dissection and minimal disruption of the overlying cortical bone. The technical aspects may be challenging depending on whether anaesthesia can be performed in the radiology suite where the CT scanner room is. The location of some lesions may make it possible for the procedure to be performed under local or regional anaesthetic blocks while in some settings patients may need to be transported between theatre and the radiology unit while under general anaesthetic. Another potential problem is the radiation dose associated with CT which is significantly greater than other imaging techniques.[27] While each of the described techniques differ slightly in their execution, all CT guided percutaneous techniques involve placing a guide wire within the lesion, the placement of which is confirmed by CT imaging in the coronal, sagittal and axial plane and using this wire as a reference to gain entry into the nidus to perform intralesional resection. The nidus can then be destroyed by either mechanical or thermal means with or without adjuncts.

CT Guided Direct Curettage (Intralesional)

CT guided intralesional resection using a drill over a guide wire was first described by Doyle and colleagues in 1989.[57] After placing the guide wire into the lesion under CT guidance and confirming the position, a cannulated drill is passed over the wire to breach the overlying cortex. A small hole (between 4-8 mm) through the bone now allows the surgeon direct access to the nidus. Small sharp spoon shaped curettes is be used to scrape out the nidus. This excised material is then sent for laboratory investigations, including histological examination and microbial culture. Other instruments can be used to excise the nidus.

Kholer describes a specially designed trephine cutter that is used to over drill the nidus and in an initial series of 27 patients had a histological yield in 50 % and a clinical success rate of 88% (24/27). [59] Other authors reporting on the same technique with histological yield of 70-80% and cure rates of
80-90%. [22, 26, 58] Voto and colleagues report that the procedure can safely be performed on paediatric patients.[21] The histological confirmation of the diagnosis is critically important for both medico-legal and prognostic reasons[20], as accurate excision of an OO nidus results in almost universal immediate relief of symptoms. Reverte-Vinaixa et al assessed the histological yield and clinical outcomes of percutaneous CT guided intralesional excision of OO in 54 patients.[48] They achieved cure in 50/54 (92%) and histological confirmation in 41/54 (75%). Other studies have a range of 50-100% histological confirmation with cure rates ranging from 84-100%.[48] Minor complications including superficial infection, wound haematoma and neuropraxia have been reported but are rare.[48] Major complications were reported in one series where 2 post operative fractures occurred in a series of 38 patients (5%).[62] The technique may be repeated should the there be failure of the primary procedure. Fenichel and colleagues had 100% success rate on repeat procedures in the 12% of patients who had a failure of the initial procedure.[20]

Radiofrequency ablation under CT guidance

First described by Rosenthal in 1992 [64] numerous authors have since reported on this surgical technique [16, 51, 53, 55, 56, 63-88], considered by many to represent the gold standard of care. As for CT guided excision an anaesthetised patient is placed in a CT scanner and the lesion is approached percutaneously with a sterile guide wire. A radiofrequency (RF) ablation probe is then inserted into the nidus. Ablation refers to destruction of tissue; in this case by thermal necrosis caused by local tissue conduction of radiofrequency energy. Temperatures in excess of 60 degrees Celsius are immediately cytotoxic. RF current is able to pass through tissue because of the abundance of ionic fluid and this current causes resistive heating due to the Joule effect. Direct heating occurs in contact with the probe while a wider zone of thermal necrosis is caused by conducted heat.[67] Two techniques are described; a RF only technique and a biopsy and RF, or combined technique. In RF only technique, a drill hole large enough to accommodate only the RF probe is made and no tissue is taken for histology. For a combined technique, a larger drill hole is created so that a biopsy of the nidus can be taken by either needle aspirate or core drilling before insertion of the RF probe. The histological yield of a combined technique is lower than CT guided intra-lesional excision

of the entire nidus. This is because only a small part of the nidus is biopsied and may not be a representative sample. Histological yield of core biopsy followed by RF in the literature ranges from 17-100% (mean 55%) which is less than CT guided excision, which has a yield ranging from 50-100% (mean 73%).[48] Overall, complications and success rates are very similar and no study has clearly shown one technique to out perform all the others. Lanzo and colleagues performed a systematic review and grouped data from 27 published articles including 1227 patients in an attempt to determine best practice guidelines.[55]
They found a 5% primary failure rate (no resolution of symptoms post RF ablation) and a 2% (44/1227) complication rate. Complications include 12 cases of skin burn, 5 cases of muscle burn, 4 cases of infection, 3 cases of nerve injury, 5 technical difficulties, 1 case of fracture, 2 cases of delayed skin healing, 2 cases of hematoma and 3 anaesthetic complications. Earhart describes 2 noteworthy complications in their series of 21 cases; 1 fracture 1 deep muscle burn. The fracture occurred 9 weeks post procedure in a patient who had 2 drill holes on the lateral, tension side, of the femur distal to the lessor trochanter. The fracture occurred despite non-weight bearing for 3 weeks and protection from contact sports for 6 weeks. The authors advised caution when approaching OO's through the lateral cortex of the femur.[56] Several authors have attempted to quantify the degree to which a cortical defect weakens mechanical integrity of bone.[89] McBroom et al tested strength reduction from unicortical drill holes of various sizes in canine cadaveric femurs tested under bending loads. They found a 20% decrease in strength from a defect of 10% of the bone diameter. This increased sharply to 35% reduction in strength with a 20% defect.[90] These results suggest that a critical point may be reached somewhere between 10% and 20% of the bone diameter at which point a defect becomes a clinically relevant stress riser, putting the bone at risk for fracture.[89, 90]

Table 2:List of complications associated with RF ablation (N=1248)

Primary failure	61
Skin burn	12
Muscle burn	6
Nerve injury	3
Fracture	2

Technical difficulty	5
Infection	2
Anaesthetic complication	3
Delayed healing	2

f. Novel Treatment options

CT Guided Laser photocoagulation

The use of Laser photocoagulation to induce thermal necrosis in the treatment of OO has also been described[91-93]. The technique is very similar, the major difference being that high intensity laser probe is used to cause heat necrosis of the nidus rather than radiofrequency. This can be performed under CT guidance[93] in the same way as RF ablation or using MRI. The advantage of MRI is that there is no ionizing radiation but the cost of this imaging modality is more expensive. Gangi et al published the largest series, of 114 consecutive patients, describe the use of MRI guided Laser photocoagulation and they had a 95% primary success rate and a 99% secondary success, with 1 failure. Only one complication, reflex sympathetic dystrophy (RSD) was reported in this series.[91] The reported operative time ranges from 60-95 min cannot be directly compared with RF ablation as no study documents total procedural time in the same way.[93, 94] The time for the actual thermal ablation (heating time of the probe) for RF is between 4 and 9 minutes [66] which is similar to the 10 minutes reported for Laser photocoagulation [93]. None of these studies reports on histological confirmation of the diagnosis, which may be considered a major shortcoming.

Overall the rate of complication and cure for the percutaneous image guided techniques are very similar. The possible shorter surgical time of drill curettage may result in a more cost effective treatment. Dual technique RF may have equal histological yield and the same cure rates but longer procedural time (and possibly higher cost) while RF ablation alone does not allow for histological confirmation.

Arthroscopic excision

Intra-articular OO may also be approached by arthroscopic means and lesions can be excised by curettage or using a high-speed bur. The use of this technique has been described in the hip (both femoral and acetabular sided lesions), knee, shoulder, ankle and talus.[49, 95-97] As very few OO's are suitable for this surgical approach no large series has been published. Proposed advantages are the minimally invasive surgical approach and limited articular

injury when compared with RF ablation and open surgical excision. Arthroscopic surgery is technically demanding and has a prolonged learning curve.

Magnetic resonance-guided focused ultrasound

Magnetic resonance-guided focused ultrasound (MRgFUS) is a novel treatment of OO that is currently under investigation.[98] MRgFUS works by inducing coagulative thermal necrosis as focused high intensity ultrasound energy is absorbed by the tissue. Local temperatures exceeding the cytotoxic threshold of 60 degrees Celsius are induced. There is also a cavitatory effect as the sound waves induce mechanical destruction of tissue due to high frequency vibration. Advantages include the non-invasive nature of procedure; there is no ionizing radiation and a claimed low complication rate. It is a closed technique and thus avoids some of the complications associated with a surgical procedures but regional or general anaesthesia is still necessary. MR imaging confirms the location of the lesion and computer software is used to guide the focused ultrasound. Specific MR sequences allow real-time monitoring of temperature and tissue reaction to the focused ultrasound. Biopsy is not performed which makes histological confirmation of the diagnosis impossible. In a series of 29 patients Geiger and colleagues report a 90% primary success rate with no adverse events.[99] Potential problems include high cost of the specialised imaging and interventional equipment necessary to perform the procedure and the fact that biopsy is not performed to confirm the diagnosis.

h. An area for future research: Cost implications

The cost of health care in both developed and developing economies is increasing at an alarming rate and the importance of cost containment cannot be overemphasized.[100] It is almost impossible to compare the costs of the various treatments across countries as economies, treatment priorities, health models and access to equipment is so different. Hoffman et al. has shown that RFA is the most cost effective treatment for OO performed as an outpatient procedure. However, we consider the use of CT guided intralesional curettage to be cost effective in our setting, as it utilises existing equipment and resources and does not require the purchase of expensive consumables, which are required in RFA and Laser photocoagulation. Only one study directly compares the cost of consumables between two surgical techniques, Laser photocoagulation and RF ablation. Costs are very similar; the energy generator for RF ablation and Laser photocoagulation are equal at around €30 000 Euro each while the laser probe was cheaper €300 Euro vs. €500 Euro, more than one (up to

three) laser probes may be necessary in larger lesions.[93] Cost of imaging CT, MRI, fluoroscopy, theatre time, anaesthetic, hospital stay, postoperative rehabilitation and time away from work has not been assessed. Hoffman et al. found RF ablation, which was performed as an outpatient procedure, to be the most cost effective with a base price of $6583 USD. While open resection ($13826 USD), intralesional resection ($10857 USD) and CT guided drill curettage ($8589 USD) were all significantly more expensive procedures.[73] These results from Germany cannot be extrapolated to other regions; in different economies certain elements of the treatment package may have relatively different financial weightings. In this way a procedure, which takes less theatre time but uses more expensive consumables may be cost effective in one country while being un-affordable in another. The cost of theatre time may be significantly less expensive than hi-tech consumables that are imported from a country with a stronger currency. While many studies allude to the cost effectiveness of the various surgical techniques no study to date has adequately assessed the cost taking into account all factors and this may be an area that future research can focus on.

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PART B: MANUSCRIPT IN ARTICLE FORMAT

A. Title Page

Minimally invasive CT-guided excision of Osteoid Osteoma and other Small Benign Bone Tumours: A single centre case series in South Africa.

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Ethical Approval

Ethics approval obtained. Ethics number HREC REF: 670/2016.
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Conflict of interest

All named authors hereby declare that they have no conflicts of interest to disclose

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Informed consent

Patient information was obtained from a prospective database at Groote Schuur and Vincent Pallotti Hospitals. The Ethics committee approved these databases and their reference numbers respectively are R039/2013 and R001/2015.This is purely a review of medical notes and images. No patients were contacted.

Minimally invasive CT-guided excision of Osteoid Osteoma and other Small Benign Bone Tumours: A single centre case series in South Africa.

Abstract

Background: The management of osteoid osteoma (OO) and other small primary benign lesions of bone has evolved over the past 50 years from open surgery with wide resection margins to less invasive surgical techniques such as image guided intralesional excision and percutaneous radiofrequency ablation. We aim to evaluate the outcomes of patients treated with computerised tomography (CT guided) intra-lesional excision and bone grafting of small benign lesions of bone.

Method: A retrospective folder review of patients treated in a large academic hospital in Cape Town, South Africa, between March 2012 and May 2016 was performed. Patient demographics, details of presentation, clinical information and outcome following treatment were analysed descriptively. Pre-operative diagnosis based on radiological examination was compared with histological diagnosis.

Result: Eleven patients (5 male) with a median age of 16 years (range 5-33) were included. Pain was the most common presenting feature. A histological diagnosis of OO was confirmed in 5 of 9 patients with a suspected diagnosis of OO preoperatively. Of the 4 patients whose diagnosis changed after the procedure the diagnoses included a benign spindle cell lesion, a benign fibrous histiocytoma, subacute osteitis and an osteochondral defect with geode cyst formation. Of the 2 patients where OO was not suspected preoperatively, chondroblastoma was confirmed in one while a benign spindle cell lesion was reported in the other. Overall histological yield was thus 100%. There were no complications or repeat procedures at a median follow up of 42 months (range 30-52 months).

Conclusion: CT guided intralesional curettage is a safe and minimally invasive technique. This is especially useful in less accessible regions of the skeleton as it provides a means of accurately locating the lesion with minimal risk of complications and morbidity to the patient. We consider this to be the optimal method of treatment in our setting as it provides high success rates, few complications and a histological diagnosis without the need for any additional and expensive equipment.

Key words:

CT guidance, osteoid osteoma, percutaneous treatment, benign bone tumours, intralesional curettage, radiofrequency ablation.

Level of evidence: IV – Case Series

Blinded Manuscript

Introduction

Osteoid osteoma (OO) is one of the most important primary benign lesions of bone; due in part to the profound pain and disability it causes patients. It is also the most common, accounting for 12% of primary benign bone tumours.[1] Its differential diagnosis includes osteoblastoma, chondroblastoma, enchondroma and chondromyxoid fibroma as well as traumatic conditions, such as stress fracture, or infection, in the case of a Brodie's abscess.[2] The natural history of an OO is that of spontaneous resolution and malignant transformation has never been described.[3-6] Symptomatic relief can be gained with the regular use of nonsteroidal anti-inflammatory drugs (NSAID's) but side effects, particularly gastric irritation, may hamper this strategy.[4-6] In refractory cases surgical excision is usually curative.[7] This may be performed in a number of ways; either by open marginal excision or through less invasive techniques, performed under image guidance, such as direct curettage, laser photocoagulation and radiofrequency ablation with or without biopsy.[8] Novel techniques such as magnetic resonance-guided focused ultrasound (MRgFUS) [9-11] and arthroscopic excision are also currently being evaluated.[12-15]

While the use of novel techniques to deal with small benign bone tumours are becoming ever more popular, the additional time and cost are not yet justified by better patient outcomes.[16]

At our centre computer tomography (CT) guided percutaneous curettage and bone grafting is performed as this method has a high success rate, a low number of complications and provides a histological diagnosis without the need for costly additional equipment.[17]

Materials & Methods

Following institutional ethical approval (HREC REF: 670/2016) a retrospective folder review was performed. Included were all patients who underwent minimally invasive CT guided intralesional excision of a primary benign bone tumour between March 2012 and May 2016. Excluded were extraosseous lesions, inadequate follow-up (less than 1 year), incomplete records and lesions that were malignant or located outside of bone. Patient demographics, details of presentation, clinical information and outcome following treatment were

analysed. Pre-operative diagnosis based on radiological assessment was compared with histological diagnosis.

Surgical Technique and Aftercare

A senior surgeon performed the surgery in all cases at a single centre and all patients gave informed consent prior to surgery. Patients were admitted on the morning of surgery and discharged on the same day. Prophylactic Cefazolin 1g or Clindamycin 600mg, in the case of Penicillin allergy, was administered. Anaesthesia was induced in theatre after which the patient was transferred to the radiology suite where a threaded tipped Kirschner wire (K-wire) was inserted by a qualified radiologist under sterile conditions using CT guidance (Figure 4 & 5). The K-wire was then cut to within 3 cm of the skin and covered with a sterile dressing. Back in theatre a full standard preparation and draping of the patient was performed. A small skin incision was made to allow a 6mm cannulated drill bit to be passed over the K-wire and drilled down into the lesion. The K-wire was lubricated with K-Y Jelly (Reckitt Benckiser, Berkshire, UK) to prevent it from spinning with the drill bit and inadvertently advancing beyond the lesion. A long-handled curette was passed down the drill hole (after removing the K-wire) and the contents of the lesion curetted and sent for histology and microbiological culture. Fluoroscopy was used to confirm the position of the K-wire and ensure adequacy of the curettage. Allomatrix (Wright Medical, Middlesex, UK) demineralized bone matrix (DBM) calcium sulphate putty was injected into the cavity and the incision closed in a standard fashion. Post operatively patients with lower limb lesions were kept non-weight bearing on crutches for 2 weeks for comfort with graduated return to full weight bearing status at 6 weeks. No specific rehabilitation or weight bearing protocol was prescribed. Patients had x-rays (XR) post operatively to assess recurrence and adequacy of healing.

Statistical analysis

Due to the small cohort identified, meaningful statistical analysis was not feasible. We therefore report on descriptive statistics only.

Results

All patients presented due to limb pain and had a delay to final diagnosis. A histological diagnosis was available in all cases and there were no complications or recurrence. Four of the 9 patients with suspected OO had histological diagnosis of a different benign lesion.

Patients

Thirteen patients were identified who had undergone CT-guided percutaneous excision of a primary bone lesion. Two patients were excluded. These included a biopsy of a metastatic renal cell carcinoma from within the muscles of the shoulder girdle and the other a biopsy of a retroperitoneal Schwannoma.

Demographics

Overall five patients were male and 6 were female with a median age 16 years (range 5 - 33). Of the 5 patients with an OO, 3 were male, and the median age was 19 (range 12 - 20).

Symptoms at presentation

Localised pain was the primary presenting complaint in all patients with a median duration of 6 months (range 1 – 26 months). In 4 of the 11 (36%) patients the pain was associated with a limp, 7 of the 11 (63%) complained of night pain and 3 (27%) had activity related pain. Six (54%) patients reported pain relief with NSAID use. All 5 of the patients with OO complained of night pain and 3 of these reported transient relief of symptoms with NSAID use. One patient with a proximal tibia OO had mechanical knee symptoms including knee locking and an effusion. This patient had a delay in diagnosis of 26 months as meniscal pathology was suspected and the initial magnetic resonance image (MRI) failed to diagnose OO. These symptoms resolved following excision of the OO. There was no difference in clinical presentation between patients with OO and those with other diagnoses.

Imaging studies

Imaging included conventional XR (Figure 1), CT (Figure 2) and MRI (Figure 3). All patients had an XR initially, 8 went on to have an MRI and 3 had a CT scan. Of the patients who had an MRI scan (n=8), 3 had no further imaging while 5 patients subsequently underwent a CT scan, as the result of the MRI was inconclusive but OO was suspected. OO was accurately diagnosed on 4 of these CT scans.

Location and histology

The location of the lesions as well as the initial and final diagnoses are summarised in Table I. No lesion was larger than 20mm in diameter with a median of 9mm (range 4-20mm). Microbial culture was negative in all cases. Nine patients were thought to have an OO on clinical and radiological assessment preoperatively. In 2 of these patients subacute osteitis was included in the differential diagnosis. Histological examination confirmed OO in 5 of these 9 patients and subacute osteitis (Brodie's' abscess) in one. The other 3 histological diagnoses were an osteochondral defect of the talus with an associated geode cyst, a benign spindle cell lesion and a benign fibrous histiocytoma.

Two patients had a primary diagnosis that did not include OO. One patient was thought to have a chondroblastoma of the calcaneus that was confirmed on biopsy while the other patient, with a lesion in the ilium adjacent to the sacroiliac joint, had a wider radiological differential diagnosis including osteoblastoma, chondroblastoma or a subchondral geode Histology proved this to be benign spindle cell lesion.

Outcomes and Follow-up

The median follow-up time was 42 months (range 30-52 months). No patients had recurrence of symptoms, surgical complications or secondary surgical procedures. In the patients who had histologically confirmed OO (n=5), all patients had pain relief following surgery and remained symptom free with no radiological signs of recurrence, as did 5 of the 6 patients with other diagnoses. The patient whose symptoms did not resolve had a diagnosis of an osteochondral lesion of the talus and was referred to a foot and ankle specialist for further treatment.

Discussion

The aim of this study was to present our experience with CT guided intralesional curettage of benign bone tumours, with an emphasis on OO.

Localised pain is the most common primary presenting complaint (85% of cases) and is classically described as being worse at night and relieved by NSAIDs.[18, 19] Night pain was present in all of our patients with OO as well 2 patients with other tumour diagnoses. Six of the 11 patients reported symptomatic relief with NSAID use. Of these 6, 3 had a final diagnosis of an OO. The natural history of OO is to resolve over time and up to 40% of

patients experience long term relief with NSAID's.[20] For this reason some authors advocate non-operative management.[5] All patients in our series had failed a trial of conservative management prior to surgical intervention of a median of 14 months (1 – 25 months).

OO has been described mainly in young patients and is most common in the long bones of the lower limbs, especially in the metaphyseal region of the femur and tibia.[18, 19] We noted similar findings of age and location in our case series, but found that the clinical presentation was neither sensitive nor specific for predicting the diagnosis. Hence, we believe histological confirmation should be an essential part of the surgical management of these lesions.

The time from onset of symptoms to surgical treatment ranged from 1 – 25 months (median 14 months). This diagnostic delay is not unique to our setting and is due to the rarity of the condition and wide differential for limb pain in the active young patient. Cantwell noted a mean delay to diagnosis of 16 months.[21] Richardson describes a missed case of intra-articular OO in the hip of an 18 year old patient where the diagnostic delay was 2 ½ years due to inadequate imaging and failing to suspect the diagnosis.[22] In our series a young male sportsman with a proximal tibia OO initially presented with knee pain and meniscal symptoms. An MRI failed to diagnose an OO and the presumed cause of his pain was meniscal pathology. After a failed course of conservative treatment, a repeat MRI and a CT scan diagnosed an OO that was successfully treated by the method described above. Skeletal imaging plays a major role in the diagnosis of OO. Initially plain X-rays are the modality of choice due to the relatively low cost and radiation exposure but the diagnostic yield is far superior with CT.[23-25] The potential advantage of MRI over CT is in decreased radiation exposure, particularly to the paediatric patient but the diagnostic accuracy has been shown to be inferior.[26, 27] Hosalker et al. found MRI only had a 19% (7/36) accuracy in diagnosing OO, while all lesions in this series were accurately diagnosed preoperatively on fine cut CT imaging.[28] The use of gadolinium enhancement in MRI scanning may improve diagnostic accuracy but this increases cost and it has not been shown to be superior to CT.[29] In our series CT was more accurate in diagnosing OO with 4 of the 5 patients with an OO had an inconclusive MRI who then went on to have a CT that accurately diagnosed OO.

Microbiological culture was negative in all patients, despite one patient having subacute

osteitis on histological examination. Negative cultures in subacute osteitis are well described.[30]

The role of surgical management and different techniques

The most common indication for surgery is failed medical management.[17] Other indications include prevention of growth deformity in intra-articular or juxta-epiphysial lesions and the need for histological confirmation of the diagnosis.[18] While some authors advocate treatment without biopsy[8] we believe it is an essential part of management. Surgical options range from open marginal resection to less invasive image guided techniques such as radiofrequency ablation (RFA), laser photocoagulation and intralesional curettage. These are summarised in Table II.

Marginal resection is associated with prolonged surgical time, local morbidity, fracture in up to 4,5% of cases [31] and a recurrence rate of up to 9%.[32] Less invasive procedures are therefore preferred.[33] Open intra-lesional excision is less invasive, results in less local morbidity and a more rapid recovery.[31, 32, 34] Intra-operative imaging can be augmented with tetracycline labelling and intra-operative scintography to improve accuracy where these technologies are available.[19] There is no consensus on the benefit of adjuncts (liquid nitrogen, ethanol or PMMA) and there is ample evidence that simply removing the nidus is sufficient to bring about symptomatic relief.[1, 16] The use of CT to accurately localise the nidus allows for a minimally invasive percutaneous surgical approach.[23] Clinical success is achieved in 84-100% and importantly histological yield is reported between 50 and 100%.[17] Complications are rare but fracture has been reported with open lesional excision.[35]

RFA is considered by many to represent the gold standard of care.[36] Two techniques are described: an RFA only technique and a combined technique, biopsy and RFA. Histological yield ranges from 17-100% (mean 55%) with the combined technique as the entire lesion is not available for examination.[17] Lanzo *et al* grouped data from 27 published articles including 1227 patients in an attempt to determine best practice guidelines for RFA.[16] They found a 5% (61/1227) primary failure rate and a 2% (44/1227) complication rate. These complications are listed in Table III.

The use of Laser photocoagulation to induce thermal necrosis has also been described and can be performed under CT guidance or using MRI.[9-11] The advantage of MRI is that there is no ionizing radiation but it may be more expensive and is not available in all centres. Histological specimens are not usually sent.

Overall the rate of complications and cure for the percutaneous image guided techniques are very similar. The possible shorter surgical time of drill curettage may result in a more cost effective treatment. Dual technique RF may have equal histological yield and the same cure rates but longer procedural time and possibly higher cost due to the cost of the probes. Thermal ablation alone does not allow for histological confirmation. Our preferred approach is CT guided excision, as no additional potentially costly equipment is needed and it can be performed as day case surgery.

Intra-articular OO may be approached by arthroscopic means and lesions can be excised by curettage or using a high-speed bur. The use of this technique has been described in the hip (both femoral and acetabular sided lesions), knee, shoulder, ankle and talus.[12-15] Proposed advantages are the minimally invasive surgical approach and limited articular injury when compared with RF ablation and open surgical excision. However arthroscopic surgery is technically demanding and has a prolonged learning curve.

Magnetic resonance-guided focused ultrasound (MRgFUS) is a novel treatment of OO that is currently under investigation.[37] It is a closed technique and thus avoids some of the complications associated with a surgical procedure but regional or general anaesthesia is still necessary as the procedure is painful. In a series of 29 patients Geiger and colleagues report a 90% primary success rate with no adverse events.[38] Problems include high cost of the specialised imaging, interventional equipment necessary to perform the procedure and the lack of a tissue diagnosis.

Cost implications of different treatment modalities

The cost of health care in both developed and developing economies is increasing at an alarming rate and the importance of cost containment cannot be overemphasized.[39] Moser *et al* found the cost of consumables for Laser photocoagulation and RFA to be equivalent,[11] while Hoffman *et al* found RF ablation, which was performed as an outpatient procedure, to be the most cost effective with a base price of $6 583.00 USD (R81

359.00). Open resection $13 826.00 USD (R170 876.00), intralesional resection $10 857.00 USD (R13 4182.00) and CT guided drill curettage $8 589.00 USD (R106 150.00) were all more expensive.[36] However these results from Germany cannot be extrapolated to other regions as in different economies certain elements of the treatment package may have relatively different financial weightings. For example a procedure, which takes less theatre time but uses more expensive consumables, may be cost effective in one country while being unaffordable in another. Also of note is that cost of CT, MRI, fluoroscopy, theatre time, anaesthetic, hospital stay, postoperative rehabilitation and time away from work have not been assessed in the above figures and impact on the economic cost to hospital and patient.

Limitations

Our study was limited by the small, heterogeneous sample and the retrospective nature of data gathering. No specific pain or functional scores were used and no specific statistical tests could be applied to our data. CT scan was not performed post operatively.

Conclusion

In conclusion, a high index of suspicion is required to diagnose small benign lesions of bone, which are often elusive and can cause a large amount of morbidity for the patient. While CT scan is the imaging modality of choice, histological confirmation remains an essential part of surgical management. For the included patients, CT guided biopsy and intralesional curettage was a safe, effective, minimally invasive treatment option with high histological yield. Future research should focus on cost effectiveness and duration of these procedures compared to conventional techniques. Sufficiently powered multicentre trials are necessary to support recommendations for South African Orthopaedic Surgeons treating these lesions.

Consent

For this study formal consent was not required.

Ethics

Institutional Ethical Approval was obtained. (HREC REF: 670/2016)

Funding

No funding was received for this study

Contribution of co-authors

Contribution of co-authors as listed below

Dr. Hilton

1.Development of the study protocol

2. Application to the departmental research committee and ethics board.

3. Gathering of patient data

4. Writing-up of the manuscript for submission

Dr. Held

1. Writing-up of the manuscript for submission

Dr. Hosking

1. Inception of the research idea

2. Primary surgeon in all cases

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Figures and Tables

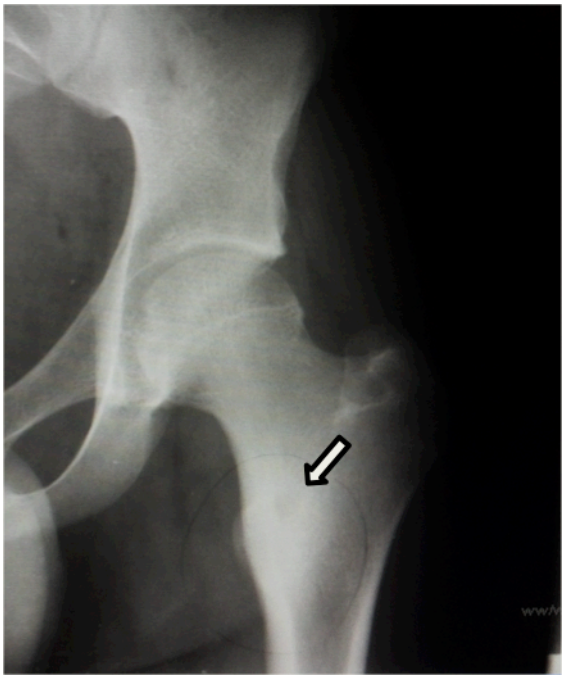

Figure 1: XR of an OO in the left proximal femur (Bold arrow)

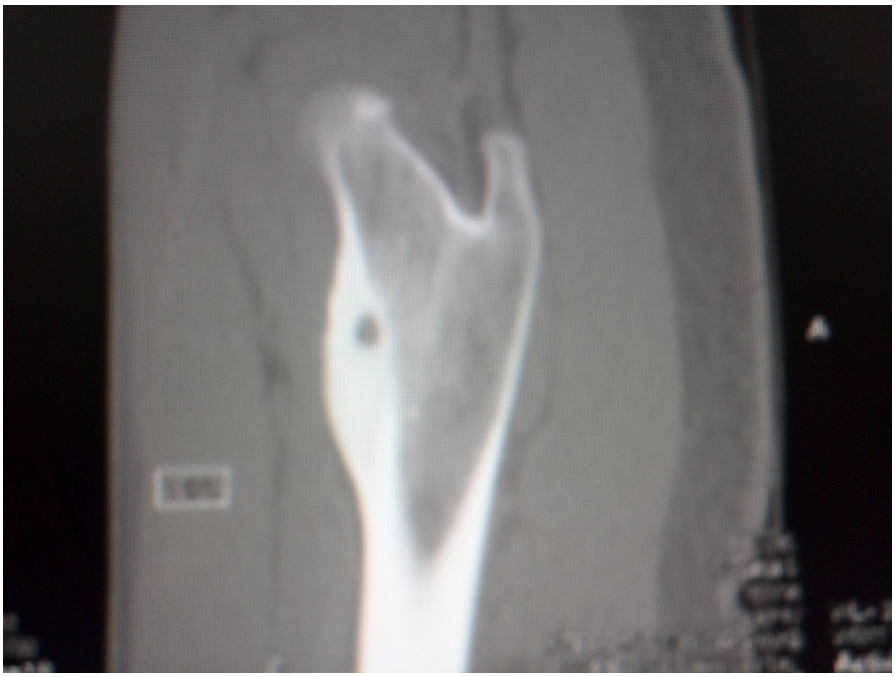

Figure 2: Coronal CT of the left proximal femur, note the clearly defined nidus.

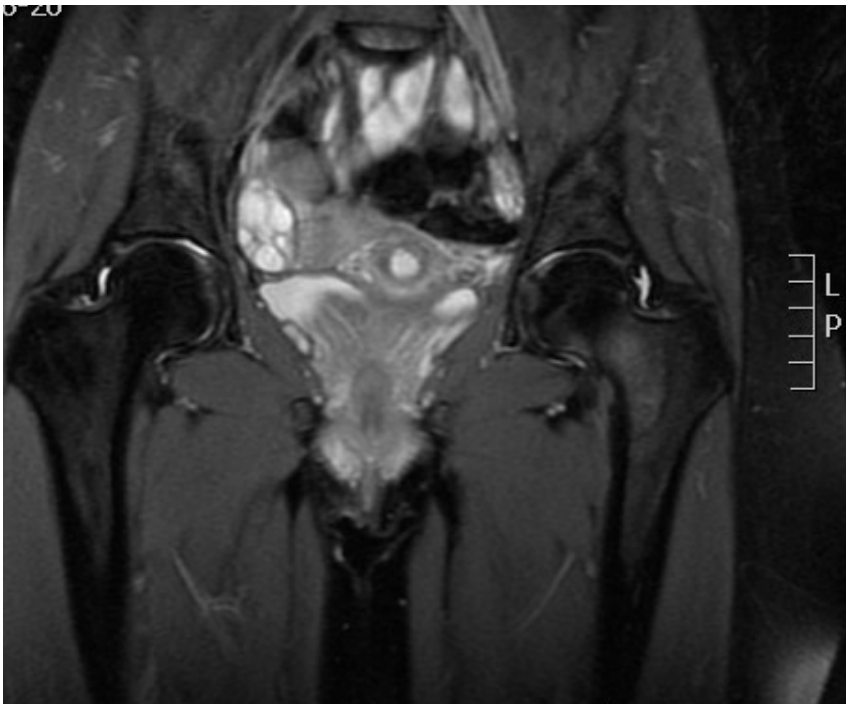

Figure 3: MRI of the same patient as in figure 4; note the poor differentiation of the nidus and marked surrounding bone oedema (PD Fat Sat).

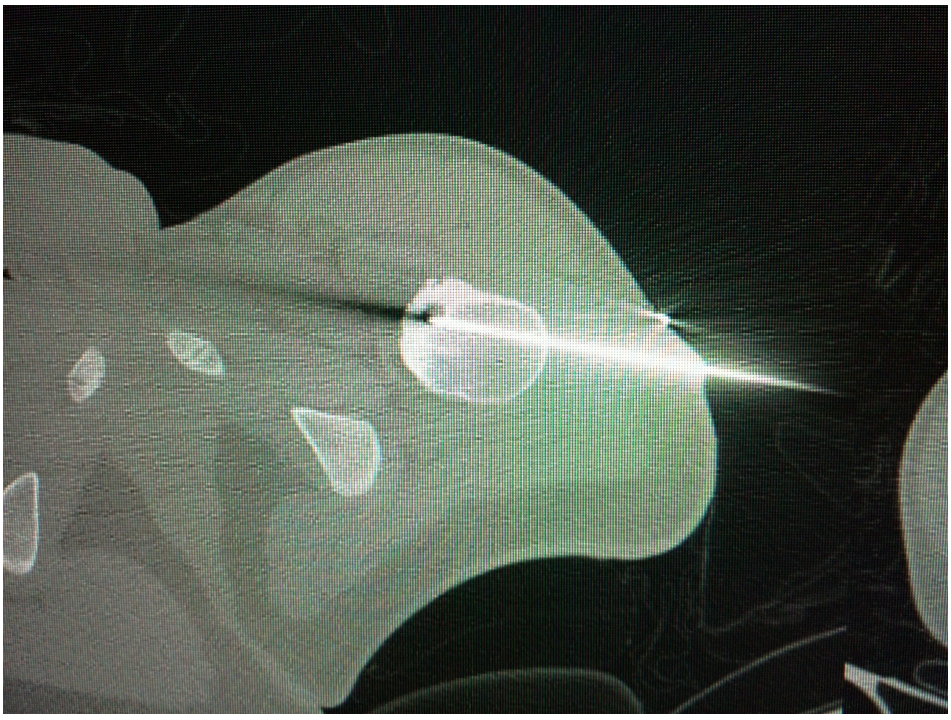

Figure 4: Axial view of a dynamic CT scan shows the K-wire tip located within the nidus of a proximal femur OO.

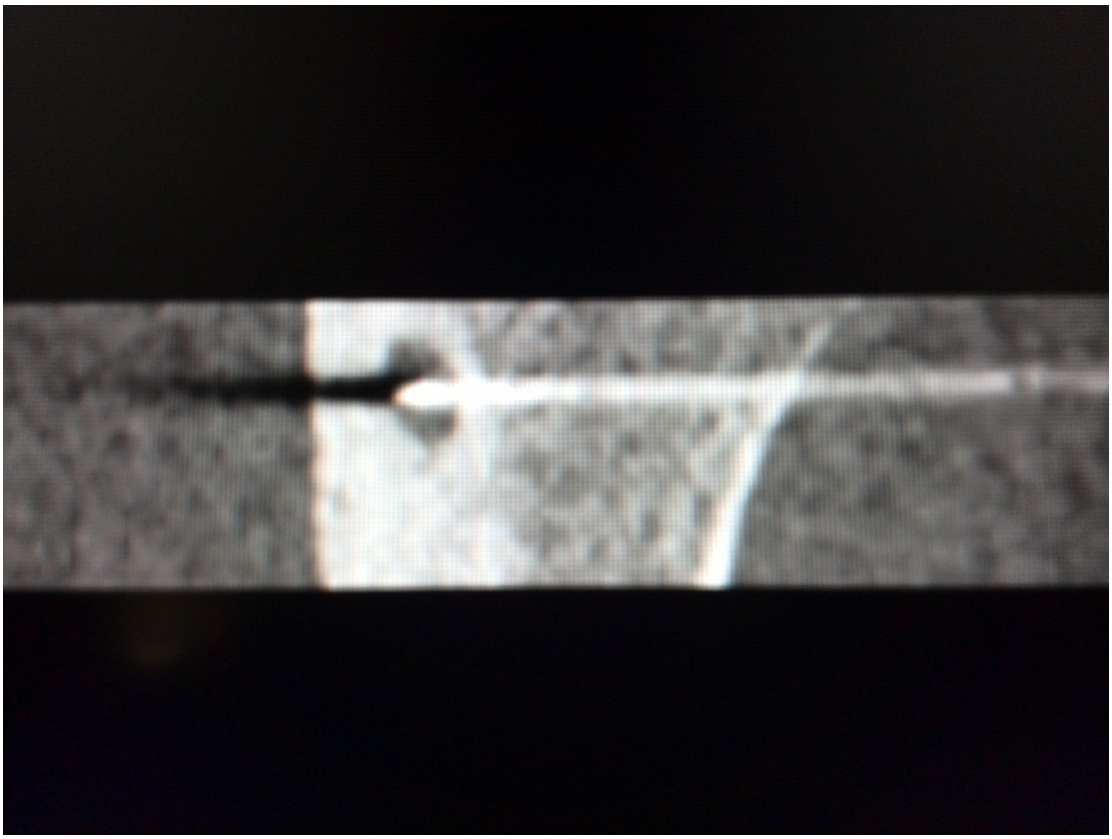

Figure 5: Magnified axial view of the same lesion as in figure 2 with K-wire in situ.

Figure 1: XR of an OO in the left proximal femur

Figure 2: Coronal CT of the left proximal femur, note the clearly defined nidus.

Figure 3: MRI of the same patient as in Figure 4; note the poor differentiation of the nidus and marked surrounding bone oedema.

Figure 4: Axial view of a dynamic CT scan, which shows the K-wire tip, located within the nidus of a proximal femur OO.

Figure 5: Magnified axial view of the same lesion as in Figure 2 with K-wire in situ.

Table I: Summary of patient's demographics, lesion location and diagnoses.

	Age	Sex	Location	Duration of Symptoms (Months)	Provisional Diagnosis	Histological diagnosis
1	19	Male	Calcaneus	3	Chondroblastoma	Chondroblastoma
2	20	Female	Proximal femur	26	Osteoid Osteoma	Osteoid Osteoma
3	19	Male	Proximal tibia	6	Osteoid Osteoma	Osteoid Osteoma
4	33	Female	Talus	13	Osteoid Osteoma	OCD/Geode cyst
5	16	Male	Prox. tibia	18	Osteoid Osteoma	Osteoid Osteoma
6	11	Female	Calcaneus	3	Osteoid Osteoma	Benign fibrous histiocytoma
7	12	Male	Distal femur	6	Osteoid Osteoma or Subacute Osteitis	Subacute Osteitis (Brodie's abscess)
8	19	Female	Proximal femur	3	Osteoid Osteoma	Osteoid Osteoma
9	9	Female	Pelvis	1	Osteoid Osteoma, osteoblastoma or Osteitis	Benign Spindle Cell Lesion
10	25	Female	Pelvis	3	Osteoblastoma, Chondroblastoma or a subchondral geode cyst	Benign Spindle Cell Lesion
11	12	Male	Tibia	26	Osteoid Osteoma	Osteoid Osteoma

Table II: Descriptions of interventional techniques for the treatment of benign lesions of bone

Description	Technique	Advantage	Disadvantage
Wide marginal resection ("En-bloc")	Extensive open surgical procedure. Lesion excised with margin of normal bone.	No additional equipment needed, technically relatively simple.	Large soft tissue dissection. Moderate bone defect. Longer recovery time, fracture risk.[40]
Open intralesional resection ("Burr-down")	Open procedure. Nidus directly removed without any margin of bone under image guidance.	Less soft tissue dissection and minimal bone excised.	Difficulty in locating lesion may require the use of adjuncts. Recurrence risk.[31, 32, 34]
Percutaneous CT guided intralesional curettage	Guide wire placed under CT. Nidus is removed by indirect means under fluoroscopic guidance.	Percutaneous procedure, minimal soft tissue trauma. Low fracture risk. Histology specimen.	Requires radiology services to place guide wire.[17]

Percutaneous CT guided RF ablation	CT guided wire placement followed by RFA. . Nidus ablated by thermal necrosis	Percutaneous procedure, minimal soft tissue trauma.	Requires radiology services to place guide wire. Lower histological yield. Additional equipment needed including RF generator and single use probes.[36]
Percutaneous CT (or MRI) guided laser photocoagulation	As for RF ablation but uses Laser to ablate lesion.	Potentially less radiation than RFA (can be performed under MRI guidance.	Increased cost with no proven benefit over RFA.[9-11]
Arthroscopic excision	Lesion excised under arthroscopic visualisation with a bur.	A minimally invasive technique.	Requires specialised skill and surgical equipment. Only suitable for intra-articular lesions.[12-15]
Magnetic resonance-guided focused ultrasound	MRI guided focussed US causes heat necrosis of the lesion.	A non-invasive, transcutaneous technique.	Requires specialised equipment, not readily available in most centres. As for surgical procedures regional or general anaesthesia is required. No histology. [38]

Table III: List of complications associated with RF ablation (N=1227) [16]

Primary failure	**61 (5%)**
Skin burn	12
Muscle burn	6
Nerve injury	3
Fracture	2
Technical difficulty	5
Infection	2
Anaesthetic complication	3
Delayed healing	2

PART C: ADDENDA

a. Journal Information

Article submitted to:

South African Orthopaedic Journal

ISSN 1681-150X *printed version*

ISSN 2309-8309 *online version*

South African Orthopaedic Association (SAOA)

P.O. Box 12918, Brandhof, Bloemfontein, Free State, ZA, 9324,

Tel: +27 51 430 3280 Email: pat@saorthopaedicjournal.com

b. **Instructions for Authors**

South African Orthopaedic Journal

INSTRUCTIONS FOR AUTHORS

ISSN 1681-150X *printed version*

ISSN 2309-8309 *online version*

Scope and Policy

The scope of publication encompasses all orthopaedic surgery sub–disciplines including paediatric orthopaedics, hip, knee, tumour and sepsis, spine, shoulder and elbow, foot and ankle and hand surgery. In addition the journal addresses the subjects of orthopaedic service delivery, teaching, training and research. Publications should influence orthopaedic care on our continent.

The *South African Orthopaedic Journal* aims to advance the knowledge of all aspects of musculoskeletal medicine through publication of:

- Original research articles.
    - Clinical research
    - Basic science and theoretical research
- Review articles.
- Invited expert opinions.
    - A review of significant local or international publications journal article or cluster of articles dealing with a similar topic for the purpose of conveying a useful message.

- Editorials.
- Letters to the editor.
    - Forum to raise issues or debate aspects of previously published papers.

Criteria for publication

- The article falls within the scope of the journal.
- Methods, statistics, and other analyses are performed to a high technical standard and are described in sufficient detail.
- Results reported have not been published elsewhere.
- Conclusions are presented in an appropriate fashion and are supported by the data.
- The article is presented in an intelligible fashion and is written in standard English (British usage).
- The research meets all applicable ethical standards.
- The article adheres to guidelines provided in the instructions for authors section.

Guidelines for authorship

- Each author should participate and is responsible for the content and design of the study, the preparation of the manuscript and its revisions, and final approval.
- Other 'contributors' can be acknowledged at the end of the manuscript together with their contribution.
- Authors of manuscripts representing a multi–centre study may list members of the group in the footnote on the title page of the published article and their affiliations are listed in an appendix.
- The authors should clearly indicate the predominant surgeon or surgeons who have contributed patients to the study.

Registration of clinical trials

- A clinical trial is defined as any research study that prospectively assigns human participants or groups of humans to one or more

health–related interventions to evaluate the effects of health outcomes. Interventions include drugs, surgical procedures, devices, behavioural treatments, dietary interventions, and process–of–care changes.

- Clinical trials should be registered in a public trials registry in accordance with International Committee of Medical Journal Editors recommendations.
- Trials must be registered and approved by the relevant authorities before the onset of patient enrolment.
- The Medicines Control Council (MCC) reference number and the SA National Clinical Trial Register (SANCTR) registration number should be included at the end of the abstract of the article.
- Purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) do not require registration.

Reporting guidelines

- All articles should be prepared in accordance with the guidelines relevant to the study design that was used (listed below):

Randomised trials	CONSORT
Observational studies	STROBE
Systematic reviews	PRISMA
Case reports	CARE
Qualitative research	SRQR
Diagnostic / prognostic studies	STARD
Quality improvement studies	SQUIRE
Economic evaluations	CHEERS
Animal pre–clinical studies	ARRIVE
Study protocols	SPIRIT

- Randomised trials should be accompanied by a flow diagram that illustrates the progress of patients through the trial, including recruitment, enrolment, randomisation, withdrawal and completion, and a detailed description of the randomisation procedure.

Role of funding source

- Authors are requested to identify who provided financial support for the conduct of the research and/or preparation of the article and to briefly describe the role of the sponsor(s), if any, in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. If the funding source(s) had no such involvement, then this should be stated.

Formatting of Submissions

Text formatting

- Use Helvetica or Arial font, size 11.
- Use double line spacing throughout the document.
- Number the pages of the blinded manuscript consecutively.
- Use italics for emphasis.
- When referring to an article with multiple authors please use the following format: Rabinowitz *et al*. published their retrospective review.
- Do not use field functions.
- Use tab stops or other commands for indents, not the space bar.
- Use the table function, not spreadsheets, to make tables.
- Use the equation editor or MathType for equations.
- Save your file in docx format (Word 2007 or higher) or doc format (older Word

versions).

Headings

- Use no more than three levels of displayed headings.

Abbreviations

- Define abbreviations and acronyms at first mention and use consistently thereafter.

Units

- Follow internationally accepted rules and conventions: use the international system of units (SI). If other units are mentioned, please give their equivalent in SI.

Figures

- Figures should be numbered consecutively with illustration Arabic numbers 1, 2, 3, etc.
- The figure should be listed in the text as follows: … wound irrigation and splinting (*Figure 1*).
- Figures should be clear and easily understandable with a full descriptive legend stating any areas of interest and explaining any markings, letterings or notations. All figures should be understandable without the main text.
- For radiographs please ensure you state the view used and the time point at which it was taken, as well as the demographic details of the patient if applicable.
- Figures should not be imbedded in the text file, but should be submitted as separate individual files. Each figure should be a separate file, entitled Figure 1, Figure 2, etc.
- Remove all markings, such as patient identification, from radiographs before photographing.
- All line or original drawings must be done by a professional medical illustrator.

- We accept a maximum of six figures.
- Do not submit any figures, photos, tables, or other works that have been previously copyrighted or that contain proprietary data unless you have obtained and can supply written permission from the copyright holder to use that content.

Tables

- Tables should carry uppercase Roman numerals, I, II, III, etc.
- Tables should always be cited in the text in consecutive numerical order.
- The table should be identified in the text as follows: Details of results are listed in *Table I*. Or, alternatively, … high–energy trauma that is often associated with these fractures (*Table II*).
- Tables should be used to present information in a clear and concise manner. All tables should be understandable without the main text.
- For each table, please supply a table heading explaining the components of the table.
- Identify any previously published material by giving the original source in the form of a reference at the end of the table heading.
- Footnotes to tables should be indicated by superscript lower–case letters and included beneath the table body.
- Please submit tables as editable text and not as images. They should be created using the Table tool in Word.
- Do not embed tables in the text file, but submit them as separate individual files. Each table should be a separate file, entitled Table I, Table II, etc.
- We accept a maximum of eight tables.
- Do not duplicate information given already in the text.
- Do not submit any figures, photos, tables or other works that have been previously copyrighted or that contain proprietary data unless you have obtained and can supply written permission from the copyright holder to use that content.

References

- References should be numbered consecutively in the order that they are first

mentioned in the text and listed at the end in numerical order of appearance.

- Identify references in the text by Arabic numerals in superscript after punctuation.
- References should not be a listing of a computerised literature search but should have been read by the authors and have pertinence to the manuscript.
- Authors should add DOIs to all references in articles.
- Accuracy of references is the author's responsibility and the author is to verify the references against the original documents.
- Manuscripts in preparation, unpublished data (including articles submitted but not in the press) and personal communications may not be included in the reference listing. They may be listed in the text in parentheses only if absolutely necessary to the contents and meaning of the article.
- The titles of journals should be abbreviated according to the style used in Index Medicus, obtainable through the website http://www.nlm.nih.govshould
- The following format should be used for references:

Journal article:

Sidhu GS, Ghag A, Prokuski V, Vaccaro AR, Radcliff KE. Civilian gunshot injuries of the spinal cord: a systematic review of the current literature. Clin Orthop Relat Res 2013;471:3945-55.

Ideally, the names of all authors should be provided, but the usage of 'et al.' in long author lists (more than six authors) will also be accepted: Fong K, Truong V, Foote CJ, et al. Predictors of nonunion and reoperation in patients with fractures of the tibia: an observational study. BMC Musculoskelet Disord 2013;14:103.

On–line journal article:

Caetano–Lopes J, Lopes A, Rodrigues A, et al. Upregulation of inflammatory genes and downregulation of sclerostin gene expression are key elements in the early phase of fragility fracture healing. PLoS One 2011;6:e16947.

Web reference (with authors):

Cierny G, DiPasquale D. Adult osteomyelitis protocol. http://www.osteomyelitis.com/pdf/treatment_protocol.pdf. (date last

accessed 05 March 2013).

Web reference (no authors listed):
No authors listed. International commission on radiological protection. http://www.icrp.org (date last accessed 20 September 2009).

Chapter in a book:
Young W. Neurophysiology of spinal cord injury. In: Errico TJ, Bauer RD, Waugh T (eds). Spinal Trauma. 3rd ed. Philadelphia: JB Lippincott; 1991: 377-94.

Dissertation:
Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Abstract:
Peterson L. Osteochondritis of the knee treated with autologous chondrocyte transplantation [abstract]. ISAKOS Congress, 2001.

Structure and content of submission

- We accept a maximum of 3500 words including the abstract and body of the text (excluding references).
- Exceptions to this rule may be made for systematic reviews and meta–analysis, at the discretion of the Editor–in–Chief.
- Please follow the following structure when preparing your submission.
    - Title page (Title, authors and affiliations, corresponding author and declarations)
    - Blinded manuscript (Abstract, key words, introduction, methods, results, discussion, funding sources, conflict of interest statement, ethical statement, acknowledgements and references)
    - Tables (with headings), each as a separate file.
    - Figures (with legends), each as a separate file.

<u>Title page</u>

Title

- The title should be concise and informative.

Author names and affiliations

- Please provide the following information for each author:
    - Full names and surname, as well as title
    - Qualifications
    - Affiliation and address
    - ORCID ID (see Article Submission section)
- Please check that all names are accurately spelled.
- Indicate all affiliations with a lower–case superscript letter immediately after the author's name and in front of the appropriate affiliation details.
- Provide the full postal address of each affiliation, including the country name and, if available, the e–mail address of each author.

Corresponding author

- Clearly indicate who will handle correspondence at all stages of refereeing and publication, including post–publication.
- Ensure that the e–mail address and permanent address is given and that contact details are kept up to date by the corresponding author.
- Please note that the corresponding author's contact details will be provided in the final article.
- Provide the following information for the corresponding author:
    - Full names and title
    - Affiliation
    - Physical address
    - Postal address
    - Telephone Number
    - E–mail address

Declarations

Authors are to insert a section at the end of the title page entitled declarations. Following the declarations all authors need the to sign the document (please provide

name of author, signature and date). The following statements are required under the declarations section:

a. Authorship

   The authors confirm that all authors have made substantial contributions to all of the following:

   - The conception and design of the study, or acquisition of data, or analysis and interpretation of data
   - The drafting the article or its critical revision for important intellectual content
   - Final approval of the version to be submitted.

b. Sound scientific research practice

   The authors further confirm that:

   - The manuscript, including related data, figures and tables has not been previously published and is not under consideration elsewhere
   - No data have been fabricated or manipulated (including images) to support conclusions.
   - This submission does not represent part of a single study that has been split up into several parts to increase the quantity of submissions and submitted to various journals or to one journal over time (e.g. 'salami–publishing').

c. Plagiarism

   The authors confirm that the work submitted is original and does not transgress the plagiarism policy of the journal.

   - No data, text or theories by others are presented as if they were the authors' own.
   - Proper acknowledgements of others' work has been given (this includes material that is closely copied, summarised and/or paraphrased); quotation marks are used for verbatim copying of material.

- Permissions have been secured for material that is copyrighted.

d. Conflict of interest statement

A conflicting interest exists when professional judgement concerning a primary interest (such as the patient's welfare or the validity of research) may be influenced by a secondary interest (such as financial gain or personal rivalry). It represents a situation in which financial or other personal considerations from authors, reviewers or editors have the potential to compromise or bias professional judgment and objectivity. It may arise for the authors when they have a financial interest that may influence their interpretation of their results or those of others. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding. All potential conflicts of interest need to be declared. The conflict of interest statement should list each author separately by name, i.e.,

'John Smith declares that he has no conflict of interest. Paula Taylor has received research grants from Drug Company A. Mike Schultz has received a speaker honorarium from Drug Company B and owns stock in Drug Company C.'

If multiple authors declare no conflict, this can be done in one sentence.

e. Funding sources

All sources of funding should be declared. Also define the involvement of study sponsors in the study design, collection, analysis and interpretation of data; the writing of the manuscript; and the decision to submit the manuscript for publication. If the study sponsors had no such involvement, this should be stated.

f. Compliance with ethical guidelines

- For all publications:

  'The author/s declare that this submission is in accordance with the principles laid down by the Responsible Research Publication Position Statements as developed at the 2nd World Conference on Research Integrity in Singapore, 2010.'

  Available from:
  http://publicationethics.org/resources/international-standards-for-editors-and-authors

  Institutional Review Board (IRB) ethical approval must have been given if the study involves human subjects or animals. Please provide the approval number. IRB documentation should be available upon request.

  'Prior to commencement of the study ethical approval was obtained from the following ethical review board: *Provide name and reference number*'

- For studies with human subjects include the following:
  'All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.'

  'Informed written consent was or was not obtained from all patients for being included in the study.'
- For studies with animals include the following sentence:
  'All institutional and national guidelines for the care and use of laboratory animals were followed.'
- For articles that do not contain studies with human or animal subjects:
  'This article does not contain any studies with human or animal subjects.'

- If doubt exists whether the research was conducted in accordance with the Helsinki Declaration, the authors must explain the rationale for their approach, and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study. If any identifying information about patients is included in the article, the following sentence should also be included: Additional informed consent was obtained from all patients for which identifying information is included in this article.

  The Helsinki Declaration 2008 can be found at http://www.wma.net/en/30publications/10policies/b3/

Blinded manuscript

Abstract

- A structured abstract (maximum of 350 words), summarising the most important points in the article is required.
- The abstract consists of four paragraphs with the subheadings:
  - Aims (it is unnecessary to include an introductory section)
  - Patients and methods
  - Results
  - Conclusion
- References should be avoided. Avoid uncommon abbreviations. If essential they must be defined at their first mention in the abstract itself

Key words

- Immediately after the abstract, provide a maximum of six key words, using standard searchable terms. These key words will be used for indexing purposes.

Level of evidence

- Level 1 to 5.
- Please follow the level of evidence guidelines provided by the Oxford Centre

for Evidence–Based Medicine (OCEBM); version 2.1.

- Available from: OCEBM Levels of Evidence Working Group. 'The Oxford Levels of Evidence 2'.Oxford Centre for Evidence–Based Medicine. http://www.cebm.net/index.aspx?o=5653

Introduction

- The introduction should contextualise the study by providing the background to the research; explain the problem that is to be addressed and provide the rationale for the study.
- Briefly outline the relevance of the study with respect to the current literature. Avoid a detailed literature survey or a summary of the results.
- The last sentence should outline the research question or hypothesis.

Patients (or Materials) and methods

- State the methods, outcome measures, and selection criteria. The following aspects need to be described:
    - The study design and research methodology
    - Whether randomisation (with methods) was applied
    - If case controlled, how the controls were selected
    - The time period under review
    - Number of patients/subjects under investigation and why this number was chosen
    - Inclusion and exclusion criteria
    - Case and outcome definitions
    - A description of the procedure or intervention, including post–operative protocol
    - The outcome measures or scores used
    - The minimum follow–up period
    - Statistical analysis paragraph. This should be included at the end of this section to detail statistical tests and package used, the reasons why these tests were used, and what p–value was considered statistically significant. A power analysis is recommended for studies comparing two or more groups.

- Provide sufficient detail so that another researcher can replicate the study.
- The reader should understand from this description all potential sources of bias such as referral, diagnosis, exclusion, recall or treatment bias. This includes the manner in which investigators selected the patients. Consecutive inclusion implies all patients with a given diagnosis are included, while selective implies patients with a given diagnosis but selected according to certain explicit criteria (e.g., state of disease, choice of treatment).
- Do not describe standard procedure for common operations. Only include new procedures or adaptations to standard procedure.
- If you name any specific product, then it requires the name, city and state/country of the manufacturer.
- Present information in the narrative format and use the past tense.
- Where relevant, tables or figures may be included to provide information more clearly.
- Generally, no data should be presented in this section.

Results

- Describe the relevant results and analysis thereof.
- Provide details of the number of patients included and excluded, as well as the reason for exclusion.
- It is important to state the follow–up period (mean and range).
- The results can be broken down into separate sections, e.g. Treatment, Functional outcome, Complications, etc.
- Tables may be used but avoid repeating data reported in the text in the tables.
- All appropriate data should be presented as means with ranges, not with standard deviations (SDs). Medians should only be used when the data is skewed, accompanied by an interquartile range (IQR).
- Avoid using percentages in studies involving well under 100 subjects.
- All results must be backed up with p–values or survivorship analysis. All Kaplan–Meier data should be presented with the confidence intervals. Always present exact absolute p–values, whether significant or not, unless $p < 0.001$.
- However, p–values do not always convey the entire picture and where

relevant the confidence interval will also be required (in addition to the power of the study reported in the methods section).

Discussion

- The question or hypothesis stated at the end of the introduction should be discussed and either supported or rejected.
- The results must be interpreted clearly and any deficiencies expressed. All possible confounding factors, sources of bias, or weaknesses in the study should be identified.
- Explore the significance of the results of the work, rather than repeating the results.
- The discussion must point out the relevance of the work described in the paper and its contribution to current knowledge.
- Explain what can be deduced from the results and how will it affect clinical practice.
- Include a review of the relevant literature, placing the results of the study in the context of previous work in this area.
- Discussion of relevant prior research and references must be concise. Avoid extensive citations and discussion of published literature but put emphasis on previous findings that agree (or disagree) with those of the present study.
- Do not repeat the introduction.
- Present the limitations of the study and suggest how the study could have been improved for a future study.
- Avoid making inferences from non–significant trends unless you believe your study is adequately powered to answer the question; in that case, provide a power analysis.

Conclusion

- Provide a summary statement which conveys the conclusions of the findings.
- Do not draw conclusions not supported by the data obtained from the specific study presented.

Conflict of interest

- 'Author A.B. (*use initials of relevant author, not full name in order for the document to remain blinded*) has received research grants from Company A. Author B.C. has received a speaker honorarium from Company X and owns stock in Company Y. Author C.D. is a member of committee Z.'
- If no conflicts of interest exist, state this as follows: 'The authors declare they have no conflicts of interest that are directly or indirectly related to the research.'

Ethical statement

- For studies involving human subjects please include an ethical statement as follows: 'All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.'
- For animal studies please include the following ethical statement: 'All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.'
- If the study did not involve human or animal subjects state that: 'This article does not contain any studies with human participants or animals performed by any of the authors.'
- Please also include an informed consent statement: 'Informed consent was obtained from all individual participants included in the study.'
- Or alternatively, for retrospective studies, please add the following sentence: 'For this study formal consent was not required.'
- If identifying information about participants is available in the article, the following statement should be included: 'Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.'

Funding sources

- List all funding sources as follows: 'This work was supported by the xxxx (grant numbers xxxx, yyyy).'
- When funding is from a block grant or other resources available to a university,

college or other research institution, submit the name of the institute or organisation that provided the funding.

- If no funding was received, state as follows: 'No funding was received for this study.'

Acknowledgements

- Acknowledgements should be placed at the end of the discussion and before the references.
- In this section persons who were involved but did not earn authorship can be acknowledged.
- Statements should be brief. A person can be thanked for assistance or for comments.
- Should not include contributions by editors or referees.

References

- Please refer to the section on Formatting of submissions.

Tables and figures

- Table and figures should not be imbedded in the text file, but should be submitted as separate individual files. Each table should be a separate file, entitled Table I, Figure 2, etc.
- Each table and figure should be provided with a heading or legend.
- Please refer to the 'Formatting of submission' section for further guidelines.

DRC PROTOCOL

Minimally invasive CT-guided excision of benign bone tumours**.**

Investigators: Dr T Sluis-Cremer, Dr T.L. Hilton, Dr K Hosking
Department of Orthopeadic Surgery
University of Cape Town
Groote Schuur Hospital & Vincent Pallotti Hospital

Introduction and aim of study

Osteoid osteoma and osteoblastoma are benign osteogenic tumours, and together are the most common benign bone forming lesions accounting for 3% of all bone tumours. These occur most commonly in young male patients and aside from the spine are found predominantly in the metaphyseal regions of the lower limbs. The hallmark feature is that of lytic nidus circumscribed by an area of sclerotic bone. Histologically the nidus is composed of osteoid. Osteoblastoma and osteiod osteoma are very similar lesions with the only difference being that in osteoblastoma, which may be locally aggressive, the nidus is usually larger than the 15mm size of osteiod osteoma and unlike osteiod osteoma is usually painless. The pain caused by osteoid osteoma is worse at night and is dramatically relieved by non-steroidal anti-inflammatory medications (NSAID's). There is no risk of malignant transformation and the natural history is thought to be that of resolution. Management is either medical, with NSAIDS, or surgical. The surgical options included en-block excision, percutaneous ablation using either radiofrequency induced thermal coagulation, or intra-lesional injection of phenol, cryotherapy or laser photocoagulation and CT guided intra-lesional excision. CT guided excision involves anaesthetizing the patient, transfer to CT scanner, insertion of a guidewire under CT guidance by the radiologist. The patient is then transferred back to theatre where a small incision is made in the skin and a drill placed over the guidewire to open the cortex of the involved bone. A curette is then used to excise the lesion. These techniques may be augmented with bone graft to fill the resultant defect. CT guided intra-lesional excision has the advantage of providing a histological diagnosis through a minimally invasive approach, especially in less accessible regions while maintaining the structural integrity of the bone from which the lesion is excised. The aim of this study is to review the clinical outcomes of patients treated with CT guided intra-lesional excision and bone grafting of benign osteogenic tumours.

Study hypothesis

We hypothesize that percutaneous CT-guided intra-lesional excision of benign bone forming tumours is an acceptable surgical technique with low incidence of complications. It successfully alleviates symptoms with the additional benefit of histological confirmation of the diagnosis.

Aims and objectives

Aim:
Main aim to describe case series – procedure
Complications and symptom resolution

Objectives:
Describe the imaging done pre-diagnosis
measure pain resolution immediate post op and during follow up
Measure complications – surgical

- During follow up
- Last follow up

Describe histological yield

Study population

All patients who were treated for benign osteogenic tumours (osteoid osteoma and osteoblastoma) by CT-guided percutaneous intra-lesional excision at Groote Schuur and Vincent Pallotti Hospitals will be included in the study population. Clinical case notes, Radiology and Laboratory results will be reviewed retrospectively. Patients with incomplete records or patients with these tumours who were treated by methods other than CT guided intra-lesional excision will be excluded from the study.
Age limit?

Study design

Retrospective folder review

Study method

A search of the GSH and Vincent Pallotti tumour databases will find all patients who were treated by CT-guided intralesional resection of osteoid osteoma and osteoblastoma. All guide wires were placed by a consultant radiologist. A retrospective review of their records will be performed for the following parameters:

1. Age at presentation
    a. Often the diagnosis is not one of osteoid osteoma. Age will help us correlate with diagnosis
2. Site of involvement (clinically and radiologically)
    a. To ensure that we are consistent with current literature describing the more common sites of osteiod osteoma
3. Size of lesion
    a. To distinguish between osteoid osteoma and osteoblastoma. <1.5cm osteiod osteoma, >1.5cm osteoblastoma.
4. Radiological features
5. Histological diagnosis
6. Pre-operative symptoms Yes/No
7. Post-operative resolution of symptoms Yes/No
8. Intra-operative, early post-operative and late complications
    a. Possible:
        i. Wound sepsis
        ii. Fracture
        iii. Recurrence

iv. Incomplete excision

9. Clinical and radiological outcome
    a. Clinical outcomes will include resolution of preoperative symptoms.
    b. Radiological outcomes will include excision of lesion and subsequent new bone formation.

At what time interval are you measuring these outcomes? 1 yr ? 1 month? What if this info is missing from the folder? Are you going to exclude every patient whose info isn't complete? Bc then you will have a lot of exclusions.

Analysis of the data

An osteoid osteoma is a rare lesion and the lesions that benefit from CT guided excision are fewer still. We expect between 10 and 20 cases. Descriptive analysis of the data will be performed.

Data collection will take approximately 1 month, with analysis of the data a further month, write up and submission 2 – 3 months.

During analysis of the results we will be looking at the following points;

- ➢ Pre-operative vs post-operative visual analogue pain score
- ➢ Proportion of recurrence
- ➢ Incidence of infection
- ➢ Number of complications
- ➢ Number of re-operations
- ➢ Histological diagnosis

Pilot study

Not applicable

Report of findings

Results will be submitted for publication in peer review journals. Results will also be discussed at national or international Orthopaedic conferences and research or faculty meetings.

Ethical considerations

This is purely a retrospective study utilising available clinical notes and radiographs. No intervention is to be performed on any patient outside of acceptable clinical practice. No extra risks will be entailed by any of the subjects within the study. No patients will be identified by name or hospital number and every effort will be made to protect their privacy. There are no immediate benefits to the study subjects as this is a retrospective analysis. The knowledge gained will influence the future management of similar patients seen within the context of locally available resources and expertise.

Budget and funding

Costs will be incurred by the investigators involved in the study. There is no financial incentive for the investigators involved in the study.

References

(1) Assoun J, Richardi G, Railhac JJ, Baunin C, Fajadet P, Giron J, et al. Osteoid osteoma: MR imaging versus CT. Radiology 1994 Apr;191(1):217-223.

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(3) Busser WM, Hoogeveen YL, Veth RP, Schreuder HB, Balguid A, Renema WK, et al. Percutaneous radiofrequency ablation of osteoid osteomas with use of real-time needle guidance for accurate needle placement: a pilot study. Cardiovasc Intervent Radiol 2011;34(1):180-183.

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06 March 2017

HREC REF: 670/2016

Dr T Hilton
Orthopaedic Surgery
H49, OMB
Groote Schuur Hospital

Dear Dr Hilton

PROJECT TITLE: MINIMALLY INVASIVE CT-GUIDED EXCISION OF BENIGN BONE TUMOURS (Sub-study linked to R039/2013 and R001/2015)
MMed Candidate Dr Tim Sluis

Thank you for your letter to the Faculty of Health Sciences Human Research Ethics Committee dated 01 March 2017.

The HREC acknowledges that the following MMed Candidate, Dr Tim Sluis is also involved in this study.

Approval was granted for one year until the 30th September 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

e. Description of surgical Margins for excision of bone tumours (Enniking)

Types of surgical margins for the resection of bone tumours

According to Enniking surgical margins for the resection of bone tumours may be divided into four groups

1. Intralesional resection

   Margins are entirely within the tumour, not all tumour material is excised

2. Marginal resection

   Margins are situated at the immediate extent of the tumour

3. Wide resection

   Margins include the tumour and a cuff off normal tissue

4. Radical resection

   Margins include the tumour and the entire compartment in which the tumour was located

In the case of benign bone lesions radical resection is never indicated as this is reserved for malignant tumours. Wide, marginal and intralesional resection techniques have all been described in the management of OO.

f. Bone Graft and Bone Substitutes

Following excision of a bone lesion the resultant defect may need to be addressed. The natural cycle of bone formation and resorption is carried out by osteoblasts, osteocytes, and osteoclasts under the direction of the bone-signaling mediators. This will result in remodelling and filling of a bone defect but this can be augmented by the addition of bone graft. Not all bone graft and bone graft substitutes have the same properties and this warrants some consideration. The four fundamental properties of bone graft are osteoconduction, osteoinduction, osteogenesis, and structural support.

Structural bone graft imparts mechanical strength to the surgical defect. The structural integrity of the bone graft material may change with time as resorbtion occurs.

An osteoconductive material will act as a structural framework for bone growth.

An osteoinductive material contains factors that stimulate bone growth and induction of stem cells down a bone-forming lineage. An osteogenic material directly provides cells that will produce bone. This includes primitive mesenchymal stem cells, osteoblasts, and osteocytes. Mesenchymal stem cells can potentially differentiate down any cell line while osteoprogenitor cells differentiate to osteoblasts.

Autologous bone graft (fresh autograft and bone marrow aspirate) is the only bone graft material that contains live mesenchymal precursor cells. Autograft can be cancellous, cortical, cortico-cancellous and may include bone graft that is transposed with an intact blood supply. The donor locations for cancellous bone graft include the ilium and metaphyseal regions of long bones. Cortical graft, which is used where structural support is of critical importance, is usually harvested from fibula or ribs. Another source is the medullary canal of the femur where bone graft is harvested using a reamer-irrigator-aspirator (RIA). Disadvantages related to autograft include the limitation in the amount that can be harvested and the donor site morbidity.

Allograft is harvested from human cadaveric donors. It is available in many forms including demineralized bone matrix, morselized and cancellous chips, corticocancellous and cortical grafts, osteochondral and whole-bone segments. The process of freeze-drying (lyophilization) allows bone to be stored un-refrigerated for prolonged periods. This increases the availability to the surgeon as it can be used as an "off the shelf" product. Alternatively fresh frozen graft must be stored at sub-zero temperatures (-18 degrees Celsius) for up to 1 year while deep frozen grafts (-70 degrees Celsius) can be stored for up to 5 years. Fresh allograft is more likely to induce tissue reaction than freeze dried. The risk of transmission of disease from donor to host exists with allograft, particularly fresh frozen, while the process of preserving allograft reduces this risk significantly. The risk of HIV transmission is quoted as 1 in 1,5 million.

Demineralised bone matrix (DBM) is a form of processed allograft. Allograft bone is crushed to powder demineralized by submersion in hydrochloric acid and washed in sterile water, ethanol and ethyl ether leaving the protein structure and growth factors. It has osteoconductive and osteoinductive activity. Many commercially available preparations exist but there is no evidence to demonstrate superiority of any one product. DBM may be combined with a calcium substrate, such as calcium sulphate in the case of Allomatrix (Wright Medical, Middlesex, UK).

Ceramic bone graft substitutes include calcium phosphate, tricalcium phosphate, hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$, and calcium sulphate. Coralline or structured calcium phosphate is structural and osteoconductive while the other forms of ceramic bone graft substitutes are osteoconductive void fillers and are suitable for contained bone defects only. These may be in the form of paste, pellets or injectable putty and may be used as a delivery vehicle for DBM or osteogenic factors such as bone morphogenic proteins (BMP), bone marrow aspirate, platelet rich plasma (PRP) or collagen. Bioactive glass is a combination of silica, calcium oxide, disodium oxide, and pyrophosphate. It is a structural ceramic with osteoconductive properties. There is at present little evidence in support of one form of bone graft substitute over another and autograft remains the best choice but at the cost of donor site morbidity. The size of the defect, need for structural support and availability are all factors which dictate the choice of graft material.