PSEUDOTUMOURS FOLLOWING HIP RESURFACING; MINIMISING THE CLINICAL IMPACT

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ABSTRACT

PSEUDOTUMOURS FOLLOWING HIP RESURFACING; MINIMISING THE CLINICAL IMPLACT

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Metal-on-metal hip resurfacing arthroplasty (MoMHRA) is an alternative treatment option to total hip arthroplasty (THA), especially in the young and active. Despite the early successful results, reports of adverse soft-tissue reactions around the MoMHRA have caused increased concern. These reactions have been termed pseudotumours and have been shown to be associated with increased wear. However, their incidence and aetiology is not known. The broad aims of this thesis were to 1) determine the clinical impact of pseudotumour; and 2) identify ways of reducing the risk of pseudotumour.

The clinical impact was determined by examining the incidence and prevalence of pseudotumours needing revision and the subsequent outcome following revision. At the Nuffield Orthopaedic Centre, the 10-year survival of the BHR, commonest MoMHRA used, was 87.1% (95%CI: 83.0% to 91.2%) and the 10-year incidence of revisions due to pseudotumour was 7.5% (95%CI: 4.3% to 10.7%). In a prevalence study of two tertiary referral centres, pseudotumour was identified as the most common revision indication. An outcome based, case-control study characterised outcome following revision due to pseudotumour as inferior to that following revision for any other failure mode, and inferior to the outcome of matched primary THAs. The inferior outcome was associated with the extensive tissue damage at revision.

Risk factors contributing to development of pseudotumour were found to be both patient and surgeon related. Patient factors significantly increasing risk included female gender and small component size. Case control studies demonstrated two surgical factors that were associated with significantly increased risk; cup malorientation and a reduction in head neck ratio (HNR) at operation particularly in females. Furthermore, evidence based recommendations were provided on optimum cup orientation and screening practice. Surgeons should aim for a radiographic cup inclination/anteversion zone of 45°/20° ± 10°. Patients with mal-positioned cups, those with high HNR prior to surgery, and those that had significant HNR reduction with the MoMHRA should be considered at increased risk of developing a pseudotumour.

An *ex vivo* study demonstrated that the majority of pseudotumours occur due to high prosthesis wear, and result from an exaggerated innate response with an accompanying variable immune response. However a small but significant number of pseudotumours (20%) were observed with low wear and a prominent immune response. Furthermore, the cups oriented within the optimum zone were associated with less wear.

Hence, subsequent *in vivo* research focused on providing evidence-based guidance on how to achieve the target cup orientation and factors to consider in minimising the scatter in cup orientation observed following hip arthroplasty. This great scatter was mostly due to two factors: 1) the variability between surgeons at orientating a component at implantation and 2) the difference in the pelvic position between implantation and radiographic assessment. The angular offset was 5° for inclination and 8° for anteversion because of the different definitions at impaction and X-Ray. Surgeons should need to be aware of these factors. Greater amount of pelvic movement occurs during MoMHRA, in comparison to THA. To achieve the target MoMHRA cup orientation surgeons should implant the cup with an intra-operative inclination/anteversion of 40°/30°.

It is concluded that pseudotumour following MoMHRA has a significant clinical impact. In order to minimise it, surgeons should appropriately select patients and optimise surgical technique to achieve optimum cup orientation and try to avoid reducing the native head neck ratio. Appreciation of risk factors for pseudotumour development (female gender, small size component, cup orientation, HNR reduction), would aid detection prior to extensive soft-tissue damage and improve inferior outcome associated with revision.

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GLOSSARY

AHP	Artificial hip profiler
ANJR	Australian National Joint Registry
ALTR	Adverse local tissue reaction
ALVAL	Aseptic lymphocytic-dominated vascular associated lesions
AP	Anteroposterior
APC	Antigen presenting cell
ARMD	Adverse reaction to metal debris
ASA	American Society of Anaesthesiologists
ASR	Articular surface replacement
AUC	Area under curve
AVN	Avascular necrosis
BHR	Birmingham hip resurfacing
C+	Conserve plus
CI	Confidence interval
CIA	Combined inclination anteversion
CMM	Coordinate measurement machine
CO	Calibration object
Co	Cobalt
CoCr	Cobalt-chromium
CoCrMo	Cobalt-chromium-molybdenum
Cr	Chromium
CPR	Contact patch to rim
CT	Computer tomography
DDH	Development dysplasia of the hip

DNA	Deoxyribonucleic acid
DZ	Designer's zone
EBRA	Ein Bild Roentgen Analyse digital measurement system
EPOS	Exeter primary outcome study
FDA	Food and drug administration
FISH	Fluorescent In situ hybridisation
GF-AAS	Graphite furnace atomic absorption spectrophotometry
HRA`	Hip resurfacing arthroplasty
HHS	Harris hip score
HNR	Head neck ratio
ICC	Inter-correlation-coefficient
ICP-MS	Inductively coupled plasma mass spectroscopy
IFN	Interferon
IL-1	Interleukin 1
IL-6	Interleukin 6
IOA	Intra-operative anteversion
IOI	Intra-operative inclination
LTT	Lymphocyte transformation test
LZ	Lewinnek's zone
MHRA	Medicines and Healthcare products Regulatory Agency
MMT	Midlands Medical Technology
Mo	Molybdenum
MoM	Metal-on-metal
MoP	Metal-on-polyethylene
MRI	Magnetic Resonance Imaging
NDORMS	Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences

NICE	National Institute of Clinical Excellence
NJR	National Joint Registry
NOC	Nuffield Orthopaedic Centre
NSA	Neck-shaft angle
MoMHRA	Metal-on-metal hip resurfacing arthroplasty
OA	Osteoarthritis
OHS	Oxford hip score
OZ	Optimum zone
SPG	Stereophotogrammetry
PT	Patch test
RA	Radiographic anteversion
RANKL	Receptor activator of nuclear factor kappa-B ligand
RCA	Radiographic cup anteversion
RCI	Radiographic cup inclination
RI	Radiographic inclination
ROC	Receiver operating characteristics
ROM	Range of movement
SA	Stem angle
SD	Standard deviation
SRA	Simulated radiographic anteversion
SRI	Simulated radiographic inclination
SSA	Stem-shaft angle
STL	Stereolithographic file
THA	Total hip arthroplasty
TLW	Total linear wear
TLWR	Total linear wear rate
TNF-α	Tumour necrosis factor – α

TVW	Total volumetric wear
TVWR	Total volumetric wear rate
UCLA	University of California, Los Angeles
US	Ultrasound
XPS	X-Ray photoelectron spectroscopy
2-D	Two dimensional
3-D	Three dimensional

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1 INTRODUCTION

1.1 Overview

Third generation Metal-on-Metal Hip Resurfacing Arthroplasty (MoMHRA) was introduced in the late 1990's as an alternative to Total Hip Arthroplasty (THA) for the treatment of young adults with hip osteoarthritis[3]. The proposed advantages over THA, along with favourable early- and mid-term results led to a resurgence of MoMHRA use. According to the 2008 National Joint Registry England and Wales Annual Report, MoMHRA accounted for 46% of all primary procedures in patients younger than 55 years old[4]. Initially, concern over peri-prosthetic femoral neck fractures stimulated interest on how to prevent their occurence and risks for development[5,6]. However, more recent reports of soft-tissue masses around MoMHRAs have raised further concerns[7].

These soft-tissue masses were initially presented as case reports; but latelly, recent case series and studies have lead to their being recognised as an important failure modality following MoMHRA[8,9]. The terminology used to describe these masses varies greatly and some authors have used the term pseudotumours[8]. Pseudotumours have caused concern in both the general public and the orthopaedic community.

This growing concern has led to increased interest in determining the patho-aetiology of pseudotumours. Most pseudotumours are associated with increased bearing wear[10-12]. Studies on failed implants has resulted in a greater understanding of MoMHRA wear process[13]; and recently, implant-related risk factors have been identified, which has resulted in the withdrawal of an implant from the market due to design issues. To-date, two key questions remain unanswered:

- What is the clinical impact associated with pseudotumour following MoMHRA?
- How can the clinical impact be reduced?

Answering these questions will enable orthopaedic surgeons to provide evidence-based advice to their patients (those with a MoMHRA and those considering the option of having a MoMHRA) and to stratify their practice in order to mimise the risk of pseudotumour.

1.2 Overall scope of the proposed Thesis

The scope of this thesis is to determine how significant a complication pseudotumour is following MoMHRA, and whether factors can be identified contributing to its development that can be addressed by surgeons in order to decrease its occurence or associated significance. Thus, the broad aims of this thesis are to: (1) determine the clinical impact of pseudotumour; and (2) provide evidence-based guidelines on how to reduce it.

1.3 Specific objectives

The specific objectives of this thesis are:

1. To establish the ten-year survival of the most commonly used (worldwide) MoMHRA.

2. To establish the ten-year incidence of revision due to pseudotumour and the prevalence of pseudotumour amongst MoMHRA failures likely to be encountered in specialist units.

3. To determine the outcome following revision of MoMHRA due to pseudotumour.

4. To investigate whether surgical factors such as component placement and size selection contribute as risk factors to pseudotumour development.

5. To determine whether the histological features of pseudotumour are associated with the amount of prosthesis wear.

6. To investigate whether different pseudotumour sub-types exist and determine whether these are associated with different levels of wear.

7. To provide evidence based guidelines on how to more accurately implant an acetabular MoMHRA component to achieve a desired target orientation without requiring navigation.

1.4 Structure of Thesis

The thesis is presented in the following chapters:

Chapter 2 provides a literature review of the current research into MoMHRA, wear of metal-on-metal bearings, wear particles and pseudotumours following MoMHRA.

Chapter 3 includes two clinical studies. Study 3A reports on the ten year survival of a MoMHRA and the ten year incidence of revision due to pseudotumour. Study 3B reports the prevalence of MoMHRA failures due to pseudotumour encountered in two specialist hip centres.

Chapter 4 presents a clinical study conducted, in a single tertiary referrral centre, to identify the outcome following MoMHRA revision for different modes of failures and compares the outcome with a cohort of primary THAs.

Chapter 5 presents clinical studies that were performed in order to investigate the effect of surgical factors, such as component orientation and sizing of the components, on the risk of developing a pseudotumour.

Chapter 6 reports on an *ex vivo* retrieval study conducted to measure wear, assess histological features and review radiological features of revised MoMHRAs due to pseudotumour.

Chapter 7 presents a photogrammetric study developed to investigate the orientation of the cup during surgery at the time of impaction. It reports on the correlation between the intra-operative and radiographic cup orientations, and factors that affect it, in a cohort of MoMHRAs and THAs.

The final chapter (Chapter 8) summarises the important findings and conclusions presented in the thesis. In addition, it discusses the relevance of the work presented, and provides ideas and recommendations for future work in the field.

2 LITERATURE REVIEW*

2.1 Introduction

Surface arthroplasty of the hip has been an alternative to total hip arthroplasty (THA) in the treatment of hip osteoarthritis since the 1950s. Amongst some surgeons, hip resurfacing arthroplasty (HRA) may seem the intuitive arthroplasty option with a number of presumed advantages over THA[14]:

1. Allows for preservation of the femoral head and neck
2. Allows for normal femoral loading, thus reducing stress-shielding
3. Has a reported reduced risk of dislocation compared to THA with 28 to 32 mm diameter heads
4. May be a superior alternative to THA in cases with extra-articular femoral deformity and/or pre-existing metalwork
5. Has a lower prevalence of thrombo-embolic phenomena
6. Allows for an easier first-time revision due to the preserved femoral neck and intramedullary canal.

2.1.1 Evolution of design

Smith-Petersen was the first to introduce the concept of articular surface operation

* Part of the work described in this chapter has been published as:

Gill HS, Grammatopoulos G, Ashead S, Tsialogiannis E, Tsiridis E, Molecular and immune toxicity of CoCr nanoparticles in MoM hip arthroplasty. Trends in Molecular Medicine 2012, 18(3): 145-55.

of the hip in the 1940s[15]. His mould arthroplasty, initially made of glass and later replaced by Vitallium, intended to enhance cartilage regeneration and remain *in situ* for the short-term. However, his concept was abandoned as the regeneration of hyaline cartilage failed; subsequently the majority of moulds were never removed.

Charnley in the 1950's developed the first cementless all Teflon surface arthroplasty replacement ('double cup arthroplasty')[16], which failed due to accelerated wear, component loosening and an intense tissue reaction. Müller and Boltzy in the 1960s used a cementless metal-on-metal double cup arthroplasty[17]; however the smooth surface design of the implants allowed movement between the implant and underlying bone which subsequently led to loosening.

In the early 1970s, with the introduction of fixed cemented components, surface arthroplasty devices were re-introduced with a large diameter femoral component articulating with a cemented thin polyethylene acetabular component (1st generation). Amongst the designs introduced were the Wagner from Germany[18] and the Imperial College London Hospital resurfacing from the United Kingdom[19]. These designs exhibited poor long-term survival due to loosening and osteolysis[20,21]. Although implant failure is typically considered a multifactorial process, it is now understood that the principal mechanism of failure was that of polyethylene wear-induced osteolysis[22]. However, at the time such failures were attributed to osteonecrosis of the femoral head underlying the femoral component and high frictional torque at the implants' interface leading to cup loosening[23].

Increased understanding of metal-on-metal (MoM) bearing tribology and advances in the manufacturing process enabled the re-introduction of MoM bearing couples in hip arthroplasty in the early 1990s. The first two designs were the Wagner (Aesculap-Werke, Tullinger, Germany) and McMinn (McMinn Hybrid Resurfacing, Corin Medical Ltd, Cirencester, UK) metal-on-metal-hip-resurfacing-arthroplasties (MoMHRAs) (2nd generation)[3,24]. Initially, both designs were all cementless. The Wagner design used a forged cobalt-chrome (CoCr) alloy (F799 with high carbon) which had a grit-blasted, titanium alloy shell with macro-features for fixation to the bone. The initial McMinn device was made from uncoated cast CoCr alloy. These cementless designs experienced early failure due to aseptic loosening of both components. These failures led to a change of practice and the re-introduction of acrylic bone cement fixation of both components. However, the smooth surface finish cemented socket resulted in high incidence of early loosening due to cement-cup debonding[25].

2.1.2 Contemporary designs

Lessons learned over the previous years about the design, tribology and technique of implantation combined with advancements in the precision of MoM manufacturing led to the development of the 3rd generation of HRA. The contemporary designs are characterised by the use of high carbon content (> 0.2%) CoCr alloy for the bearing couple, with cementless fixation of the acetabular component and cemented fixation of the femoral component.

McMinn in 1997 introduced the Birmingham Hip Resurfacing (BHR) (Midland Medical Technologies, Birmingham, UK), which was machined from 'as cast' CoCr alloy in accordance to British Standards 7252 part 4, with 5% carbide content (Figure 2.1)[25]. In the same year Amstutz in the United States, introduced the Conserve Plus (C+) hip resurfacing (Wright Medical, Arlington, Tennessee, USA). The Conserve Plus components were made of cast CoCr alloy but were heat treated and solution annealed [26].

Other contemporary designs of hip resurfacing systems were subsequently introduced including the Cormet System (Corin Group PLC, Cirencester, UK), the Durom (Zimmer Ltd, Swindon, UK), the Articular Surface Replacement (ASR) (DePuy International, Leeds, UK) and the Recap (Biomet Ltd, Swindon, UK). Different design features of each system are described in Table 2.1.

Figure 2.1: The Birmingham Hip Resurfacing (BHR) System. (Image source: Smith & Nephew, http://global.smith-nephew.com/master/birmingham_hip_33360.htm)

	ASR	BHR	Conserve Plus	Cormet	Durom	Recap
Year	2003	1996	1996	1997	2007	2004
Process	Cast	Cast	Cast	Cast	Wrought	Cast
Heat Treatment	HIP	None	HIP, SHT	HIP, SHT	NA	None
Acetabular Shape	Truncated hemisphere	Hemisphere	Truncated hemisphere	Equatorial expansion	Truncated hemisphere	Hemi-sphere
Subtended Angle/°	148 to160	154 to166	162 to 165	154 to 166	166	154 to 166
Acetabular Surface	Sintered CoCr beads + HA	CoCr bead cast in + HA	Sintered CoCr beads ± HA	Ti-VPS + HA	Ti-VPS	Ti-VPS + HA
Acetabular Rim Thickness / (mm)	3.1	3.6	3.8	5.6	4.6	3.4
Radial Clearance/(µm)	50	100-150	80	150 – 400	150	53 – 273
Surface Roughness/(µm)	0.025	0.029	0.020	0.030	0.034	0.031
Cement Mantle /(mm)	0.5	0	1	0	1	0.5

Table 2.1: Most commonly implanted hip resurfacing systems. HIP: Hot Isostatically Pressed, SHT: Solution Heat Treatment, Ti-VPS: Titanium Vacuum Plasma Sprayed, NA: Non-Applicable, HA: Hydroxyapatite.

2.1.3 Implant survival

The published short-term survivorship rates have varied between 75% to 100%. Data from national registry reports and studies have shown an implant-specific risk factor for survival. The ASR system has shown poor early/mid-term survivorship in both independent centre studies as well as in the national registry data[9,27,28], and this subsequently led to the withdrawal of the ASR resurfacing system.

Amongst other MoMHRA systems, mid-term data is encouraging with survival of 88 to 99%. These figures represent a significant improvement in comparison to previous 1st and 2nd generation HRA implants. At mid-term, survival appears to be

similar amongst designer and non-designer series. Treacy *et al* reported a five year survival of 98%[29]. Independent studies by Steffen *et al*[30] and Hing *et al*[31] reported five year survival rates of 95% and 98% respectively. These initial reports of favourable survival led to MoMHRA being recommended by the National Institute of Clinical Excellence (NICE) as "*a surgical option in the treatment of patients with advanced hip disease who would otherwise receive a conventional primary Total Hip Replacement (THR) and are likely to live longer than the device is likely to last*"[32].

Most of the data on mid/long-term survivorship is from designer-centre series. Treacy *et al*[33] reported a survival rate of 94% at 11 years, whilst Amstutz *et al*[34] reported on a 12-year survival of 89%. Recent reports from independent, experienced, high volume surgeons from both the UK[35] and Australia[36] have reported ten year survivals of 94.5% and 95% respectively (Table 2.2).

Study	Implant	Number of Hips	Gender (% males)	Age at surgery (years, range)	Follow-up (years, range)	Survivorship for revision
Bergeron *et al* 2009[37]	ASR	228	80	54 (25 to 73)	3 (2 to 5)	95%
Langton *et al* 2011[27]	ASR	418	56	56 (28 to 77)	4 (2 to 6)	75%
Daniel *et al* 2004 [38]	BHR	446	79	48 (26 to 55)	3 (1 to 8)	99%
De Smet *et al* 2005[39]	BHR	252	n/a	49 (16 to 75)	3 (2 to 5)	98%
Hing *et al* 2007[31]	BHR	230	66	52 (19 to 82)	5 (4 to 6)	98%
Steffen *et al* 2008[30]	BHR	610	59	52 (16 to 81)	4 (2 to 8)	95%
Ollivere *et al* 2009[40]	BHR	463	66	56 (20 to 70)	4 (1 to 9)	96%
Treacy *et al* 2010[33]	BHR	144	74	52 (17 to 76)	11 (10 to 12)	94%
Coulter *et al* 2012[36]	BHR	230	66	52 (18 to 82)	10 (10 to 12)	95%
Holland *et al* 2012[35]	BHR	100	74	51 (21 to 68)	11 (10 to 13)	92%
Amstutz *et al* 2007[41]	C+	350	77	41 (14 to 49)	5 (2 to 9)	94%
Amstutz *et al* 2008[42]	C+	1,000	75	50 (14 to 78)	6 (1 to 11)	95%
Amstutz *et al* 2010[34]	C+	100	66	49 (15 to 71)	12 (11 to 13)	89%
Spencer 2011[43]	Cormet	747	n/a	n/a	3 (2 – 6)	95%
Naal *et al* 2011[44]	Durom	100	70	53 (20 to 72)	5 (4 to 6)	88%

Table 2.2: Survivorship of the currently used hip resurfacing implants. n/a: information not available from paper. C+: Conserve Plus

2.1.4 Modes of failure

Failure modes occuring in the early-term following 3rd generation MoMHRA appear to be similar to those reported with previous generations of resurfacing.

The most common early-term failure mode is femoral neck fracture with a varying incidence up to 12%[6,45]. Patient and surgical technique related risk factors for femoral neck fracture have been described, including gender[6], proximal femoral bone quality, vascular compromise[5], prosthesis placement[6] and cementation. Other early-term recognised failure modes include component loosening[30,42], avascular necrosis of the femoral head[5] and painful impingement[46].

As experience with MoMHRA has grown, a further recognised complication leading to revision is the occurrence of a peri-prosthetic soft-tissue mass around the resurfaced hip. Such masses have been termed 'pseudotumours'[8] and have been shown to be associated with metallic wear debris production[11,47].

Ball *et al*[48] reviewed the outcome following revision of failed MoMHRAs due to femoral side failures (fracture of the femoral component and aseptic loosening). A study group with 21 patients of failed MoMHRAs converted to metal-on-metal total hip arthroplasties (MoMTHA) were compared to a control group of 64 primary MoMTHAs which were matched for age and gender. The authors identified no significant difference between the two groups with regards to operative time, blood loss, University of Califoria Los Angeles (UCLA) activity score[49], Harris Hip Score[50], Short Form (SF) - 12 scores and complication rate. The study concluded that 'conversion of a MoMHRA with a femoral-side failure to a THA appears to be comparable with primary THA in terms of surgical effort, safety, and early clinical outcomes'. However, the outcome following revision for other causes of failure remains to be characterised.

2.2 Wear of MoMHRA

2.2.1 Tribology

Tribology is defined as the science and technology of interacting surfaces in relative motion and all practices related thereto, including wear, friction and lubrication[51]. The importance of the tribological understanding of materials used for hip arthroplatsy is highlighted by the association between wear debris, particularly polyethylene particles, and aseptic loosening[52] – the most common cause of failure in THA[28]. This finding has driven the search for lower wear bearing surfaces; logically reducing wear would reduce the future revision burden.

Wear of a bearing surface is defined as the progressive removal of material from contacting surfaces in relative motion[51]. Wear can be measured either as mass of material removed from the implant surface per unit time, or as the volume of material lost. Friction describes the force that opposes motion between articulating surfaces[51]. Lubrication between two bearing surfaces of hip implants and its effects on friction are illustrated by the Stribeck curve (Appendix 1). The low-wear characteristics of MoM bearings are related to the generation of either a full- or a partial- thickness lubricating fluid film between the implants. The lubricating film reduces wear by decreasing friction between the moving surfaces and sharing part of the load. Design parameters determining the probability of generating fluid-film lubration include femoral head diameter and clearance between femoral and acetabular components.

Wear in MoM bearings differs from the characteristic continuous linear wear of metal-on-polyethylene (MoP) bearings. MoM is characterised by an initial high wear, known as the run-in phase, followed by a lower wear rate termed as steady-state wear[53]. During the run-in phase, the high wear is thought to occur secondary to the removal of the surface asperities of the passive oxide layer or of the substrate by either adhesive (removal of asperities as a result of friction and cold welding) or abrasive (removal of softer material by hard asperities on countersurface and hard particles) wear and may be increased by forced conformity of the articulating surfaces during loading until all asperities are corrected. As the bearing surface is subjected to contact stresses, the micro-structure of the surface changes and can incorporate organic material from the lubricant fluid in the joint forming the tribolayer[54]; which generally has a finer grain structure than the bulk material forming the rest of the implant.

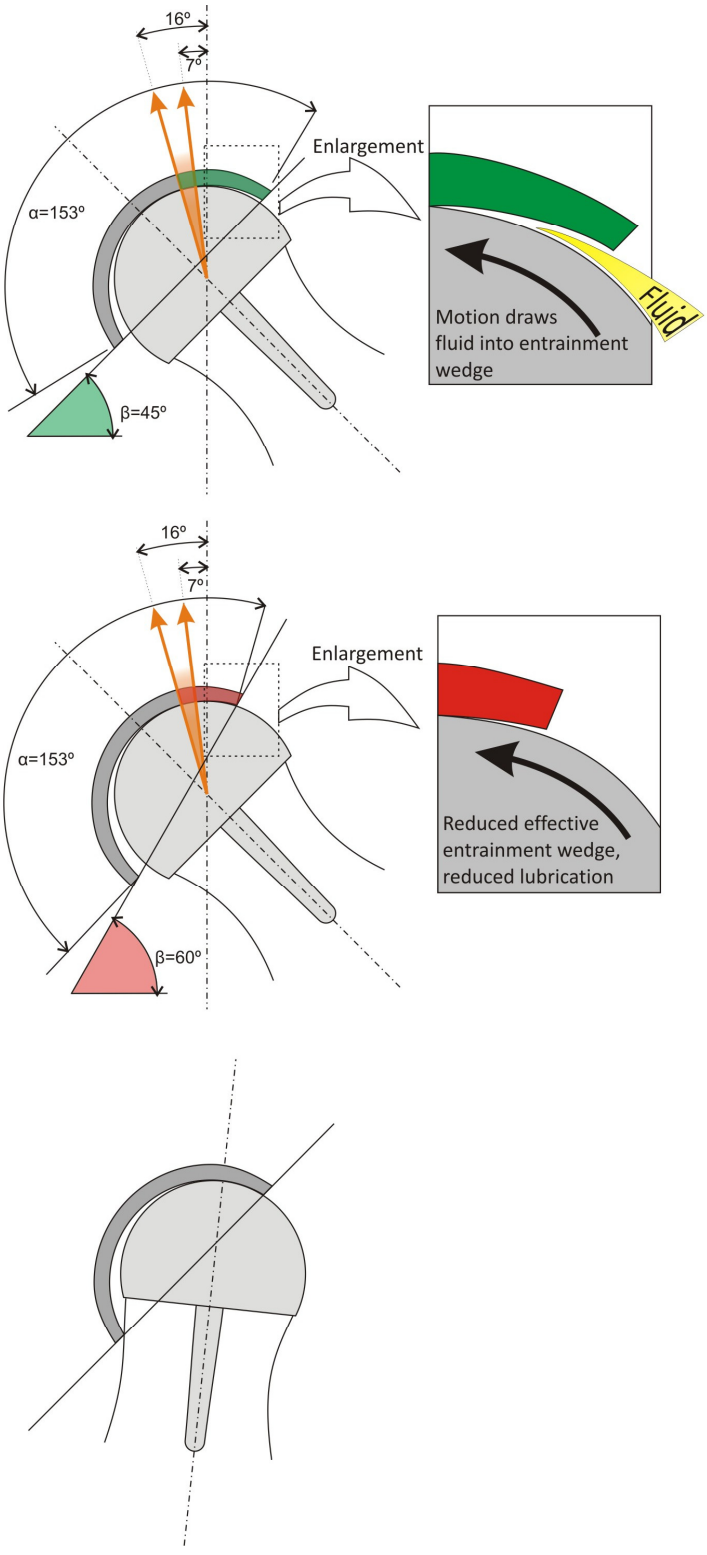
Wear-simulator studies have shown MoM bearings to have up to 100 times less wear than MoP bearings[55]. Similarly, hip joint simulator and retrieval studies have shown that MoM wear rates are sensitive to material properties (carbon content, material process, heat treatment), design (clearance, subtended angle of the acetabular component) and manufacturing process (surface roughness, tolerance, sphericity)[53,56]. As there is a wide variation of the aforementioned characteristics between different implant systems (Table 2.1), conclusions on wear regarding a specific implant may not necessarily apply to other implant systems.

2.2.2 Wear mechanisms

An active patient may subject a hip prosthesis to three million steps per year[57], each step representing a loading cycle which could potentially give rise to wear between the metal bearing surfaces even under optimal operating conditions. Simulation studies have shown that under optimal conditions, low volumetric wear rates exist, typically in the order of <1 mm^3 per million cycles[55], and wear debris particles produced are predominantly in the nanometre size range (40 to 80 nm)[58]. In order for low wear to occur, the femoral and acetabular components should be orientated in such a way that the contact patch (area of contact between the two components) does not occur at the edge of the acetabular component. This allows for an entrainment wedge to form. The presence of the entrainment wedge aids lubricant to enter between the bearing surface (Figure 2.2).

Lubrication is essential for optimal function of the MoM bearings; MoM implants exhibit increased wear when the fluid film lubrication is disturbed, leading to inability to form or maintain the tribolayer[54]. This typically occurs under edge loading conditions (contact patch on the head comes into contact with the edge of the rim), preventing the entrainment wedge effect and fluid entrainment[13]. Furthermore, finite element modelling has shown that edge-loading can double the contact stresses[59]. Both the femoral head and acetabular component have six independent degrees of freedom, three rotational and three translational. Edge loading could theoretically occur as a result of either rotational or translational mal-positioning. Simulator studies have shown that rotational mal-positioning can lead to wear of 1 to 5 mm^3/ million cycles, whilst translational mal-positioning has

been shown to further increase wear rate as much as 10 to 100 mm^3/ million cycles[60-62]. Rotational malpositioning leading to edge loading (1° edge loading) occurs when the acetabular component is implanted with excessive inclination or inappropriate version. Translational mal-positioning occurs when impingement or joint laxity (e.g. decreased offset, medial or superior translation of the centre of acetabular rotation) would lead to levering out of femoral head and contra-coup edge loading occurs (2° edge loading).



Well functioning:
Contact well within acetabular component, adequate lubrication with diametric mis-match between femoral and acetabular components creating an entrainment wedge. Orange vectors indicate range of measured coronal hip joint contact forces from Bergmann et al.

Under a low wear regime a *tribolayer* can form, the micro-structure of the surface changes and can incorporate organic material from the fluid in the joint.

Primary Edge Loading:
Contact closer to edge of acetabular component, reduces potential for lubrication entrainment, reduced effective entrainment wedge. As contact moves to the edge, lubrication becomes more disturbed. As included angle (α) of acetabular component becomes smaller and inclination angles (β) becomes larger, the risk of primary edge loading increases.

Secondary Edge Loading:
Impingement between bone and acetabular rim causes contra-cue edge loading, and disrupts lubrication.

Edge-loading increases contact stress. In high contact stress conditions tribolayers are not found, and are thought to have either not formed or have been worn away.

Figure 2.2: Schematic of well functioning, primary and secondary edge loading conditions and the consequences for lubrication and development of a tribolayer. Data on hip vectors (orange vectors) is from the studies of Bergmann *et al*[2]

2.2.3 Metal wear particles

Cobalt (Co) and chromium (Cr) are the principal elements of the CoCr alloy used in all MoMHRAs (Appendix 2). Both Co and Cr are naturally occuring trace elements vital for biological function. Co is a co-factor for vitamin B_{12} and Cr is an essential co-factor in the interaction between insulin and its receptor[63].

Although the wear rates of MoM implants are lower than the conventional MoP articulation, the number of nanometre sized particles produced is greater than the number of micrometre sized particles produced in MoP articulations. For a MoM hip implant, it has been estimated that an average of 6×10^{12} to 2.5×10^{14} particles are being produced per year, which would equate to 500 times more particles than a MoP articulation (5×10^{11} particles/year)[58]. The size of the particles is thought to vary between 30 nm to 500 nm[58,64]. The majority are oval in shape, although some appear to be needle shaped. Most of the smaller particles have been shown to be chromium oxide, whilst the larger ones are cobalt-chrome-molybdenum (CoCrMo) particles[58,64].

The origin of the wear particles is hypothesised to be the implant surface. Different wear processes as described previously are thought to lead to different particles. Under optimal low-wear conditions, the wear debris are thought to arise from the tribolayer; the grain size of the tribolayer material is similar to that of wear particles isolated from well functioning devices, which are between 30 to 80 nm in size[54]. The formation of a tribolayer requires a low wear regime, with adequate lubrication and relatively low contact stress. In high contact stress

conditions, tribolayers are not found, and are thought to have either not formed or have been worn away. When a tribolayer is not present, the wear particles generated are generally larger. *In vitro* wear studies indicate that particles in the size range of 100 to 500 nm are generated under these conditions and these are thought to be derived from the bulk material[64].

2.2.4 Metal ions

MoM wear debris may exist in a number of states, including metallic particles produced by mechanical wear and the products of corrosion[65] (destruction of material caused by interaction with the biological environment[51]). Exposure to extracellular fluid leads to the formation of a passive layer of corrosion upon all exposed surfaces of metal including the articulating surface and wear debris[66]. X-ray photoelectron spectroscopy (XPS) analysis of this corrosion layer reveals high levels of carbon, oxygen, nitrogen and chromium compounds, with trace amounts of metallic and oxidised cobalt[67].

These constituents may dissolve in both intra- and extra-cellular fluids leading to the presence of ionic species namely Co^{2+}, Cr^{3+} and possibly Cr^{6+} [68,69]. A study by Milosev *et al*[67] confirmed the presence of Cr^{6+} compounds by identifying chromium (VI) oxide (CrO_3) within the passive layer of corrosion along with chromium (III) oxide (Cr_2O_3), and chromium (III) hydroxide ($Cr(OH)_3$). However, Hart *et al*[70] analysed implant-derived debris from retrieved hip capsules and found Cr^{3+} to the most abundant metal in the form of chromium phosphate. No Cr^{6+} could be detected in the tissue, whilst Co and Molybdenum were only

occasionally present. The metal ions released from the metal particles are thought to produce more profound effects, than the metal particles themselves, as they have been shown to circulate freely in the body[71]. Depending on the chemistry of the biological environment, various corrosion products can be produced including metal-protein complexes, inorganic metal oxides and salts[72].

The rate of corrosion is not known and depends on the local environment[73]. Germain *et al*[74] whilst investigating the effect of particles on cell cultures observed *in vitro* that metal ion levels in the solution increased very rapidly within 24 hours. One possible interpretation was that the majority of metal particles generated corrode rapidly and hence the circulating metal ion levels reflect on the rate of production of wear debris.

2.2.5 Metal excretion

As both cobalt and chromium are trace metals, they are mostly eliminated via gastro-intestinal and renal excretion[73]. The majority of excretion occurs via the kidneys, with little excretion occuring via sweat glands and through faeces[75].

Therefore, kidney disease may interfere with metal clearance, leading to systemic accumulation. Brodner *et al* reported on elevated ion levels in patients with end-stage chronic renal failure that normalised following renal transplantation[76].

The potentially detrimental effects of metal ions on kidney function have been investigated in both animal models and *in vivo* with patients with MoM hip arthroplasties. Daniel *et al* investigated whether the renal excretion threshold is exceeded at higher metal levels and found no evidence of cumulative build-up even at high levels of metal generation[77]. Similar results of increased Co clearance with increased Co serum level were reported in a heterogenous group of unilateral and bilateral MoM hip arthroplasties *in vivo*[77]. Marker *et al* investigated serum metal ions and creatinine clearance in a group of unilateral and bilateral MoM hip arthroplasty patients and found normal level of creatinine clearance in all patients[78].

2.2.6 Wear measurement

2.2.6.1 Wear measurement *in vivo*

Measurement method

The concentration of trace metals in the human body is so small (order of parts-per-billion) that introduces a significant contamination risk when measured. In addition, the analytic tools used to measure ion levels are operating at close to the qualitative and quantitative limits of the equipment. As a result, adherence to strict protocols aiming to reduce contamination risk, rigorous calibration and operator expertise is paramount in order to avoid measurement error and produce sound data[79].

Metal ions can potentially be measured in all body fluids including whole blood, serum, urine and joint fluid. At collection, needles, syringes and collection tubes used should be verified as being contamination free. Furthermore, at venepuncture, a plastic needle should be used instead of a metallic one or the first few milliliters should be discarded if collected with a metallic needle. Specimens should be stored and processed in a way verified by the laboratory to be contamination risk-free. Madonald *et al* [79]have a described a consensus protocol. An exaple of local practise would be to perform venepuncture using a disposable Venosafe (Terumo Europe NV, Leuven, Belgium) 21-gauge stainless-steel needle. The first 5 millilitre (ml) of withdrawn blood is discarded in order to minimise contamination risk. All collected samples are places into 6 ml vacuum tubes (Venosafe VF-106SAHL, Terumo Europe NV, Leuven, Belgium), kept at room temperature and are transported overnight. The tubes used have been verified to free of any metal parts that could act as a source of contamination.

Urine analysis requires a 24-hour urine sample as metal ion levels from spot urine test vary pending on hydration level[80]. Although there is good correlation of ion levels between blood and 24-hour urine sample[81], the latter is more difficult to reliably obtain and introduces a higher likelihood of contamination by the patient. Thus, blood analysis is usually reported in the literature. In blood, metal ions are transported both in the plasma and the erythrocytes. As some metals, especially Cr, may not be in dynamic equilibrium with the extracellular environment, serum analysis leads to different concentration measurements in comparison to whole blood[82,83]. However, blood analysis requires a matrix digestion protocol which may increase risk of contamination. In a consensus statement on metal ions,

MacDonald *et al* recommended that due to the relative ease of analysis, all future studies should report on the metals in serum for comparison purposes[79].

Inductively coupled-plasma mass spectroscopy (ICP-MS) has been shown to improve the detection limits compared to graphite furnace atomic absorption spectrophotometry (GF-AAS)[79]. The high temperature of the inductively coupled argon plasma ion source breaks the sample components into charged ions, which are then separated based on atomic mass-to-charge ratio. The ICP-MS can detect more than one element at once, reducing the sample size and time needed. High resolution overcomes the interference caused by complex matrices in whole blood[84].

Metal ion level measurement units

Metal ion levels from laboratories are either expressed as micrograms per litre (µg/l) or nanomoles per litre (nmol/l). Micrograms per litre (µg/l) concentration measurements are the same as the concentration units of ppb (parts per billion) and nanograms per millilitre (ng/ml).

The conversion from µg/l to µmol/l is done by dividing the value expressed in µg/l by the atomic weight of the specific metal ion which is 51.996 for Cr and 58.933 for Co. In order to convert from µg/l to nmol/l, one can multiply the µg/l results with a factor 19.23 (=1000 : 51.996) for Cr, and with a factor 16.97 (=1000 : 58.933) for Co.

Metal ion levels in the general population

Muniz *et al* established the reference values of trace elements in 59 normal, healthy subjects (control) using ICP-MS[85]. The serum cobalt levels were ≤0.15 µg/l with a limit of detection of 0.02 ppb and serum chromium levels were ≤0.26 µg/l with a detection limit of 0.01 ppb.

Metal ion levels in MoM hip arthroplasty

Published reports on contemporary MoMHRA designs have shown higher serum Co and Cr levels when compared to pre-operative values (Table 2.3). Serum metal ions have been prospectively measured in a number of studies which show a peak of ion levels within the first 12 months followed by a gradual decline. Metal ion levels in MoMHRA have shown to be higher in comparison to MoP THA[47].

Metal ion levels as a marker for wear

Assessing metal ion level in serum is a valuable tool in the evaluation of the extent of wear in patients with MoM hip arthroplasties[86]. As radiographic assessement of wear is not possible in MoM bearing couples, blood concentrations have been considered as a surrogate marker of wear.

De Smet *et al* showed that the linear wear measurements (maximum depth of wear scar) of 26 retrieved femoral components significantly correlated with serum metal ion (Cr^{3+} and Co^{2+}) measurements[87]. Similar observations were reported by

Hart *et al* in 55 failed BHRs; patients with higher ion (Cr^{3+} and Co^{2+}) levels pre-revision had implants with greater material loss[88].

Study	Implant	Analytic Technique	Sample	No. of implants	Mean follow-up/ months	Median Co level/ ppb	Median Cr level/ ppb
Back *et al* 2005[89]	BHR	ICPMS (Co) / GFAAS (Cr)	Serum	20	Pre-op	0.3	0.3
					3	2.9	3.9
					6	3.3	4.4
					12	2.4	4
					24	1.9	3.5
Kim *et al* 2006[90]	C+	ICP-MS	Erythrocyte	60	12	0.8	1.2
			Serum		12	1.1	1.9
			Erythrocyte		24	1.1	1.2
			Serum		24	1.6	3.3
Smolders *et al* 2011[83]	C+	ICP-MS	Whole blood	60	Pre	0.1	0.1
			Serum	60	Pre	0.1	0.1
			Whole blood	51	6	1.3	1.2
			Serum	51	6	1.2	1.9
			Whole blood	42	12	1.4	0.9
			Serum	42	12	1.3	2.3
			Whole blood	21	24	1.2	1.1
			Serum	21	24	1.5	1.9
Allan *et al* 2007[91]	Cormet	ICMP-MS	Serum	37	6	3.7	4.5
					12	4.3	5.1
					24	2.8	3.8
					36	2.6	4.3
Vendittoli *et al* 2007[92]	Durom	ICP-MS	Whole blood	64	Pre-op	0.2	0.9
				50	3	0.9	2.0
				51	6	0.8	1.9
				53	12	0.7	1.6
				27	24	0.6	1.4

Table 2.3: Reported metal ion levels in MoMHRA patients.

2.2.6.2 Wear measurement *ex-vivo*

Two methods are commonly used to measure bearing surface wear. The wear can be measured gravimetrically by sequential measurements of any weight loss of the material[55,93]. Wear is then presented as the weight loss of the material, which is converted to the volumetric loss of the material. In hard-on-hard bearings, the volume of material removed is small compared to the mass of the component and as a consequence it is difficult to assess small mass changes against large component masses. Furthermore, in the case of explanted bearings the use of gravimetric methods is not feasible as there is no 'zero-cycle' (i.e. pre-wear) data.

Alternatively, wear can be measured by scanning the bearing profile and comparing this to the original manufactured shape; wear is therefore quantified as the maximum deviation from the ideal sphericity[94,95]. This method allows determination of both the magnitude and the location of wear. Established methods of measuring wear by scanning the bearing profile include the use of a roundness machine, a Coordinate Measuring Machine (CMM) or the use of the Artificial Hip Profiler (AHP, RedLux Ltd, Southampton, UK).

The roundness machine measurement method has previously been used both in ceramic-on-ceramic bearings and MoMHRA[11,96]. It is a two dimensional (2-D) method, that provides information around the bearing surface by measuring deviations in roundness, with a resolution of ten nanometers. It can evaluate discrete surface traces and hence enables comparison between the worn and unworn surfaces. It is well suited to measure linear wear. The machine measures

both partial and full circles and hence determines the roundness of both components in several planes. Provided enough measurements in various planes around the joint are made and the deepest point of the wear scar is found, the maximum linear wear value can be determined. It has been used to demonstrate the morphological pattern of edge wear occuring with MoMHRAs.

CMM provides a three-dimensional (3-D) image of the joint by scanning the surface with a stylus[94,97]. Approximately 300 to 400 points along equally spaced traces radiating from the centre of the implant-bearing-surface are digitised in order to produce the image. The computer software enables the operator to fit a sphere to the points. The radial distance of the data points from the surface to the sphere indicates the local depth of wear. The resolution of the CMM is smaller (i.e. worse) than that of the roundness machine (1µm vs 0.01µm). Furthermore, the wear data on acetabular components has been shown to be unreliable in cases with insufficiently worn surface because in such cases, the software can not accurately fit a nominal sphere.

The AHP is a novel, validated, technique that utilises an optical CMM. It is able to measure spherical bearing surfaces with a resolution of 20 nm and allows for typically 30,000 points to be traced along the bearing surfaces[12,95]. The system software allows for the 3-D point cloud to be analysed. It calculates a best-fit sphere to the unworn part of the component and computes the deviation from the best-fit sphere at each point, thus determining the wear area. The software is also able to estimate the wear volume. The AHP has been proven to estimate linear

wear with a similar accuracy to a roundness machine and volumetric wear with a similar accuracy to gravimetric measurements[12,98].

2.2.6.3 Factors influencing wear

There is recent evidence to suggest that *in vivo* wear is influenced by many factors including material properties, implant design, implant size, and patient gender. However, it is often difficult to compare studies due to variations and differences in the study design, matrix of analysis, implants used, surgical technique and patient cohort.

Vendittoli *et al* measured whole blood ion levels in patients with the Durom hip resurfacing system (Zimmer, Warsaw, IN, USA), which has a high carbon-content, wrought CoCr alloy (Table 2.3). The authors reported lower ion levels in the study's patient cohort in comparison to other hip resurfacing designs[92].

Langton *et al* compared the whole blood ion levels of the ASR prosthesis and the BHR in a single surgeon series (n=160)[99]. The ion levels were inversely related to the component size for both groups. There was no statistically significant difference in the ion levels between the two design groups. However, patients with acetabular components with high inclination had higher ion levels in the ASR group in comparison to the BHR group. The difference observed was attributed to the difference in the subtended angle of the two designs (Table 2.1) The subtended

angle (α angle) of a component influences the arc of cover of an acetabular component as illustrated in Figure 2.2.

Surgical factors have also been shown to contribute to the wear process. De Haan *et al* found significantly higher metal ions levels (Cr^{3+} and Co^{2+}) in females and in patients with steeply-inclined acetabular components (radiological cup inclination > 55°) and observed that ion levels correlated significantly with the arc of cover of the acetabular component[100]. The arc of cover is influenced by component size, subtended angle of cup and cup inclination (Appendix 3). A coverage arc of less than 10 mm was correlated with a greater risk of higher ion levels.

Similarly, Langton *et al* described an association between Contact Patch-Rim (CPR distance) and serum ion (Cr^{3+} and Co^{2+}) levels[99,101]. No large values of ion levels were detected in patients with cups with CPR distance greater than 15 mm. The CPR distance takes into consideration Bergmann's joint reaction force data[2], radiographic cup inclination and anteversion, component size and α angle (Appendix 4). Bergmann's data shows that the hip joint contact force is directed 14° infero-laterally in the anteroposterior (AP) plane and 14° anteriorly in the sagittal plane.

Hart *et al* reviewed the component orientation in 45 patients with failed implants and correlated component wear, measured with a roundness machine, with component orientation measured with computer tomography (CT)[102]. The authors noted that cup inclination strongly correlated with *ex vivo* wear, whilst cup

anteversion and combined anteversion (femoral and cup anteversion) only weakly positively correlated.

2.3 Systemic adverse consequences of wear particles

The systemic consequences of high cobalt related to malfunctioning MoM arthroplasties (arthro-prosthetic cobaltism) have been reported in patients presenting with a variety of neurological, cardiological and endocrine symptoms [103].

Due to their small size and large numbers, nanoparticles have the potential to disseminate systemically, with possible cytotoxic, genotoxic and immunological consequences, both local and distant to the implant. It may be necessary to map the systemic distribution of MoM wear particles in order to fully appreciate their biological consequences. Urban *et al* described the widespread dissemination of metallic debris from orthopaedic cobalt chromium alloys to local and distant lymph nodes, bone marrow, liver and spleen with associated necrosis and fibrosis of lymphoid tissue[104]. The study focused on micron-sized metal particles from MoP prostheses which were of non-bearing origin. Thus, the findings may not be representative of, and probably underestimate, the distribution of CoCr nanoparticles from the bearing surfaces of MoM implants.

2.3.1 Cellular

The cytotoxic effect of nanosized wear particles is poorly understood, with much of the present knowledge coming from *in vitro* reports; how well this evidence translates to the *in vivo* situation remains unclear.

Of particular relevance to pseudotumours are the studies on macrophages and lymphocytes, as both of these cells are reported by histological studies of pseudotumours. Kwon *et al* reported a significant dose dependant decline in macrophage viability with cobalt nanoparticles (30 to 60 nm) and Co^{2+} ions; however chromium nanoparticles and Cr^{3+} failed to produce a significant reduction in cell viability at the same concentrations[105]. The increased cytotoxicity capability of cobalt ions over chromium ions was also reported in an earlier study by Catelas *et al*[106]. The authors were able to demonstrate a significant reduction in macrophage viability occurring at 8 to 10 ppm for Co^{2+} and 350 to 500 ppm for Cr^{3+} ions.

The effects of Cr^{6+} and Co^{2+} on human lymphocyte number and function were studied by Akbar *et al*[107]. A significant reduction in cellular viability and increase in apoptosis was seen with high concentrations (10 – 100 μM) of both ions. Cell proliferation and function (i.e. cytokine release) were affected with non-toxic concentrations. Similar to previous studies, lymphocytes appeared to be more susceptible to Co^{2+} than Cr^{6+}.

The mechanism of fibroblast cell death in response to CoCr nanoparticle exposure was studied by Papageorgiou *et al* using electron microscopy[108]. They reported an accumulation of well defined nanoparticles outside the cell which then appeared to cross the cell membrane and disintegrate within cellular vacuoles. There was damage to the membranes of these vacuoles, along with free electron dense material and randomly distributed nanoparticles in the cytoplasm, and corrosion products within the nucleus. Visible cellular changes included intracellular lipid droplets, electron dense mitochondria and cytoplasmic blebbing - an indication of cellular metabolism disruption.

The size of the wear particles produced may also be an additional factor determining the type of response. Yue *et al* examined the effect of particle size on macrophage cellular response, and reported that nanoparticles accumulate at a faster rate than micron sized particles in macrophages[109]. Nanoparticles were found to transport within the macrophage via the lysosomal pathway, whilst larger particles accumulated in the cytoplasm.

2.3.2 Genotoxicity

A variety of transition metals are known to be mutagenic and genotoxic at relatively low concentrations, a result of metal induced oxidative stress, chromosomal aberration, or disruption to DNA repair and maintenance mechanisms. Currently, the International Agency for Research on Cancer (IARC) has classified implanted metallic cobalt as class 2B – "possibly carcinogenic to humans", and implanted metallic chromium as "not classifiable"[110,111]. However,

compounds containing hexavalent chromium are described as class 1 – "carcinogenic to humans".

There have been several *in vitro* studies demonstrating the mutagenic and genotoxic effects of Co and Cr (Table 2.4). Cobalt is considered less genotoxic than chromium. Co exerts its genotoxic effects through single-strand breaks, cross-linking and inhibiting DNA repair mechanisms. Chromium is thought to induce DNA damage through the production of reactive oxygen species when Cr^{6+} is reduced to Cr^{3+}. In addition, Cr^{3+} can induce DNA damage via cross-linking, single and double-strand breaks and stable Cr-DNA adducts. *In vivo* studies on peripheral lymphocytes of MoM patients showed increased lethal and non-lethal aneuploidy and chromosomal translocations[112] that correlated with metal ion levels. The detectable genetic damage was reduced following revision to a MoP device.

Study	Technique Used	Cells Studied	Findings
Ladon *et al* 2004[112]	*In vivo* Fluorescent in situ hybridization (FISH)	Leucocytes	Significant increase in chromosomal translocations and aneuploidy compared to pre-operatively. Both were progressive with time but did not correlate with ion concentrations.
Baldwin *et al* 2004[113]	*In vitro*	Human Macrophages	Co^{2+} is a Topoisomerase II poison. There was an increase in enzyme-mediated DNA scission, partially due to a decrease in the rate of enzyme-mediated relegation.
Papageorgiou *et al* 2007[108]	*In vitro* Nanoparticles, Microparticles of CoCr. Electron paramagnetic resonance. Comet, Micronucleus, MTT assays. Scanning Electron Microscopy (SEM)	Human Fibroblasts	Both nanoparticles and microparticles caused DNA damage (single/double strand breaks and alkaline labile sites) in a dose-dependent manner. The different-sized particles may induce damage via different mechanisms (free radical, oxidative stress, damage to mitochondria proteins, inhibition of DNA repair).
Dunstan *et al* 2008[114]	*In vivo* FISH	Leucocytes	Elevated number of chromosomal aberrations (structural damage and aneuploidy gain) was detected in the MOM group in comparison to a control group and a revised from MOM group. A reduction in the number of chromosomal translocations was only seen in MOM group. Chromosomal aberrations were reduced in the revised MOM group in comparison to the MOM group.
Colognato *et al* 2008[115]	*In vitro* CoCr Nanoparticles, Co^{2+} ions, Cytokinesis-Block-Micronucleus-Assay, Comet Assay	Leucocytes	Both nanoparticles and ions caused DNA damage at subtoxic concentrations. Co^{2+} induced a greater number of binucleated micronucleated (BNMN) cells, whilst Co nanoparticles induced a greater amount of DNA tail fragmentation.
El-Yamani *et al* 2011[116]	*In vitro* Cr^{6+}, Cr^{3+} , Comet Assay	Human Lymphoblastoid Cells	Both compounds were genotoxic, Cr^{6+} more than Cr^{3+}. DNA damage occurred via oxidative damage. The repair mechanism was shown to be inhibited by both compounds.
Andrews *et al* 2011[117]	In vitro Co^{2+}, Cr^{3+}, Cr^{6+}	Human Osteoblast and Osteoclasts	Co^{2+} and Cr^{3+} did not affect osteoblast survival or function. Cr^{6+} reduced osteoblast survival and function. Osteoclasts were more sensitive to ions. A reduction in number and resorption was observed with all ions

Table 2.4: Genotoxicity findings associated with cobalt and chromium.

2.3.3 Carcinogenesis

Despite the above conclusions, thus far, no clinically relevant complications have been attributed to these effects. Visouri *et al* showed no increase in the incidence of any type of cancer and reported mortality rates of patients who had a MoM device implanted equal to, or lower than those of the general population[118,119].

2.3.4 Metallic wear and immune system interaction

Several reports have raised concerns regarding immunotoxicity caused by wear debris from MoM implants. Some cohort studies have suggested that patients with MoM devices are at a higher risk of developing lymphopenia, and metal hypersensitivity. In a cohort of 105 patients with hip implants, Hart *et al* noted lymphopenia in 15% of cases and observed an inverse correlation between metal ion concentrations in whole blood and circulating lymphocytes[120].

Although CoCr orthopaedic metals comprise alloys of the most common dermal sensitisers, the extent to which hypersensitivity may correspond to clinical problems and pseudotumours is unclear. This is partly due to limitations in the current ability to diagnose and distinguish between dermal and deep tissue hypersensitivity reactions, and a lack of longitudinal studies of the relationship between implant failure and metal hypersensitivity.

Type IV hypersensitivity reactions result from T-lymphocyte sensitisation and activation by Antigen Presenting Cells (APC). These cells present peptide/metal ion complexes to CD4+ T-lymphocytes. Thereafter, T-lymphocytes and macrophages produce cytokines (IL-1, TNF-α, IL-2 and IFN) and propagate a type IV immune response.

As it was considered that hypersensitivity may have played a role in the development of pseudotumours, there have been a number of studies examining the prevalence of hypersensitivity and its correlation to pseudotumour development (Table 2.5). The findings of Kwon *et al* suggest that, in most cases, hypersensitivity probably does not play a dominant role in the development of pseudotumour[121].

Study	Technique	Cohort	Findings
Hallab *et al* 2004[122]	Lymphocyte Transformation Test (LTT)	9 MoM, 7 MoP patients and 12 controls	MoM group demonstrated elevated lymphocyte reactivity to Co and Ni. The amount of reactivity correlated with metal ion levels.
Park *et al* 2005[123]	Patch Test (PT), microbiological cultures, histopathological and immunohistochemical examinations	18 MoM patients; 9 with evidence of osteolysis and 9 without	Patients with osteolysis had a higher rate of hypersensitivity reaction to Co (8/9) in comparison to controls (2/9). There was peri-vascular accumulation of CD3-positive T-cells and CD68-positive macrophages producing cytokines such as IL-1β and TNF-α
Kwon *et al* 2009[121]	LTT	92 patients; 10 patients with pseudotumour following MoM, 60 patients with well-functioning MoM and 22 controls without metal implants	A higher incidence of LTT to Nickel was found in patients with MoM in comparison to controls. LTT results did not differ between well-functioning MoM and those with pseudotumour.
Thomas *et al* 2009[124]	LTT, PT	16 failed MoM with lymphocyte dominated peri-prosthetic tissue.	In 81% of patients systemic metal sensitivity was found (PT and/or LTT positive). Cutaneous metal allergy was only seen in 25% of patients.
Thyssen *et al* 2009[125]	PT	Case control matched: 356 with dermatitis and 712 controls that received 1° THA between 1979-2007.	Risk of revision was not increased in patients with metal allergies and the risk of subsequent metal allergy was not increased in cases operated.

Table 2.5: Studies investigating the clinical prevalence of metal hypersensitivity in Metal-on-Metal arthroplasty cohorts (MoMHRAs and THAs).

2.4 Local adverse periprosthetic soft tissue masses

2.4.1 Terminology

In 2008, Pandit *et al* reported the first significant series of soft tissue masses associated with MoMHRA[8]. These soft tissue masses tended to be of either a solid, cystic or mixed nature. Clinically, patients presented with a variety of symptoms including pain, clicking, clunking, skin rash, palpable mass, dislocation or neurovascular compromise. In addition, in the initial biopsy of these cases it was difficult to morphologically distinguish these masses from a necrotic tumour. Based on these obervations, these soft-tissue masses were termed "pseudotumour".

Other terms have also been used to described these masses including aseptic lymphocytic vasculitis-associated lesions (ALVAL), cyst[7], mass[126], bursae[127], metal sensitivity[128], Adverse Reactions to Metal Debris (ARMD)[129] and Adverse Local Tissue Reaction (ALTR)[130].

Unfortunately none of the names are ideal. Although the names have different definitions they all appear to cover different parts of the spectrum of reactions to metal. For example, metal sensitivity implies a hypersensitivity reaction but might exclude the toxic effect of metal debris. ALVAL is a histological diagnostic feature present in the majority of MoM revisions and not uniquely associated with these masses[131]. A cyst or a bursa implies a fluid collection with a relatively thin capsule and excludes a mass. Conversely, an inflammatory mass might exclude a

cyst. A pseudotumour is, by definition, an enlargement that resembles a tumour, resulting from inflammation, fluid accumulation, or other causes[132]. It, therefore, covers the whole spectrum but also, like some of the other descriptions, includes lesions that could be unrelated to a MoM articulation. The term pseudotumour has been used previously to describe ill-defined masses in orthopaedic[133] and other medical specialities' literature[134,135]. It is, however, a controversial term as for the non-medical audience it has implications of cancer. Nevertheless, the word pseudotumour is an 'umbrella term' and is particularly useful as it describes the problem without implications about its cause; thus it will be used to describe these lesions in this manuscript. In the context of MoMHRA pseudotumours are neither malignant nor infected. They cause a spectrum of damage ranging from a small indolent cyst or mass to local invasion with substantial soft tissue destruction and sometimes bone destruction[136].

2.4.2 Concern in orthopaedic and general public communities

There has been much concern raised by recent reports of pseudotumours associated with MoM hip arthroplasty devices both in the media and peer reviewed literature. Although the initial reports were largely dismissed, the progressively increased number of cases have led to the Medicines and Healthcare products Regulatory Agency (MHRA)[137,138] and the British Hip Society issuing alerts and the recall of the ASR MoM implant by DePuy (Warsaw, IN, USA). Since the ASR recall, over 5,000 complaints concerning MoM implants have been made to the Food and Drug Administration (FDA) in the USA and an increasing number of lawsuits are being filed.

2.4.3 Patho-aetiology

Pseudotumours are thought to occur secondary to a reaction to wear derbis. Kwon *et al* showed that pseudotumours were associated with elevated levels of metals ions in patients serum and hip aspirates, which are surrogate markers of wear[47,87]. There was up to a six-fold elevation of serum metal ion levels and thirteen-fold elevation of hip aspirate metal ion levels in patients with pseudotumours compared to patients without pseudotumours. Similarly, Langton *et al* showed that hips with pseudotumours had elevated serum chromium and cobalt ion levels in comparison to asymptomatic controls[129].

In vitro analysis of explants has demonstrated high wear rates of both the femoral and acetabular components. When compared to controls, both the femoral and acetabular components of pseudotumour cases demonstrated higher linear wear[11].

Glyn-Jones *et al*[12], measured the wear of failed MoMHRAs using the AHP and compared the linear and volumetric wear between pseudotumours and controls (revised due to other reasons) in a case-control study. These authors reported significantly higher (linear and volumetric) wear in the pseudotumour cases compared to the controls. In addition, there was a significantly higher prevalence of edge wear in pseudotumour cases compared to controls. The authors also noted that two out of the 18 pseudotumour implants were asociated with low wear (<4 µm/year), which raises the possibility that excessive wear is not the sole driving force to pseudotumour development and that the individual response to any amount of wear might vary substantially. Similarly, the observation that four out

of the 18 controls had high wear (>4 μm/year) and did not develop a pseudotumour re-inforces the above hypothesis. These findings have led to the hypothesis that pseudotumours can occur either as an aftermath of metal reactivity/toxicity (expected response to an excessive/toxic wear load) or as a response of metal sensitivity (exacerbated response to an expected amount of wear load).

2.4.4 Patient presentation

Pandit *et al* reported on the possible presentation of patients with pseudotumour[8]. The most common presenting symptom was discomfort, either in the groin, on the lateral aspect of the hip or in the buttock. Patients may also present with generalised (rash, lump), neurological (femoral or sciatic) or mechanical (clicking, clunking, giving way) symptoms. Late dislocation or fracture should also alert clinicians to the presence of a pseudotumour and merit further investigations. These authors suggested that since there is no typical presentation, all MoMHRA patients with unexpected symptoms should be investigated.

Kwon *et al* reported on the prevalence of pseudotumour amongst 200 MoMHRAs and reported that patients with previously undiagnosed pseudotumours had lower Oxford Hip Score (OHS)[139] and were found to be mildly symptomatic[47]. Patients may also present with a variety of neurological, cardiological and endocrine symptoms secondary to arthro-prosthetic cobaltism[103]. Blood indices, other than metal ions, are usually within normal parameters and hence further radiological investigations are necessary to aid diagnosis[8].

2.4.5 Radiological findings

Traditionally, plain radiographs have formed the basis of prosthesis evaluation and investigation in cases with a symptomatic hip arthroplasty. Radiographs are able to show several bony pathologies around MoMHRAs such as femoral neck fracture, bone erosion due to impingement, osteolysis and lucency at the bone-cement interface. However, they are not considered sensitive enough for the detection of periprosthetic masses. In a study by Johnston *et al,* although 28 out of 96 patients with post-operative symptomatic MoM hip arthroplasties had no radiographic findings, they all had positive findings on MRI[140].

The use of ultrasound scans (USS), computer tomography (CT) and magnetic resonance imaging (MRI) in the evaluation of the prosthetic hip joint and surrounding tissues has been recommended as a mode of investigation in the radiological literature. Fang *et al* described the imaging spectrum of pseudotumours with the use of USS, MRI or CT[141]. They stated that USS is the preferred method of initial investigation as CT scans and MRI images may be degraded by the metal artefact. Ultrasound provides a good first-line modality in identifying a possible mass and can differentiate between solid and cystic masses. However, it is operator dependent and may not clearly show deeper lesions due to limited transmission. The authors also noted that the extent of the abnormality, the characteristics of the lesion and the possible communication with joint are better appreciated on cross-sectional imaging, either with MRI or CT.

MRI, like ultrasound, does not expose the patient to radiation[142], offers excellent soft tissue delineation compared to CT and is now recognised as an effective modality in the assessment of the hip arthroplasty, especially where soft tissue pathology is suspected[140,143]. Soft tissue is defined as the supportive, extra-skeletal tissue of organs other than epithelial tissue. It includes connective tissue, adipose tissue, skeletal muscle, blood and lymph vessels, and peripheral nerves.

Toms *et al* characterised peri-prosthetic tissues in painful MoMTHAs and described findings of soft tissue mass of variable size/diameters (mediolateral: 2.5 to 10 centimetre (cm), antero-posterior: 1.5 to 10 cm, cranio-caudal: 3 to 30 cm and associated mucle oedema, mucle avulsion, bone marrow oedema, and calcar fracture[144].

Hauptfleisch *et al* presented a radiological (MRI) classification system for these masses, dividing them into three classifications based on the nature of the lesion[145]. The lesions were described as cystic or predominantly solid. Cystic lesions were those in which the cystic component was dominant and greater in dimension compared to the solid component of the pseudotumour. The predominantly cystic lesions were further divided into two types: Type I with cyst wall thickness of less than 3 millimetre (mm) and Type II with cyst wall thickness greater than 3 mm. Type III lesions were predominantly solid lesions, where the largest dimension of the solid components was greater than the diameter of the cystic components. The authors noted that Type III lesions were the largest in size and were associated with more symptoms.

Similar type of MRI classification systems have been desrcibed by other authors. Matthies *et al* described pseudotumour type of lesions based on wall thickness (thin, thick or solid – cutoff of 2 mm), contents (hypointense, hyperintense) and shape[146]. Similarly, Anderson *et al* described the classification system used in their centre for these lesions into three C types (1 – 3) based on severity of disease (mild/moderate/severe)[147]. C1 type referred to a periprosthetic soft tissue mass with no hyperintense fluid signal or fluid-filled peri-prosthetic cavity; either being less than 5 cm maximum diameter. C2 type referred to a peri-prosthetic soft tissue mass/fluid-filled cavity greater than 5 cm diameter or C1 lesion with either of following: (1) muscle atrophy or edema in any muscle other than short external rotators or (2) bone marrow edema: hyperintense on STIR (Appendix 5). Lastly, C3 referred to a pseudotumour with any one of the following characteristics: (1) fluid-filled cavity extending through deep fasci, (2) a tendon avulsion, (3) intermediate T1 soft tissue cortical or marrow signal, (4) fracture.

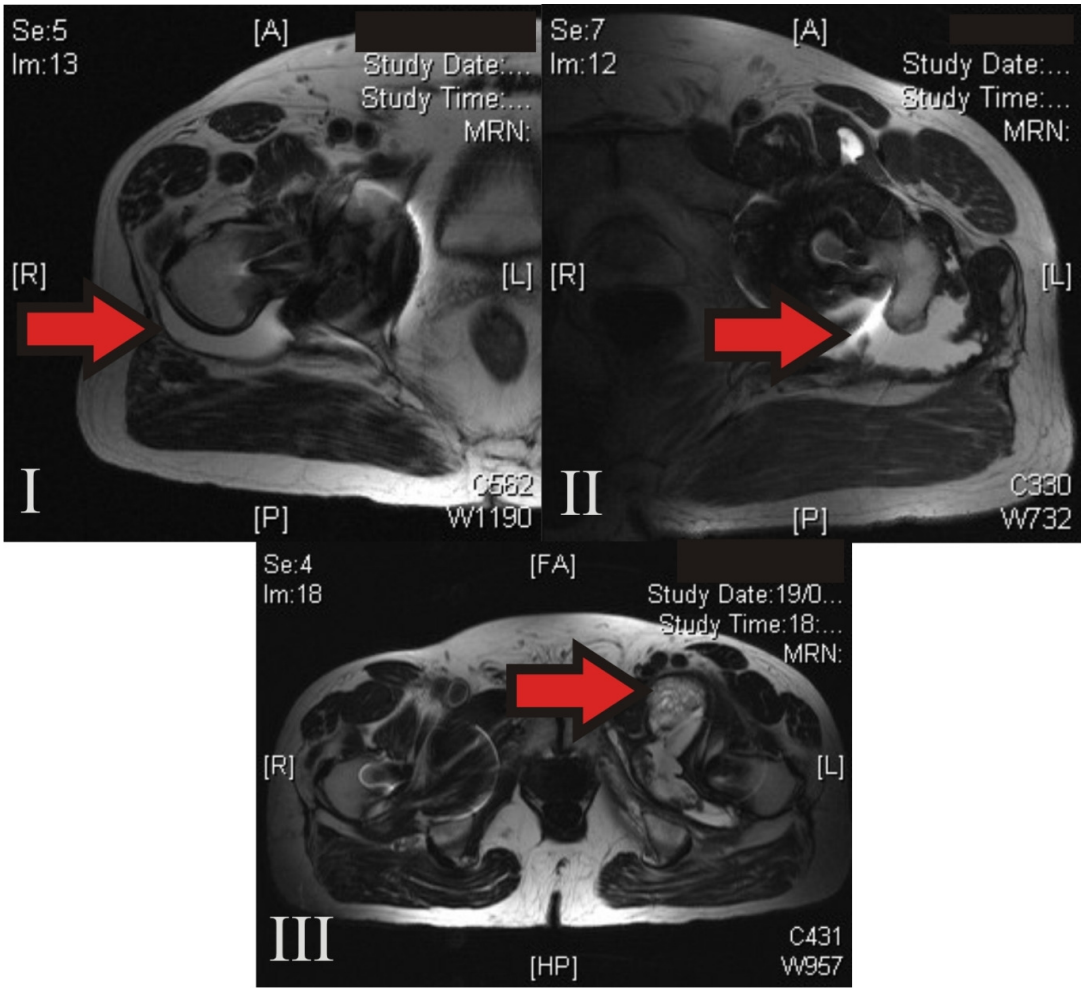


Figure 2.3: MRI appearances of different Pseudotumour types as per Hauptfleisch *et al*[145]. Type I with cyst wall thickness of less than 3 mm and Type II with cyst wall thickness greater than 3 mm. Type III lesions were predominantly solid lesions, where the largest dimension of the solid components was greater than the diameter of the cystic components.

2.4.6 Intra-operative findings

The variability in the radiological appearance described above is reflected by the variability in the macroscopic appearance of the intra-operative findings. The pseudotumour can be cystic, solid or both and it may be located anterior, posteriorly, laterally or surrounding the whole hip joint. It may be associated with extensive or little bone destruction, soft tissue necrosis and invasion of neurovascular structures.

Boardman was amongst the first to report on an anterior pseudotumour and described a necrotic mass with some liquefaction seen within the psoas at operation[126]. Similarly, Jameson *et al* described the appearance at revision of the first few cases with pseudotumour as 'gross swelling of the pseudocapsule and a similar green-gray fluid was found surrounding the implant and tracking into the psoas tendon'[148]. Those findings were associated with a varying degree of muscle necrosis. De Haan *et al* reported on 12 patients with 'a large, metal-stained bursa containing copious amounts of brown or creamy fluid under pressure present in the joint' and noted that extensive soft-tissue resection was necessary in order to remove the involved tissues[127].

The causative factors for this large variability in the macroscopic appearance described intra-operatively and on radiological investigations have not yet been identified.

2.4.7 Histological findings

Reports of histological findings following MoM implants revised for peri-prosthetic osteolysis by Willert *et al*[131] and Korovessis *et al*[149] have led to the identification of a number of characteristic changes that occur from the deposition of wear debris in peri-implant tissues of cases revised for osteolysis. These changes are predominantly characterised by a peri-vascular infiltration of lymphocytes, macrophages, vasculitis and fibrin production with drop like

inclusions. No correlation could be established in either study between the degree of metalosis and the number of infiltrating lymphocytes. This histological appearance was described as ALVAL by Willert and is considered to develop as a result of a delayed hypersensitivity response to CoCr wear debris.

Mahendra *et al* reviewed the histological features in 52 MoMHRA revisions of varying aetiology (pseudotumour, fracture, component loosening and other)[150]. Coagulative tissue necrosis was observed in the superficial and deep zones of tissues in all cases. In all cases of pseudotumour and two cases of loosening, ghost-like outlines of macrophages were seen and in many cases they appeared to lie in small aggregates. Macrophages formed a significant component of the inflammatory response to wear particles in periprosthetic soft tissues. Focal areas of cystic degeneration were also seen. In cases of pseudotumours discrete granulomatous response was seen around areas of necrosis. This morphology would be in keeping with a cytotoxic effect causing a vicious cycle in which metal particle generation leads to macrophage recruitment, particle phagocytosis, and cell death with resultant release of metal particles, macrophage recruitment and the repetition of the process. In addition, the authors also noted a diffuse lymphocytic infiltrate (T and B lymphocytes) and lymphocytic aggregates (T and B lymphocytes with scattered plasma cells) in a number of pseudotumour and loosening cases. These features would be consistent with a delayed hypersensitivity response. They concluded that the necrotic and inflammatory changes seen in peri-prosthetic tissues in response to the wear debris are likely to be due to a cytotoxic reaction, a delayed hypersensitivity reaction or a spectrum of the two.

Histological findings in keeping with the possibility of a delayed hypersensitivity (Type IV) reaction in some patients are those described by Pandit *et al* in four women that developed a pseudotumour after implantation of the second MoMHRA[151]. Histological examination in these cases were characterised by areas of coagulative necrosis in which there were large numbers of macrophages; these areas were surrounded by macrophage and giant cell granulomas as well as T-lymphocytes, plasma cells and eosinophil polymorphs.

Campbell *et al* reviewed histological findings in 32 pseudotumours and described a scoring system (ALVAL score), ranging from 0 to 10 and based on features of the synovial lining, the inflammatory infiltrate and the tissue organisation[10]. The resultant ALVAL score, is an aggregation of points based on different features as described in Table 2.6. The authors correlated histological findings with wear and identified an inverse correlation between the ALVAL score and measured wear. The higher ALVAL scores were associated with lower wear. However, certain limitations of this study need to be highlighted. Not all patients had available wear data (available in 24 out of 32). In addition, patients were divided into two different wear groups 'suspected wear related' pseudotumour and 'suspected metal allergy' without explanation of the grouping. In a more recent study by the same authors, Ebramzadeh *et al*, provided data that in 43 pseudotumour cases the linear wear rate was lower for patients with high ALVAL score (n=15, rate: 3.4 µm/yr), compared to those with low ALVAL scores (n=15, rate: 6 µm/yr)[152]. To-date the ALVAL scoring system has yet to be validated or used by other authors.

Points	Synovial Lining
0	Intact synovial lining
1	Focal loss of synovial surface, fibrin attachment may occur
2	Moderate to marked loss of synovial surface, fibrin attachment
3	Complete loss of synovium, abundant attached fibrin, and/or necrosis of lining tissue
Points	**Inflammatory Infiltrate**
0	Minimal inflammatory cell infiltrates
1	Predominantly macrophages, occasional lymphocytes may occur
2	Mix of macrophages and lymphocytes, either diffuse and/or small (<50% hpf) peri-vascular aggregates may occur
3	Mix of macrophages and lymphocytes, large (<50% hpf) peri-vascular aggregates may occur
4	Predominantly lymphocytes, mostly in multiple, large (>50% hpf) perivascular aggregates, follicles may be present
Points	**Tissue Organisation**
0	Normal tissue arrangement
1	Mostly normal tissue arrangement, small areas of synovial hyperplasia, focal necrosis may occur
2	Marked loss of normal arrangement, appearance of distinct cellular and acellular zones, thick fibrous layers may occur
3	Peri-vascular lymphocytic aggregates mostly located distally, thick acellular areas may occur

Table 2.6: ALVAL score grading system as described by Campbell *et al*[10]. Following addition of the points, three different grades exist: Low (0 – 4), Moderate (5 – 8) and High (9 – 10); hpf: high-power field.

2.4.8 Incidence

The incidence of pseudotumour revisions varies in different series (Table 2.7). This difference is in part due to differing study design (different definitions of the

lesion) and different cohort characteristics (differences in patient factors, MoMHRA system used, length of follow-up).

Study	Prosthesis	No. of Prostheses Implanted	Gender (%M/%F)	Age/ Years	Follow-up / Years	Incidence of revision due to pseudo-tumour
Pandit et al. 2008[8]	Various	≈1,300	60/40	53 (35 – 73)	3 (0 – 6)	1%
Glyn-Jones et al. 2009[153]	Various	1,419	60/40	54 (17 – 86)	4 (0 – 9)	1.8%
Ollivere et al. 2009[154]	BHR	463	66/34	56 (20 – 70)	3 (1 – 7)	2%
Beaule al. 2011[155]	Various	3,432	77/23	51 (16 – 83)	3 (2 – 9)	0.2%
Langton et al. 2011[27]	ASR	418	56/44	56 (28 – 77)	4 (2 – 6)	14%
Wynn-Jones et al. 2011[156]	ASR	75	71/29	55 (30 – 76)	3 (1 – 4)	8%

Table 2.7: Incidence of revision due to pseudotumour reported from different centres with various prostheses types and designs.

2.4.9 Risk factors for pseudotumour development

Factors that have been identified to have an effect on pseudotumour risk can be broadly divided into implant- and patient- related.

2.4.9.1 Implant-related risk factors

Registry data has demonstrated different implant survival rates for different implant systems. In the Australian Joint Registry Report of 2011, the ASR has

been shown to have a significantly higher revision rate (13%) in comparison to other implants such as the BHR (5%) at seven years[157]. Langton *et al* compared the incidence rates for pseudotumour revision between the BHR, the ASR and the Conserve Plus prostheses and demonstrated a ten-fold increase in the incidence of pseudotumour with the ASR[129]. These reports led to the withdrawal of the ASR from the market and a recall as mentioned in section 2.4.2.

2.4.9.2 Patient-related risk factors

Glyn-Jones *et al* reviewed patient characteristics of 1,418 MoMHRAs in order to identify patient-related risk factors that increase the risk of pseudotumour-revision[153]. The authors noted that the incidence appeared to progressively increase with time. Factors identified to increase the risk included female gender, small size, hip dysplasia, and in women age less than 40. However, as these factors were inter-related, on fitting a Cox proportional hazard model only gender ($p=0.002$) and age ($p=0.024$) had a significant independent influence on revision rate.

2.4.9.3 Surgery-related risk factors

To-date, no surgical technique-related factors which increase risk of pseudotumour development have been identified. Factors such as component orientation and size have been described as risk factors contributing to complications post hip arthroplasty. The characterisation of these factors in THA

has lead to recommendations regarding surgical practice in order to reduce complication and therefore reduce revision rates.

Component orientation has been shown to be important in improving function and preventing failure following THA[158,159]. Acetabular orientation is thought to effect stability, range of motion, and wear. Lewinnek identified from radiographic measurements a "safe zone" of 40°±10° of inclination and 15°±10° of anteversion, in order to minimise the risk of dislocation[160]. However, the importance of MoMHRA acetabular orientation may have been underestimated because of the very low dislocation rate associated with the large femoral head[161]. Recent studies have identified an association between cup orientation and elevated ions levels[100,101]. Although elevated metal ion levels are associated with pseudotumour, no association has been established between acetabular component orientation and the development of pseudotumour. The positioning of the MoMHRA femoral component has been reported to influence the rate of fractures[6], however no association between wear and femoral component orientation has been described to-date.

An additional surgical related factor influencing complication rate in hip arthroplasty is component size, which in turn has an effect on head-neck-ratio (HNR). MoMHRAs are associated with smaller HNRs in comparison to THA. A perceived advantage of MoMHRA over THA is the restoration of hip joint anatomy and hence normal mechanics due to retaining of the native femoral neck. However, computer assisted surgery and simulation studies have suggested that

there is a reduction in HNR and anterior offset associated with hip resurfacing[162,163], although the effects can be minimised by appropriate femoral component placement[164]. A decrease in HNR may lead to a decrease in functional range of movement[163] and is thought to increase risk of impingement and hence wear. Painful impingement has been reported around MoMHRA hips and could lead to further surgery[46]. To-date, the association between HNR alterations with MoMHRA and subsequent pseudotumour has not been studied.

2.4.9.4 Definitions of acetabular component orientation

The estimation of acetabular component orientation depends on the definition of orientation used. Three different definitions of acetabular component orientation are used in the orthopaedic literature, each stemming from a particular application of cup orientation. These refer to the anatomical, radiographic and operative orientations as defined by Murray[165]. The definitions relate to the orientation of the acetabular axis, a line that passes through the centre of rotation of the cup and is perpendicular to the face of it. Different reference planes are used for its measurement depending on the definition used.

Radiographic inclination is defined as the angle between the supero-inferio (longitudinal) axis of the body and the acetabular axis as projected onto the coronal plane. Radiographic anteversion is defined as the angle between the acetabular axis and the coronal plane. It has also been described as planar version and can be calculated from the ratio of the short and long axis of the elliptical projection of the cup opening of an AP X-ray. Operative inclination is the angle

between the acetabular axis and the saggital plane. Operative anteversion is defined as the angle between the longitudinal axis and the acetabular axis as projected on the saggital plane. Anatomic inclination is defined as the angle between the acetabular axis and the longitudinal axis. Anatomic anteversion is the angle between the transverse axis and the acetabular axis when this is projected onto the transverse plane. Figures 2.4 and 2.5 illustrate the different types of inclination and anteversion described above. The relationship between anatomical and radiological measurements can be represented by nomograms and equations as illustrated in Appendix 6.

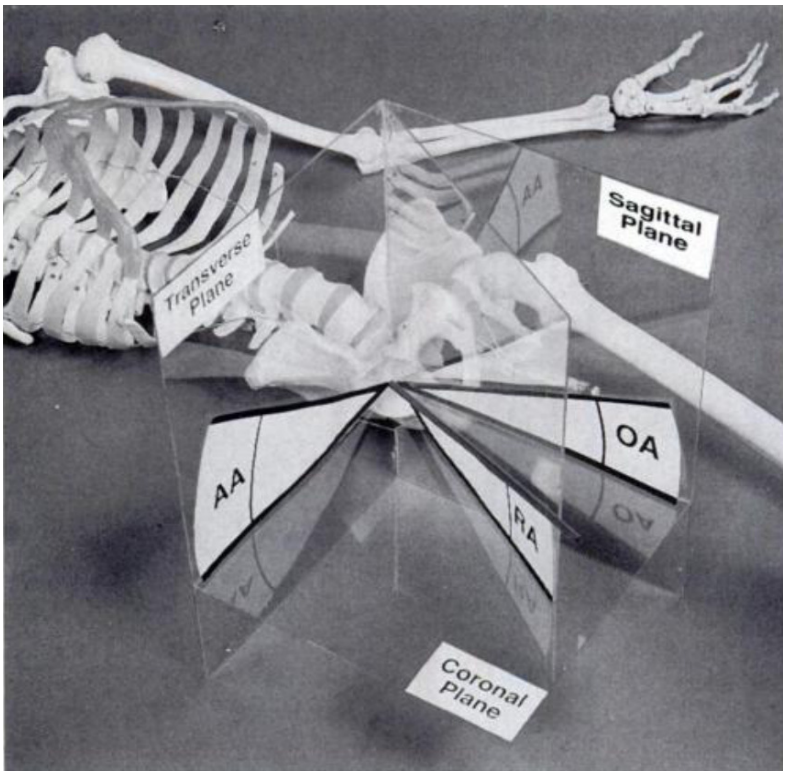


Figure 2.4: The different definitions of acetabular anteversion. Reproduced with the kind permission of D. Murray[165].

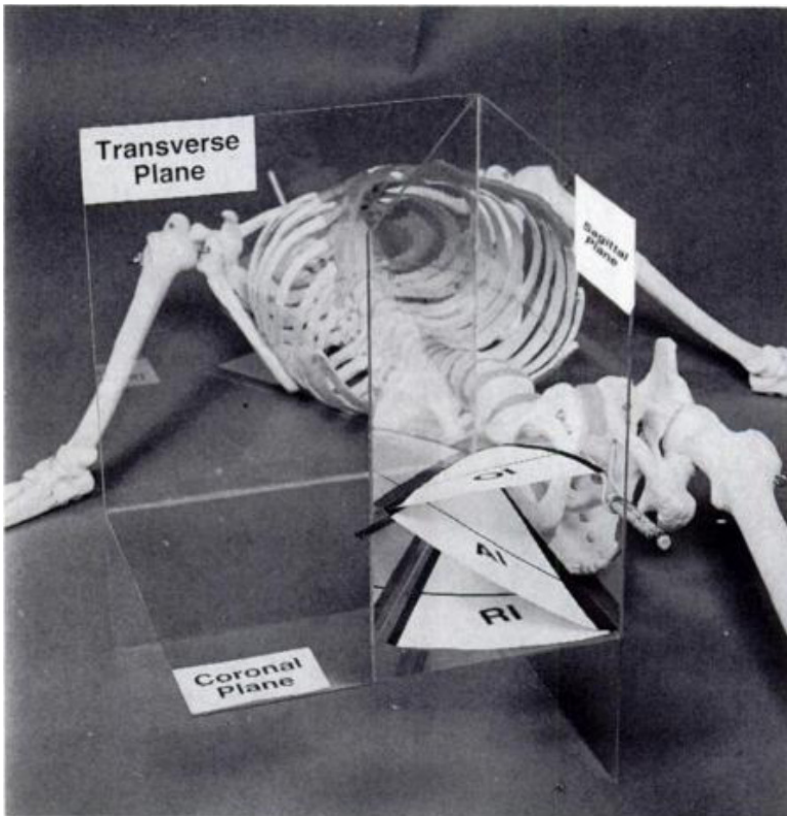


Figure 2.5: The different definitions of acetabular inclination. Reproduced with the kind permission of D. Murray[165].

2.5 Summary

- MoMHRA has been a treatment option for young adults with advanced hip disease who would otherwise receive a conventional primary Total Hip Arthroplasty and are likely to live longer than the device is likely to last. Despite the early-term satisfactory outcome, mid-term reports have raised concern over adverse biological responses to metallic wear debris both systemically and locally.
- Although MoMHRA can function with minimal wear, there have been reports of non-optimally functioning implants with high wear.
- The potential systemically adverse biological effects of wear such as risk of malignancy, carcinogenesis, genotoxicity, teratogenicity and hypersensitivity are being studied, and their effect and importance in clinical practice has been debated.
- Local adverse reactions (pseudotumours), of varying nature, associated with wear debris production are increasingly being reported and represent a complication that has caused a growing concern in the orthopaedic community and the general public. However, to date, no data exists identifying the extent of the problem (mid-term incidence of revision and outcome thereafter).
- The varying nature of macroscopic and microscopic findings raise questions on the homogeneity of pseudotumours. Further studies are needed in order to identify whether the spectrum of macroscopic appearance is an aftermath of different pathomechanisms.

- Patient- and implant- specific risk factors have been identified increasing wear and leading to pseudotumour development. Studies are warrranted in order to characterise surgical factors and their mechanism in increasing wear and risk of pseudotumour development. These would enable the provision of evidence-based recommendations for optimum surgical technique when performing a MoMHRA.

3 INCIDENCE AND PREVALENCE OF REVISION DUE TO PSEUDOTUMOUR[†]

3.1 Introduction

In order to define the revision burden (defined as the percentage of revised cases as a function of all MoMHRAs) pseudotumour poses to orthopaedic surgeons, the prevalence (number of cases that are present in a particular population at a given time) and incidence (number of cases in a particular population during a specific time period) of revisions due to pseudotumour need to be identified.

Pseudotumour revisions have mostly been described following the first two years post MoMHRA surgery. A review of the literature described in the previous chapter (Table 2.6) demonstrated variability in the incidence of revision across different centres, which can be attributed to many factors as previously explained (Chapter 2). However, these studies are only early/mid-term with a mean follow up of 3 to 4 years. Hence, longer follow-up studies are needed, given that it has been hypothesised that the cumulative revision rate will increase with time[153].

In order to identify the prevalence and incidence of revision due to pseudotumour, two studies were carried out.

[†] Work described in this chapter has been published as:

Murray DW, Grammatopoulos G, Pandit H, Gundle R, Gill HS, McLardy-Smith P. The ten year survival of the Birmingham hip resurfacing – An independent series. J Bone Joint Surg Br 2012; 94-B 1180-1186.

Study 3A was performed at an independent, tertiary referral, teaching hospital in the United Kingdom and aimed at defining the ten-year survival and incidence of revision due to pseudotumour with the BHR implant. The BHR has been shown to be a resurfacing system of good design and metallurgy, and is the most widely used implant with more than 125,000 prostheses implanted worldwide[166]. Early- and mid-term reports from designers and independent centres have shown survival rates with the BHR varying from 95 to 100% at five years. In all these early-term survival studies, femoral neck fracture is the most common failure mode and revision due to pseudotumour only accounts for 0 to 0.5% of cases[29-31,38,40,41]. However, as the cumulative percentage of revision is likely to rise with years since surgery, it is important to establish the ten year survival and incidence of pseudotumour-related revision. To date published reports on ten year survival rates have either been from MoMHRA designers or high volume surgeons[33-36]. The ten year survival ranges between 87.5 % and 97%, with an incidence of pseudotumour related revision ranging from 0 to 2.0%.

Study 3B was performed with the collaboration of two independent, tertiary referral centres with the aim of identifying the prevalence of revisions due to pseudotumour. Previous data on indication for revision amongst failed MoMHRA from multiple centres is only available from registry data and mostly represents cases with short implant survival. Prosser *et al* evaluated the 437 revisions reported in the Australian National Joint Registry (ANJR) between 2002 and 2010[167]. The most commonly encountered failure was femoral neck fracture accounting for 58% of revisions, followed by loosening/osteolysis in 31% of

cases. Other reported reasons for revision included infection (9%), metal sensitivity (6%), pain (5%), dislocation of prosthesis (3%) and other (8%). It should be noted, however, that maximum follow-up was seven years post-surgery and that pseudotumour is not a recognised revision indication in the ANJR. Thus, revisions due to pseudotumour could have been labelled as a variety of revision indications (lysis, pain, metal sensitivity or other) as a result of the variability in presentation and intra-operative findings.

Therefore, the aims of the work reported in this chapter were to:

1. Define the ten-year survival and identify the incidence of pseudotumour-related revisions with the BHR in an independent, tertiary referral, teaching hospital in the United Kingdom.
2. Identify the prevalence of revisions due to pseudotumour in specialist, tertiary referral hospital settings.

3.2 Null hypothesis

H_0: Pseudotumour is not a common revision indication as measured by the incidence of revision at ten years in an independent, tertiary referral, teaching hospital and the prevalence of failures presented to specialist tertiary referral centres.

3.3 Study 3A: Ten year survival, outcome and incidence of pseudotumour-related revisions with the BHR

3.3.1 Materials and methods

3.3.1.1 Study design

A survival analysis is a study in which the outcome of an intervention is tracked over time. It allows for variable dates of entry and for variable lengths of follow-up. Data can be analysed continuously (actuarial method) or at times of failure (Kaplan-Meier product-limit method), or a combination of both (life-table method) [168]. During a survival analysis, due care must be given to the definition of failure, the treatment of 'lost to follow-up' and death. In life-table analysis the survival rates are calculated annually, while in Kaplan-Meier analyses the rates are recalculated each time a failure occurs.

3.3.1.2 Study group

Patients were identified from the resurfacing database at the Nuffield Orthopaedic Centre (NOC), Oxford. Since 1999, 1,483 MoMHRAs have been performed with four different systems (BHR, Conserve Plus, Cormet and Recap). The BHR system was, almost exclusively, used between 1999 and 2004. In order to estimate the ten year survival, and exclude selection bias by including different systems, this survival analysis was performed for the BHR cases only. Between June 1999 and September 2009, 646 consecutive BHR's had been implanted in 554 patients and formed the cohort of this survival study. The entire group was under the care

of four orthopaedic consultants who had supervised 28 orthopaedic trainees during the implantation process.

All procedures were performed with the patient in the lateral decubitus position. The extended posterior approach as described by McMinn was used in all cases[25]. Surgeons had a choice of two types of cement, each with an antibiotic incorporated, to fix the acetabular component: CMW3 cement (DePuy Ltd, Blackpool, UK) with Gentamicin or Simplex cement (Stryker, Newbury, UK) with Tobramycin. The most-commonly used femoral component size was 46 mm (31%), followed by 50 mm (29%) and 54 mm (25%). The range of femoral component sizes varied from 38 to 58 mm. The mean femoral head size was 49 mm (SD: 4.3).

3.3.1.3 Demographics

The entire cohort included 646 BHRs in 554 patients. There were 325 males (379 hips) and 229 females (267 hips). The mean age at surgery was 51.9 years old (range: 16.5 to 81.5 years). 92% of patients were below 65 years old. There were 92 bilateral cases of which 44 were performed simultaneously. Primary osteoarthritis (1° OA) was the most common diagnosis (526 hips, 81%), followed by osteoarthritis secondary to dysplasia (OA 2° to DDH) (85 hips, 13%), avascular necrosis (AVN) of the femoral head (21 hips, 3%) and other (14 hips, 2%). Consultants performed the majority of the cases (n=524, 81%) and supervised the remaining 122 performed by the trainees.

3.3.1.4 Patient follow-up and reported outcome

Patients were contacted by post and were asked to fill in three questionnaires. One form related to the survival of their implant and the other two forms related to patient reported functional outcome. The local ethical committee was informed of this study and a waiver was granted confirming that this study did not require approval.

The patients were asked to fill in a questionnaire describing whether the BHR was still in place, whether it had been revised or whether they had further surgery on their resurfaced hip (Appendix 7). If patients had undergone further surgery, they were asked to supply details of what led to surgery and what the procedure performed entailed. Details obtained from patients were then cross-checked with details from hospital records before being entered in the database for analysis. From patients' notes, the following information was collected: revision indication and operative findings from revision surgery.

The patient reported outcome measures utilised in this study were the Oxford Hip Score (OHS, Appendix 8) and the University of California Los Angeles (UCLA) activity score (Appendix 9). The OHS is a 12-item patient based questionnaire that was developed and validated to assess hip joint function and pain after THA[169]. The modified scoring system as suggested by Murray *et al* with a minimum of 0 points (worst outcome) and a maximum of 48 points (best outcome) was used in this study[139]. The UCLA activity score ranges from a minimum of one point (wholly inactive) to a maximum of ten points (regularly

participating in impact activities)[49]. The UCLA score has been validated for use in the clinical setting. The OHS and UCLA scores were sent to all patients. If patients had undergone bilateral BHR procedures, the OHS questionnaire was completed for each hip.

Patients were categorised according to their OHS into four groups as previously suggested by Kalairajah[170]; patients with OHS > 41 (excellent outcome), those with OHS between 41 and 34 (good outcome), those between 33 and 27 (fair) and those below 27 (poor outcome). All patients with an OHS of <33 (poor or fair) were considered to be 'at risk'. These patients were invited for a clinical review and underwent further imaging including pelvic radiographs, hip ultrasound scan (USS) and MRI if deemed necessary.

For those who did not respond to the questionnaire, survival and functional outcome was established by telephone interview and General Practitioner (GP) records. Similarly, the survival for the implant in patients who had died was established by contacting their GP's to establish whether their resurfaced hip had been revised prior to the patient's death.

3.3.1.5 Data analysis

The implant survival rate for the whole cohort was established by defining revision as the final endpoint, and using the life table method for the analysis of survival as previously proposed by Murray[168]. All BHRs were included in the

analysis and the number of implant failures was determined for each post-operative year. The 95% confidence intervals (CI) were established using Rothman's equation and from the effective number at risk using an exact method as previously suggested[171]. Survival was also calculated with loss to follow-up and those who were deemed to have failing BHRs after clinical review, treated as failures, giving the worst case survival.

Sub-analyses were performed dividing the hips based on gender, age of the patients and component size. Patients were grouped on the basis of age at time of operation; the Young Group consisted of those less than 50 years old, the Older Group consisted of those aged 50 years or more. Patients were also grouped on the basis of femoral size implanted; 4 mm size increments were available in the Nuffield Orthopaedic Centre over that period. Patients with femoral components diameter <46 mm formed the Small Group (n=82), whilst those with femoral components diameter of 46 mm formed the 'size 46' group (n=197), patients with femoral components of size 50 mm formed the 'size 50' group (n=184) and those patients with femoral components diameter >50 mm formed the Large Group (n=183). The distribution of pre-operative diagnosis was different in-between the age and size subgroups (χ^2<0.001 for age and χ^2<0.001 for component size) (Table 3.1).

		Diagnosis			
		1° OA (n=526, 81%)	Dysplasia (n=85, 13%)	AVN (n=21, 3%)	Other (n=14, 2%)
Age groups	Young (n=244)	171 (33)	49 (58)	13 (32)	11 (79)
	Older (n=402)	355 (67)	36 (42)	8 (38)	3 (21)
Size groups	<46 (n=82)	54 (10)	25 (29)	1 (5)	2 (14)
	46 (n=197)	154 (29)	32 (38)	5 (24)	6 (43)
	50 (n=184)	155 (30)	15 (18)	12 (57)	2 (14)
	>50 (n=183)	163 (31)	13 (15)	3 (14)	4 (29)

Table 3.1: Distribution of pre-operative diagnoses for the different age and size groups. Other diagnoses include osteoarthritis (OA) secondary to slipped capital femoral epiphysis, Perthe's disease and rheumatoid arthritis.

Further sub-analyses included the effect of surgeon's experience and the effect of having bilateral hip resurfacings on survival and outcome. Consultant performed cases were compared with cases performed by trainees under consultant supervision. Unilateral cases were compared with bilateral ones. Bilateral cases

were further sub-divided into those performed simultaneously and those performed sequentially.

Cox proportional hazard analysis was used to estimate the independent effects of each factor in multiple regression models.

3.3.1.6 Statistics

Statistical analysis was performed using SPSS (version 18, SPSS Inc., Chicago, Illinois). The dataset was assessed for normality using the Shapiro-Wilks test. Inter-group comparisons of non-normally distributed scale data were made with the use of non-parametric tests (Mann-Witney U, Kruskal-Wallis, log-rank). Cross-tabulation and the chi-square test were used for categorical data. A multivariate stepwise logistic regression analysis was performed in order to identify any factors that influenced patient reported outcome. Statistical p values of equal or less than 0.05 were considered significant.

3.3.2 Results

3.3.2.1 Results of entire cohort

For the entire cohort of 554 patients (646 hips), ten were lost to follow-up (12 hips). The mean follow up was eight years (range: 0 to 12 years). Survival of the implant was established for all but the lost to follow-up patients. Ten patients (14 hips) had died from unrelated causes with the BHR *in situ* at the time of death.

3.3.2.2 Revisions

54 hips were revised (8.4%). Revision indications included fracture/AVN (n=12, 22%), pseudotumour (n=26, 48%), painful impingement (n=8, 15%), loose components (n=6, 6%), infection (n=1) and recurrent dislocation (n=1) (Figure 3.1). There were no other complications such as nerve injury or major medical complications. 13 failures were in bilateral cases. Seven of these were in patients who had BHRs implanted as staged procedures, whilst six were in simultaneously performed cases. Failure modes in the bilateral group included fracture (n=5), pseudotumour (n=6) and painful impingement (n=2). There were three fractures, two pseudotumours and one painful impingement in the simultaneously operated bilateral cases. Two of the late failures (one pseudotumour, one painful impingement) in the simultaneously performed bilateral cases occurred in the same patient.

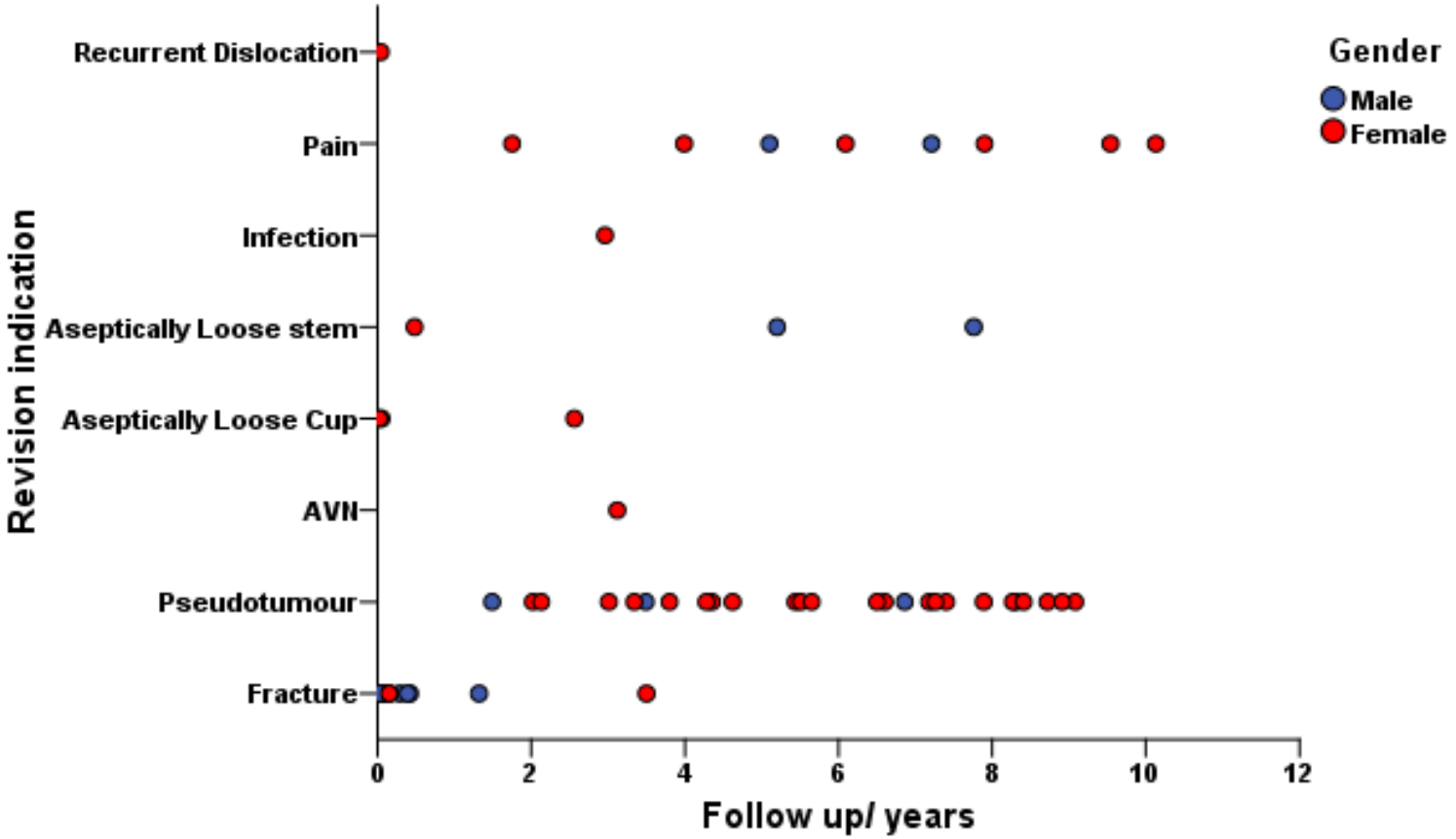


Figure 3.1: Scatter of different revision indications plotted against time interval between primary and revision surgeries. Graph is colour coded for gender.

3.3.2.3 Survival (Tables 3.2 and 3.3)

The overall survival was 87.1% (95% CI: 83.0% to 91.2%) at ten years (Figure 3.2). In the worst case scenario, with the lost to follow-up (n=12) and hips with positive findings at clinical review (n=4) hips treated as failures, the survival was 82.7% (95% CI: 77.8% to 87.6%) at ten years.

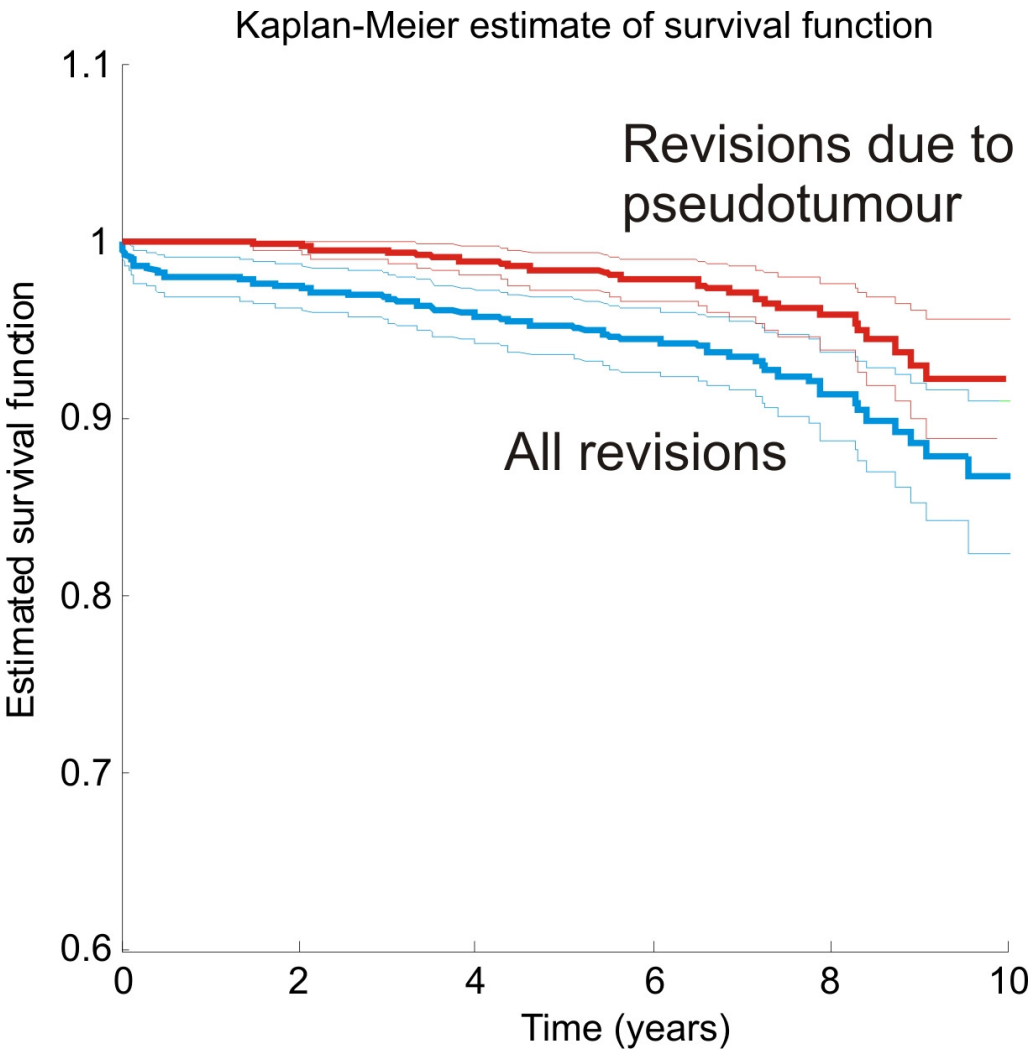


Figure 3.2: Survival of the entire cohort of BHR arthroplasties with revision for any cause (blue) and revision due to pseudotumour (red) as separate end-points.

Males had a superior ten-year survival (94.7%, 95% CI: 92.0% to 97.4%) in comparison to females (73.9%, 95% CI: 63.6% to 84.2%) (log rank p<0.001) (Figure 3.3).

Survival of MoMHRA performed for the treatment of 1° OA cases was 87.8% (95% CI: 82.8% to 91.9%) at ten years; that for all other diagnoses was 85.5% (95% CI: 76.6% to 94.1%) at ten years (log rank p=0.16).

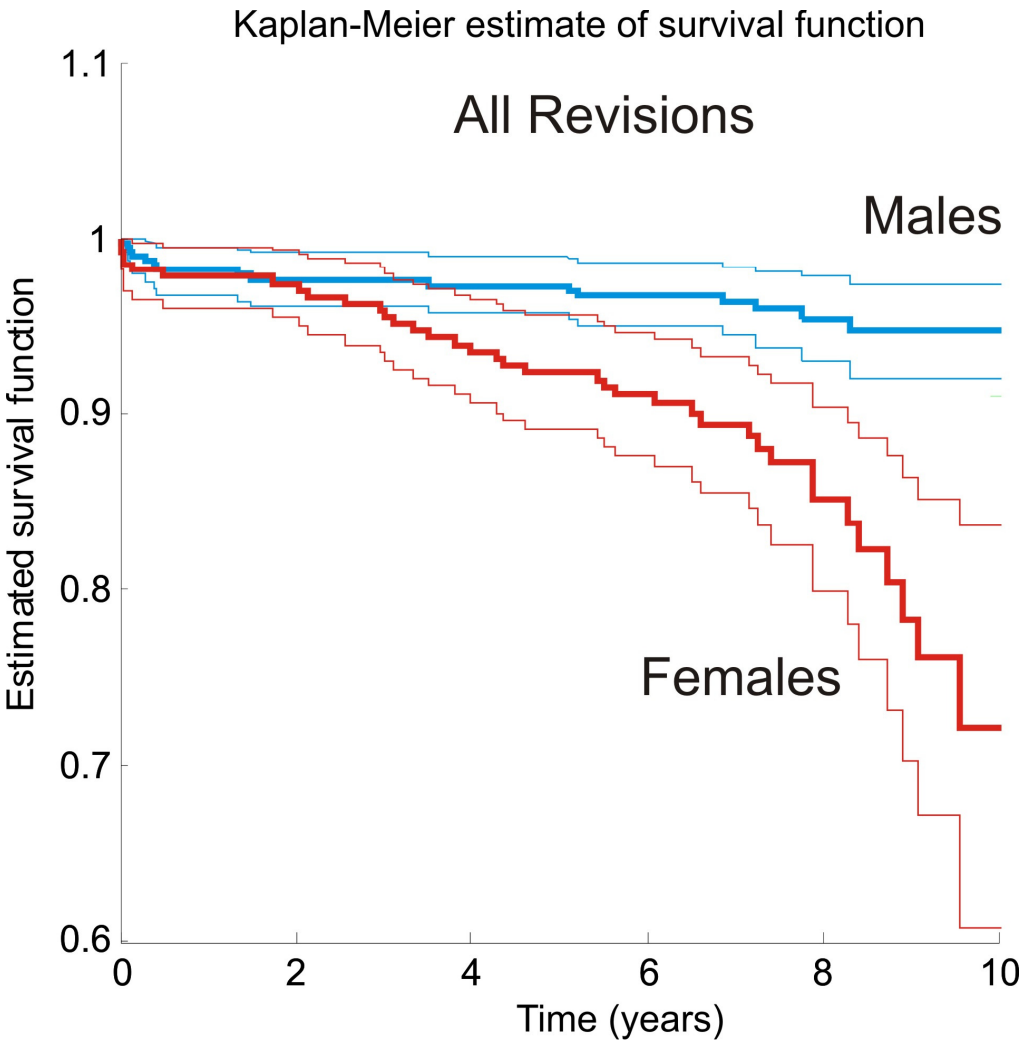


Figure 3.3: Survival analysis for the different gender groups. Analysis' end point is revision for any cause.

In the sub-analysis according to age, the Young Group appeared to have a lower ten-year survival (82.8%, 95% CI: 73.8% to 90.4%) compared to the Older Group (90%, 95% CI: 85.5% to 94.1%) but this did not reach statistical significance (log rank p= 0.14). The ten-year survival of males in the Young group that had a BHR for the treatment of primary OA (n=100) was 99% (95% CI: 97.0 to 100.0).

Considering component size, the ten-year survival for patients in the Small Group was 66.7% (95% CI: 45.4% to 88.1%), compared to 77.0% (95% CI: 64.5% to 89.5%) for the 'size 46' group, 91.1% for the 'size 50' group (95% CI: 84.6% to 97.6%) and 96.1% (95% CI: 92.9% to 99.3%) for the Large Group (Figure 3.4). There was a statistically significant difference in survival between the four size Groups (log rank p<0.001).

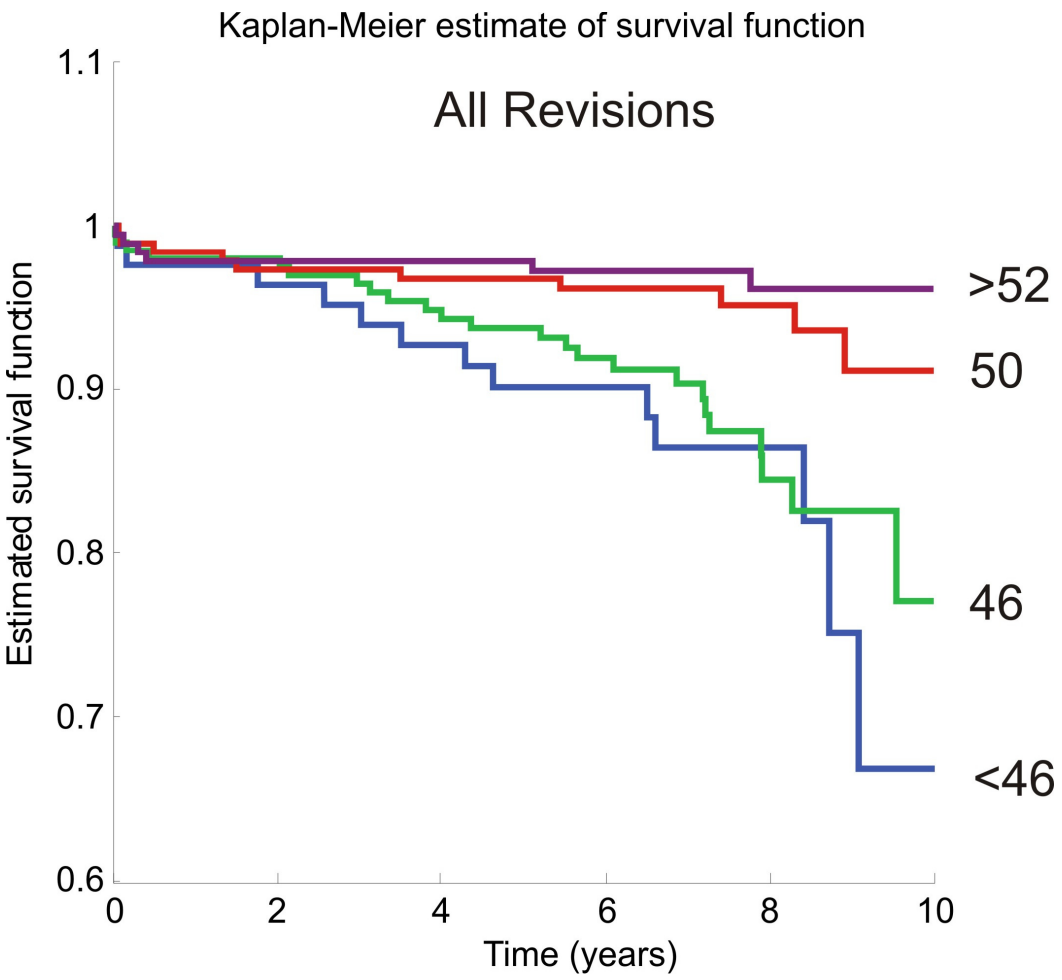


Figure 3.4: Survival analysis for the different component size groups. Analysis end point was revision for any cause.

Sub-analysis of survival as a function of surgeon's experience showed that consultant-performed cases had a ten-year survival of 87.9% (95% CI: 83.1% to 91.9%) compared to 82.4% (95% CI: 69.6% to 94.8%) for trainees; however this difference was not significant (log rank p= 0.16).

Bilateral cases had similar ten-year survival (90.6%, 95% CI: 84.9% to 95.7%) compared to unilateral cases (85.3, 95% CI: 79.1% to 90.8%) (log rank p=0.46) at ten years.

Applying Cox-regression analysis with the variables considered individually, only gender ($p<0.001$) and size ($p<0.01$) had a significant effect on revision rate. When adjusting for these variables in a multi-variable model, only size ($p=0.03$) had a significant independent effect.

		Survival % (95%CI)	Log-rank p
Cohort		87.1 (83.0 to 91.2)	
Gender	Males	94.7 (92.0 to 97.4)	<0.001
	Females	73.9 (63.6 to 84.2)	
Diagnosis	1° OA	87.8 (82.8 to 91.9)	0.16
	Other	85.5 (76.6 to 94.1)	
Age	Young	82.8 (73.8 to 90.4)	0.14
	Older	90.0 (85.5 to 94.1)	
Surgeon's Grade	Consultant	87.9 (83.1 to 91.9)	0.16
	Trainee	82.4 (69.6 to 94.8)	
Head Size	<46	66.7 (45.4 to 88.1)	<0.001
	46	77.0 (64.5 to 89.5)	
	50	91.1 (84.6 to 97.6)	
	>50	96.1 (92.9 to 99.3)	
Operated side	Unilateral	85.3 (79.1 to 90.8)	0.46
	Bilateral	90.6 (84.9 to 95.7)	

Table 3.2: Survival figures for the whole cohort and different subgroups.

Years post-op	No. of hips in study at start of the year	No. of hips withdrawn during interval	Failures	Lost to follow-up	Annual success rate	Accumulated survival	95% CI lower limit	95% CI upper limit
0 to 1	646	1	13	4	98	98	96	100
1 to 2	628	0	3	0	100	98	96	100
2 to 3	625	3	4	1	99	97	95	99
3 to 4	617	20	7	2	99	96	94	98
4 to 5	588	21	3	1	99	95	93	97
5 to 6	563	59	5	3	99	94	92	96
6 to 7	496	115	4	1	99	94	92	96
7 to 8	376	137	7	0	98	92	90	94
8 to 9	232	105	5	0	91	89	85	93
9 to 10	122	90	2	0	95	87	83	91
10 to 11	30	28	1	0	95	83	75	91

Table 3.3: Life table of all 646 BHRs.

3.3.2.4 Functional outcome

Functional outcome was obtained for 540 (95%) hips. The mean OHS was 44.0 (SD 7, range: 6 to 48). There were 37 'at-risk' patients. The mean UCLA activity score was 7.1 (SD 2.1, range: 1 to 10). Analysis as per cohort subgroups showed that gender, patient's age, surgeon's grade and component size had an effect on OHS, whilst gender, size and whether a patient had a unilateral or bilateral BHR affected UCLA activity score. Multivariate stepwise logistic regression analysis performed identified surgeon's grade (B: 0.19, $p<0.001$), component size (B: 0.16, $p<0.001$) and age (B: 0.11, $p=0.01$) as factors that influenced OHS. A similar analysis for UCLA activity score, identified component size (B: 0.18, $p<0.001$), sides operated (unilateral/bilateral) (B: 0.16, $p<0.001$), gender (B: 0.16, $p=0.003$) and surgeon grade (B: 0.09, $p=0.04$) to have an effect on UCLA activity score.

		OHS (SD)	p-value	UCLA (SD)	p-value
Cohort		44.0 (7.0)		7.1 (2.1)	
Gender	Males	44.8 (6.2)	p=0.004	7.6 (2.1)	p<0.001
	Females	42.6 (8.2)		6.4 (2.0)	
Diagnosis	1° OA	44.2 (6.8)	p=0.10	7.2 (2.1)	p=0.16
	Other	43.1 (8.1)		6.9 (2.1)	
Age	Young	42.8 (8.5)	p=0.02	7.2 (2.2)	p=0.84
	Older	44.6 (6.1)		7.1 (2.1)	
Surgeon's Grade	Consultant	44.5 (6.2)	p<0.001	7.2 (2.0)	p=0.12
	Fellow	41.3 (10)		6.7 (2.5)	
Head Size	Small	40.2 (10.4)	p=0.003	5.8 (2.0)	p<0.001
	Midsize	44.1 (6.9)		7.1 (2.1)	
	Large	45.3 (4.9)		7.8 (1.9)	
Operated side	Unilateral	44.2 (6.5)	p=0.17	7.4 (2.1)	p<0.001
	Bilateral	43.4 (8.5)		6.5 (2.1)	

Table 3.4: Patient reported functional outcome (OHS and UCLA) scores for the whole cohort and different subgroups.

3.3.2.5 Clinical review

37 patients (42 hips) that were in the fair or poorly performing group were invited to attend a clinic in order to evaluate their resurfaced hip further. 26 patients (28 hips) presented, whilst the remaining declined a clinical review. Two hips had small lucent lines around the femoral stem and one hip had a narrowed femoral neck. Signs of gluteal enthesopathy/bursitis (n=6) and the presence of a pseudotumour (n=4) were the more common USS findings. Other diagnoses included: ischial bursitis (n=1), ischiofemoral impingement (n=1), residual pain from previous pubectomy for osteosarcoma (n=1) and recurrent sickle cell episodes (n=1). In the remaining hips (n=14), there were no adverse radiological or clinical findings.

3.3.2.6 Ten-year incidence of pseudotumour revision

The overall incidence of revision at ten years due to pseudotumour was 7.5% (95% CI: 4.3% to 10.7%). The only factors identified to have a significant influence on the incidence of pseudotumour revisions were gender and size of components (Figure 3.2).

The incidence of revision at ten years due to pseudotumour was significantly higher in females (18.8%, 95% CI: 9.8% to 27.9%), in comparison to males (1.7%, 95% CI: 0% to 3.4%) (log rank p<0.001) (Figure 3.5).

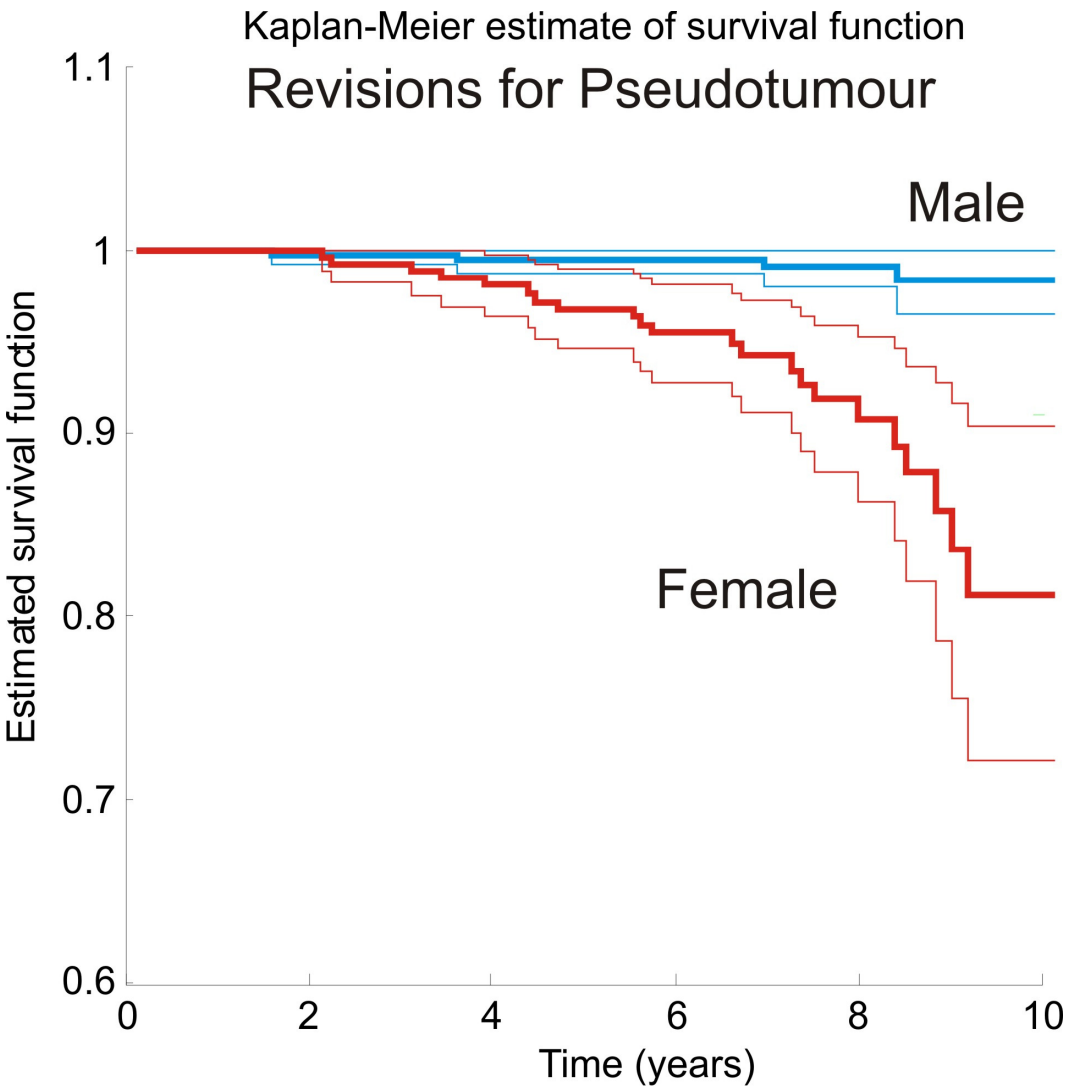


Figure 3.5 Survival of the entire cohort (colour coded for gender) of BHR arthroplasties with revision for pseudotumour as the end-point.

The incidence of revision at ten years due to pseudotumour was significantly greater in the small group (28.8%, 95% CI: 6.6% to 51.3%), in comparison to the 46 mm group (10.7% 95% CI: 4.1% to 17.3%), the 50 mm group (6.9%, 95% CI: 0.5% to 13.2%) and Large (0%) (log rank p<0.001) (Figure 3.6).

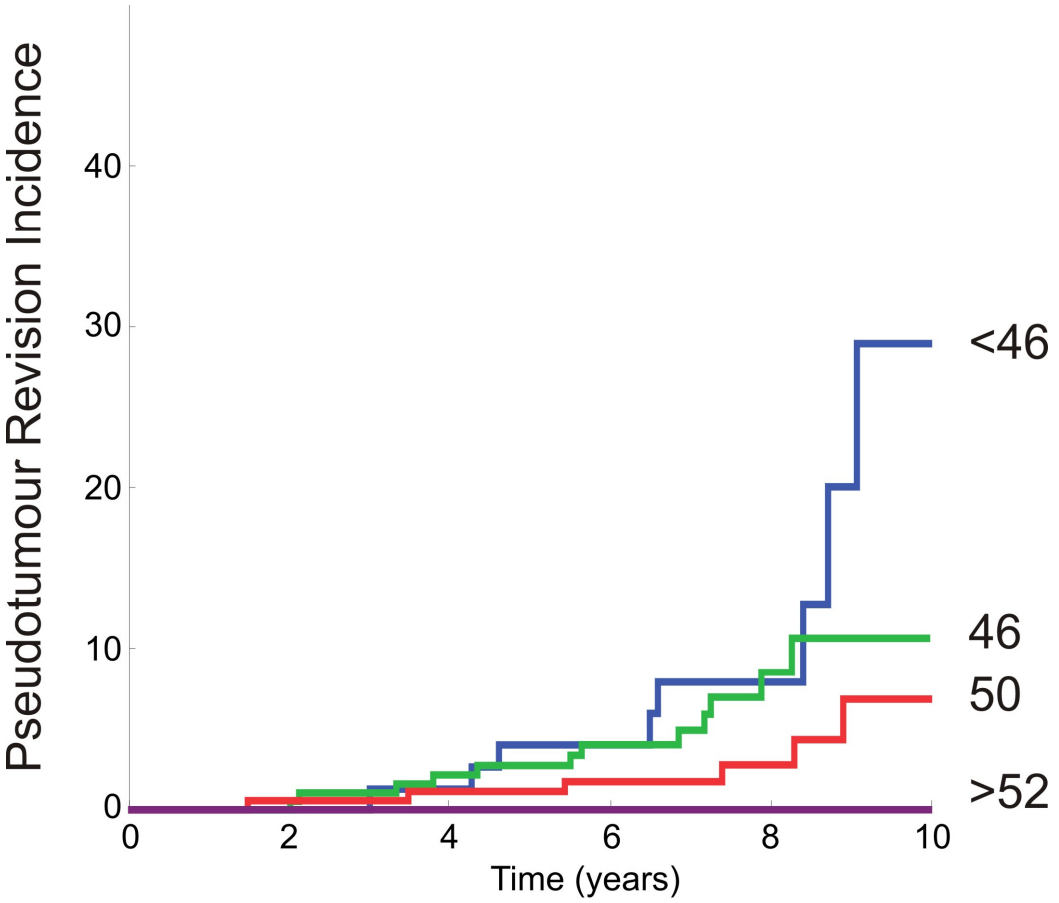


Figure 3.6: Pseudotumour revision incidence for the different component size groups (colour coded).

Factors such as primary diagnosis (log rank p=0.9), age group (log rank p=0.39), and grade of surgeon (log rank p=0.99) did not have a significant effect on the incidence of revision at ten years due to pseudotumour.

Applying Cox-regression analysis with the variables considered individually, only gender ($p<0.001$) and size ($p=0.01$) had a significant effect on revision rate. When adjusting for these variables in a multiple variable model, only gender ($p=0.03$) had a significant independent effect on pseudotumour incidence.

3.4 Study 3B: Prevalence of revision due to pseudotumour

3.4.1 Materials and methods

3.4.1.1 Study design

In a retrospective study, the outcome of interest has already occurred at the time the study is initiated. A retrospective study relies on retrieval of patient and outcome data that have already been collected (through medical records). Data used in this way may not be as reliable as data collected prospectively as it relies on the accuracy of records made at the time and on people's recall of events in the past (recall bias).

In order to avoid recall bias, only data obtained from patients records and databases were included in the study and no patients' or surgeons' recall was used to gain further information.

3.4.1.2 Study groups

Patient data was obtained from the database and medical records of two

independent, European, tertiary referral arthroplasty centres. Data obtained included all revisions of failed MoMHRAs performed between June 1999 and December 2010 at the two centres. One of the centres was the Nuffield Orthopaedic Centre (NOC), Oxford, United Kingdom and the other centre was the ANCA Clinic, Ghent, Belgium.

The NOC is a multi-surgeon, teaching hospital and specialist referral centre. Since 1999, 1,483 MoMHRAs have been performed. The ANCA clinic is a single-surgeon primary and revision arthroplasty centre with an interest in hip resurfacing arthroplasty. Since September 1998, Dr. Koen De Smet has performed over 3,500 MoMHRAs with multiple implant designs at the ANCA clinic.

The collaboration of the two specialist centres with a large volume of MoMHRAs performed and followed-up provided a unique opportunity to identify the prevalence of pseudotumour amongst the revisions of MoMHRA performed in the setting of a tertiary referral hospital.

3.4.1.3 Patient demographics (Table 3.5)

The entire cohort included 236 MoMHRAs in 224 patients. This included 87 males (90 MoMHRAs) and 137 females (146 MoMHRAs). The mean age at revision was 54.3 years old (range: 18 to 80 years). The mean interval time between primary MoMHRA and revision was 34.8 months (range: 0 to 106 months). The mean femoral component size was 47 mm (range: 38 to 60 mm).

The primary diagnosis leading to MoMHRA was available for 227 hips. Primary OA was the indication for primary MoMHRAs in the majority of cases (n=194, 86%), followed by 2° OA (n=18, 8%) and avascular necrosis (AVN) of the femoral neck (n=10, 4%). The case load was similarly distributed, with 123 revisions having been performed at the NOC and 113 at the ANCA clinic. Amongst the 236 revisions, 158 had the primary MoMHRAs at the two centres (67%), whist the remaining 78 cases had had their primary in 57 different centres from six different countries.

	Cohort	**NOC**	**ANCA**	**p-value**
Gender (% males)	38%	37%	40%	0.54
Age/ (SD) (years)	54.3/ (11.0)	56.4/ (11.3)	52.0/ (10.7)	0.002
Time to revision/(SD) (months)	34.8/ (27.6)	38.6/ (31.2)	30.8/ (22.9)	0.18
Femoral size/ (SD) (mm)	46.9/ (4.0)	46.7/ (3.8)	47.2/ (4.2)	0.34
Diagnosis (% 1° OA)	86%	87%	85%	0.68

Table 3.5: Demographics of revised cases included in study 3B.

3.4.1.4 Resurfacing systems explanted

There were eight different MoMHRA systems that were revised. The majority were BHR (n=119, 50%), followed by the Conserve Plus (n=73, 31%), the Recap

(n=11, 5%), the ASR (n=10, 4%) and the Durom (n=10, 4%). As the denominator number of the prostheses implanted could not be determined from the large number of tertiary referrals, further analysis on incidence of failure as per resurfacing implant could not be determined for the whole cohort. However, the revision rates for different implants in hips that had the primary surgery in the two centres are given in the table below (Table 3.6).

Implant	**BHR**	**C+**	**Cormet**	**Recap**	**ASR**
Revised	84	61	3	8	2
Performed	2613	1936	19	172	66
Revision Rate/ %	3.2	3.2	15.8	4.7	3.0

Table 3.6: Different types of MoMHRA devices used and revised in both centres. Numbers revised, performed and their failure rates. (C+: Conserve Plus)

3.4.1.5 Failure modes

Failure mode in all cases was decided based on clinical, radiological, intra-operative findings following review of the clinical notes pre-revision and radiographs. Failure modes identified in this cohort included fracture, pseudotumour, component loosening, painful impingement, infection, component mal-orientation and other (including component mismatch, heterotopic ossification, synovitis, unexplained pain).

3.4.1.6 Statistics

Statistical analysis was performed using SPSS (version 18, SPSS Inc., Chicago, Illinois). The dataset was assessed for normality using the Shapiro-Wilks test. Inter-group comparisons of non-normally distributed scale data were made with the use of non-parametric tests (Mann-Witney U, Kruskal-Wallis, log-rank). Cross-tabulation and the chi-square test were used for categorical data. Significance was considered when p values of less than 0.05 were obtained.

3.4.2 Results

3.4.2.1 Annual revision burden

The annual revision burden has risen in both units over a 12 year period. During the first six years (1999 – 2004), 28 revisions were performed in both centres. However, over the following six years, the revision burden appears to have risen by seven-fold (Figure 3.7), with 208 revisions performed within this later period.

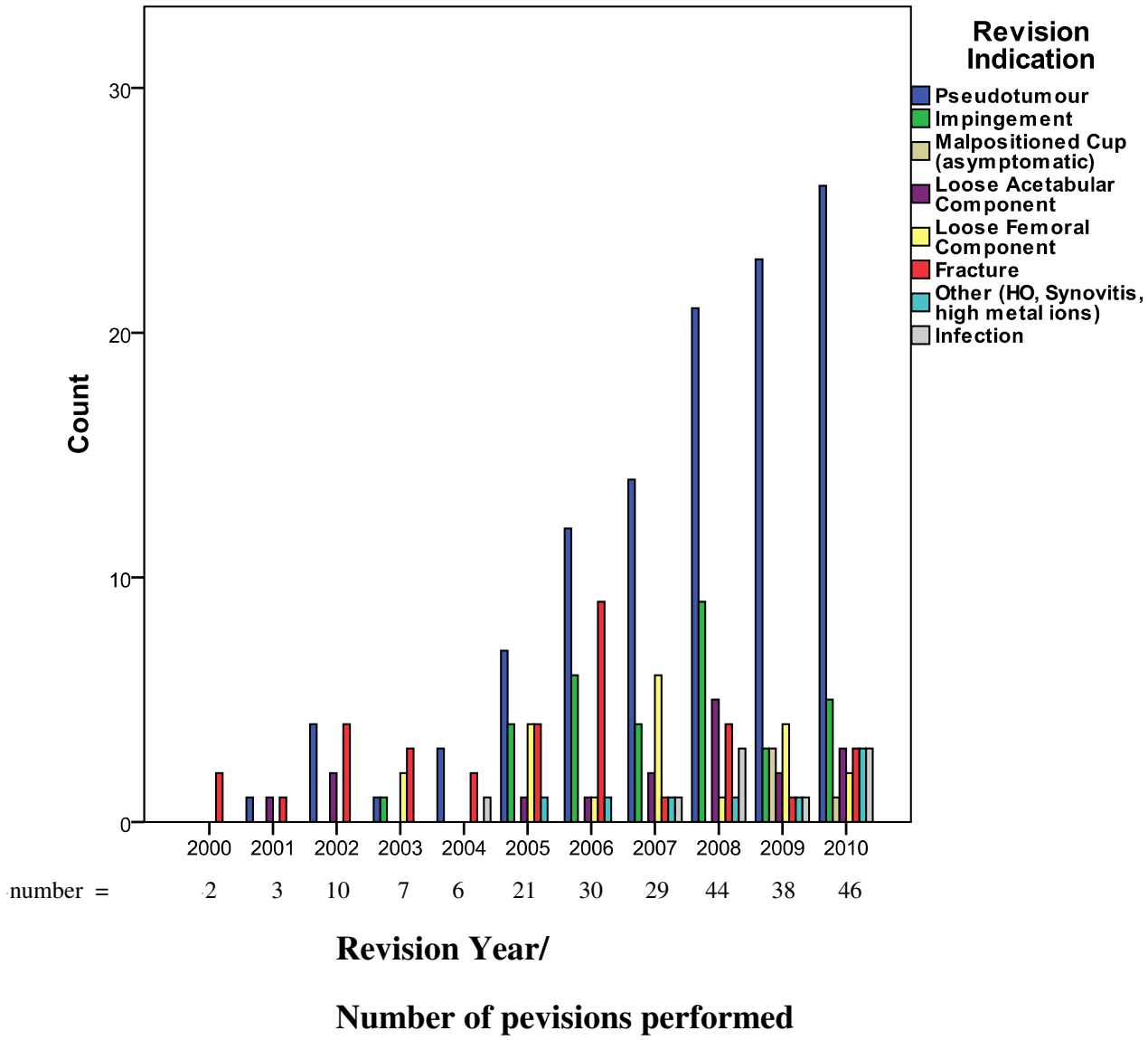


Figure 3.7 Histogram illustrating number of revisions for varying indications (colour code) performed each year between 2000 and 2010. Number below year, indicates number of revisions performed in the year.

3.4.2.2 Prevalence of different revision indication

The different revision indications and their prevalence are included in Table 3.7. The most common revision indication was a pseudotumour followed by fracture.

Revision Indication	Number of cases (%)	Gender/ % males	Femoral size (mm) / SD	Time to revision (months) / SD
Fracture	34 (14.4)	59	47.6 / 4.7	12.1 / 12.7
Pseudotumour	112 (47.5)	18	45.8 / 3.0	47.6 / 26.6
Painful impingement	32 (13.6)	69	49.0 / 3.8	31.4 / 27.3
Loose cup component	17 (7.2)	41	46.9 / 4.5	15.9 / 12.6
Loose femoral component	20 (8.5)	35	46.8 / 4.4	39.1 / 26.8
Other (HO, synovitis, mismatch)	8 (3.4)	86	50.9 / 4.9	35.4 / 29.7
Infection	9 (3.8)	78	49.3 / 3.4	26.4 / 18.9
Component mal-orientation	4 (1.7)	100	45.0 / 4.2	14.1 / 4.7

Table 3.7: Different revision indications encountered including their prevalence, gender distribution, femoral head size and time to revision.

The months to revision were significantly different between different groups ($p=0.01$) as indicated in Figure 3.8. The different revision indications also had significant gender ($p<0.001$) and femoral size differences ($p=0.006$).

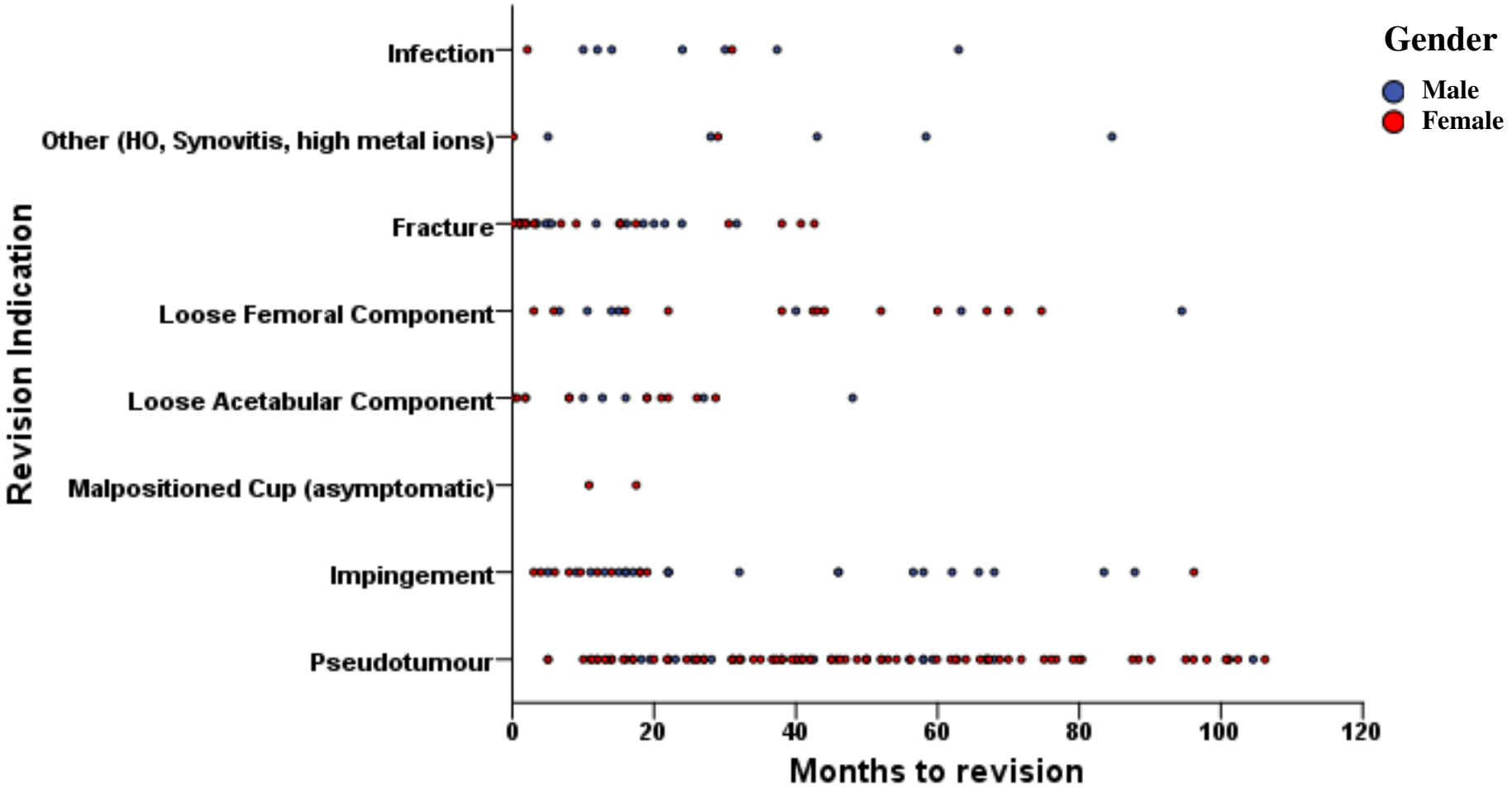


Figure 3.8: Scatter of different revision indications plotted against time interval between primary and revision surgeries. Graph is colour coded for gender.

3.4.2.3 Characteristics of pseudotumour cases

Of the 112 pseudotumour cases, 63 were revised at the NOC and 49 at the ANCA clinic. The primary MoMHRAs had been performed at either of the two centres in 81 cases (72%). Similarly to previous reports, the majority of revisions were in females (n=92, 82%). Primary OA was the diagnosis leading to the primary MoMHRA in 92 patients (87.7%). Six bilaterally revised MoMHRA-patients were revised due to bilateral pseudotumour (all women). Furthermore, two hips in two further patients with bilateral resurfacings required revision due to pseudotumour. Pseudotumours were identified around all types of resurfacing implants. The mean time to revision was 47.6 months from the primary MoMHRA (range: 5 to 106 months). Nine of the pseudotumour revisions occurred in the period 1999 – 2004, whilst the remaining 103 have occurred in the following six years.

3.5 Discussion

The findings of these studies show that the ten year-survival of the BHR in an independent centre is 87.1% and that the ten year incidence of revision due to pseudotumour is 7.5%. Furthermore, it is evident that the revision burden has significantly increased over the recent years in specialist centres and that revision due to pseudotumour is the most common failure indication with a prevalence of 47.5% amongst all failures.

There have been many reports of early-term outcome following MoMHRA both from single centres and national registries. However, the only reported ten year survival studies have either been from the designer centres or high-volume, single

surgeon series. These ten-year survival rates vary between 88.5% to 97%[25,33,34]. Furthermore, the incidence of revision due to pseudotumour in these reports varies between 0 to 0.5%. This independent, teaching hospital, single centre study with multiple surgeons of varying levels shows a ten year survival of BHRs of 87.1%, which appears to be slightly lower than that reported from the designer centres. However, differences in cohort characteristics, such as gender between this series (59% males) and those reported by the designers (66 – 74%)[25,33,34], could account for this slight difference in outcome.

The revision indications identified in the ten-year survival study are similar to what has been previously reported by the designers. However, the incidence of pseudotumour related revisions appears to be greatly different between this independent study and the designer series. Amstutz *et al* reported on his eleven years experience with the Conserve Plus hip resurfacing and reported 33 revisions[42]. Ten were for femoral neck fractures, 20 were aseptic loosening, two were for infection and one was for recurrent dislocations. There were no reports of pseudotumour. Treacy *et al* reported on ten revisions in the first 130 patients with minimum follow-up of ten years[33]. Revision indications in these ten patients included fracture/AVN (n=5), infection (n=3), aseptic loosening (n=1) and recurrent dislocation with associated pseudotumour (n=1). Similarly, Daniel *et al* reported on a ten-year pseudotumour incidence of 0.4% from McMinn's series[172]. The ten-year incidence of revision due to pseudotumour in this study was 7.5% for the whole cohort, with a significant ten-fold difference in the incidence between males (1.7%) and females (17.6%).

Steffen *et al* reported on the five-year survival of the first 610 BHRS performed in this study's cohort and reported an overall survival was 95%[30]. 23 revisions were reported and fracture was the most common indication for revision (n=12) followed by aseptic loosening (n=4); pseudotumour was only reported in 3 revisions. In the current ten year study of 54 revisions, there was no increase in the number of fractures reported and aseptic loosening only accounted for two more revision cases. However, there was a great increase in cases that were revised due to pseudotumour with 23 extra cases (total n=26) and a small number of cases revised due to pain with clinical evidence of impingement (n=8). It is therefore evident that pseudotumour is the most commonly encountered mid-term failure. The identification of factors contributing to its development is paramount in order to alter clinical practice and reduce its incidence.

Significant differences in survival and outcome were identified for different subgroups such as gender and component size leading to primary BHR. Males had a significantly superior ten-year survival and patient reported functional outcome in comparison to females. The ten-year survival of the BHR in males was 94.7% with male patients maintaining higher levels of activity compared to females. Men under 50 years old with 1° OA had a ten-year survival of 99%, with 50% of them maintaining a highly active lifestyle (UCLA ≥8). In contrast, the same group have lower survival with conventional THAs as shown by the Swedish Hip Joint Registry with young men having a survival of 85% at ten years. MoMHRA was initially offered as an alternative to THA in the treatment of this particularly challenging group, aiming to at least delay conversion to a primary THA for a number of years. The findings of this study support the original premise that

resurfacing with the BHR is an effective surgical treatment option in men with ten-year survival above the NICE target (>90% survival at ten years), and maintenance of high functional and activity scores. However, clinicians should be aware of the increasing incidence of pseudotumour identified in this gender group; incidence of pseudotumour was 0.5% at eight years and rose to 1.7% at ten years.

The significantly lower survival rate of MoMHRA amongst females reported in registry reports was also identified in this study. Females compared to males had a significantly reduced ten-year survival rate of 74%. This figure is below the NICE guidelines and below the survival figures of conventional THAs in females as reported in the registries. In addition, an alarming increase in the incidence rate of revision for pseudotumour from 9.4% at eight years to 17.6% at ten years was identified. It is likely that female gender, history of dysplasia and smaller femoral size are all factors that are interlinked and hence all contribute to the risk of development of pseudotumour. However, the above findings of this study coupled with the inferior OHS scores with the surviving BHRs provide evidence that MoMHRA should be performed with great caution in females, if at all. A greater understanding of the patho-mechanism of pseudotumour development is needed in order to implement changes that would reduce pseudotumour incidence, especially in this gender.

Similar to the findings of previous shorter-term studies, femoral head size had a significant effect on survival and pseudotumour incidence. Components <46 mm had a ten-year pseudotumour incidence of 15.9%. The effect of size on

pseudotumour can at least be partially explained by the findings of De Haan *et al*[100]. These authors showed that patients with smaller components have higher ion levels and are theoretically more likely to edge load since component size influences the acetabular component's arc of cover. Increased edge loading will lead to increased wear and increase pseudotumour risk. As previously mentioned the findings of small size and female gender having lower survival and higher pseudotumour incidence are interlinked. Previous studies had contradicting findings on which factor is predominant. Prosser *et al* reviewed data from the ANJR and reported the rate of revision was higher in females and in patients with smaller femoral heads (femoral heads ≤44 mm had a five-fold increased revision risk in comparison to femoral heads ≥55 mm)[167]. However, the higher rate of revisions amongst females could be accounted for by the smaller implant sizes in females. After adjusting for head size, there was no difference in the rate of revision between males and females. Glyn-Jones *et al* identified gender and small size to be risk factors for pseudotumour however on fitting a Cox proportional hazard model only gender had an effect[153].

Surgical experience did not have an effect on ten-year survival. This is likely to be the case due to the fact that most trainee cases were performed under consultant-supervision. It is of interest that consultant-lead cases had better OHS compared to consultant-supervised ones. The lack of pre-operative data, however, does not allow for further conclusions as it may be that the consultant-performed cases had significantly better pre-operative scores.

In order to identify the MoMHRA revision burden posed on orthopaedic surgeons in specialist units and the prevalence of pseudotumour amongst failed MoMHRAs, all revisions performed in the NOC and the ANCA clinic between 1999 and 2010 were retrospectively reviewed. This study represents the largest reported comprehensive series which is not derived from registry data.

The revision burden presented to both units increased over the last decade by seven-fold. Different reasons for this increase in revision burden include increased use of MoMHRA in the period of 2001 to 2006 as shown by registry data, the acquisition of Midland Medical Technologies (MMT) by Smith and Nephew (increasing marketing power in central Europe) in 2004 and the increased cumulative revision rate due to mid-term failure modes such as pseudotumour. This increase in revision burden was closely associated with an increase in the revision rate of pseudotumour cases.

Amongst the cases revised, pseudotumour was the most common failure mode, followed by component loosening, fracture and painful impingement. The lower prevalence of fractures in this cohort in comparison to registry data probably reflects that fractures are usually revised in the centres that performed the primary MoMHRA. All fractures revised in this cohort had their primary procedures in the two centres and reflect the fracture rates of the two centres. Pseudotumour, painful impingement and component loosening were the three most common indications for revision amongst the tertiary referral cases presented to the two units.

Pseudotumour revisions were most common amongst females, patients with smaller components and in patients that underwent a MoMHRA for their treatment of primary OA. However, they were not exclusively diagnosed and revised in these groups only. They were identified for all resurfacing systems and the mean time to revision was four years. Pseudotumour revisions were performed with a varying interval from primary surgery (0.5 to 8.8 years). Seven cases (6%) underwent a revision within the first year post resurfacing and twenty-two (20%) underwent a revision within the first two years post resurfacing. These findings suggest that diagnosis and revision due to a pseudotumour can occur in any patient with a resurfaced hip, with all different patient- and implant-characteristics and at any time post-surgery. As the cumulative incidence of pseudotumour increases with time since surgery, continued routine follow-up as per MHRA guidelines is required[137,138].

Although the findings of this study demonstrate that pseudotumour is the most common revision indication, there is currently no data regarding outcome after revision. Outcome after MoMHRA revision has only been reported for femoral-side failure by Ball *et al*[48]. Hence, further studies are needed in order to identify the outcome of revision following failed MoMHRAs and the influence of revision indication of outcome, with particular attention to pseudoumour.

The findings described in this chapter, highlight some patient-related factors that contribute to pseudotumour risk, such as gender and size. As mechanical reasons are thought to contribute to the wear process (Chapter 2), it is likely that surgical,

in addition to patient and implant factors contribute to the risk of pseudotumour development. Further studies are needed in order to highlight any possible surgical factors and provide evidence-based guidelines on how to perform the procedure in order to minimise pseudotumour-risk.

There are several limitations to the studies described in this chapter. These include the following:

1. Lack of pre-operative data of OHS/UCLA score in the BHR survival study prevented the comparison of the functional outcome before surgery and at latest follow-up.
2. Although patients with a BHR implant at possible risk were identified as per OHS, the lack of available radiographs for all patients prevented a radiological assessment in order to identify the radiolographically at-risk patients.
3. A well-described limitation in retrospective studies is the possibility of incomplete data available. Eleven patients in the prevalence study had incomplete data on pre-operative diagnosis leading to MoMHRA and eighteen on component size. All of the patients with incomplete data were patients who were tertiary referrals.
4. There were a large number of tertiary referrals in the prevalence study (n=78, 32%). The lack of data from the centres that performed the primary MoMHRAs prevented analysis of cumulative incidence of revision at different centres with varying resurfacing experience. However, the varied, multiple sources of patient referral are likely to represent the spectrum of

clinical failures from surgeons with variable skills and experience, and provide a suitable database for analysis of patient characteristics.

3.6 Conclusion

The results of these studies reject the null hypothesis set at the beginning of the chapter. The revision burden due to pseudotumour is large as evident by both the incidence of pseudotumour failures at ten years and the prevalence of pseudotumour amongst failed MoMHRAs encountered in specialist centres. Furthermore, the revision burden associated with failed MoMHRAs has increased in tertiary referral centres. Studies are needed in order to identify the revision outcome following different types of MoMHRA failure, especially pseudotumour.

3.7 Summary

- The ten year survival of the BHR was 87.1%. There was a significant difference in survival between males (94.7%) and females (73.9%).
- MoMHRA with the BHR is a very successful treatment option for young men (<50 years old) with primary osteoarthritis; the primary population target for MoMHRA. The 10-year survival of the BHR for this cohort was 99% and patients reported very good functional outcome, with 50% enjoying very high activity levels.
- Contrary to early/mid-term studies reporting femoral neck fracture being the most common cause of revision, at this longer follow-up study

pseudotumour was the most common failure mode with an overall incidence of 7.5%.

- Patient factors leading to significantly greater incidence of revision due to pseudotumour were female gender (17.6%) and patients with small size implants (<46 mm) (15.9%). Further studies are needed in order to identify any surgical risk factors for the development of a pseudotumour.
- The revision burden of MoMHRA in independent tertiary referral centres has greatly increased over the recent years. This increase is partly attributed to an increasing incidence and prevalence of pseudotumour revisions at mid-term and onwards.
- Pseudotumour is the most commonly encountered revision indication in tertiary referral units.
- Studies are required in order to define outcome of MoMHRA revision and investigate the effect of different revision indications. These are reported in the next chapter.

4 OUTCOME FOLLOWING REVISION OF FAILED MoMHRA[‡]

4.1 Introduction

The previous chapter defined the revision burden (defined as the percentage of revised cases as a function of all MoMHRAs) pseudotumour poses to orthopaedic surgeons, especially those at specialist units. However, in order to obtain a holistic view one should identify the disease burden (defined as the impact of a health problem measured by mortality, morbidity, quality of life measures) of pseudotumour relative to other modes of failure. In order to do so, one should assess whether revisions due to pseudotumour are of similar surgical effort and have similar patient outcome compared to revisions for all other failure modes of MoMHRAs.

One of the proposed advantages of HRA has been the theoretical ease of conversion to THA. This is thought to be the case due to the normal proximal femoral loading preventing stress shielding and the preservation of the native femoral neck and intramedullary canal architecture.

[‡] Work in this chapter has been published as:

Grammatopoulos G, Pandit H, Kwon Y-M, Gundle R, McLardy-Smith P, Beard DJ, Murray DW, Gill HS: Hip resurfacings revised for inflammatory pseudotumour have a poor outcome. J Bone Joint Surg Br 2009 91-B: 1019-1024.

Studies of earlier generation MoMHRAs looking at outcome after revision are limited by the lack of adequate follow-up, outcome measuring tools and comparative groups. Thomas *et al* reported on the first 17 failed first-generation HRA in 1982[173]. At a follow-up of six to 65 months the authors reviewed the failed HRA patients with clinical and radiographic evaluations. They concluded that 'the clinical results of revision and conversion were comparable with those of conventional revision surgery but were less satisfactory than those of primary surgery'. A year later, Bradley *et al* reported on 28 resurfaced hips revised to THA and concluded that 'with regard to pain, ability to walk, and range of motion, successfully revised hips functioned at a level similar to that of primary THA'[174]. However, the overall failure rate was 10.7%, which is greater than that generally reported for primary THA but considerably less than that usually found for revision THA.

To-date the only report on outcome following failed 3rd generation MoMHRA is from a case control study, from a designer-surgeon's series. Ball *et al* reviewed the outcome of 21 MoMHRAs converted to MoMTHAs due to femoral component failures (fracture and loosening)[48]. In 18 hips the acetabular component was retained and in three hips both components were revised. The converted patients were case controlled matched for age, gender and indication for surgery with 64 patients that had undergone primary MoMTHA during the same period by the same surgeon. There was no significant difference between the two groups with regard to operative time, blood loss or complication rates. Furthermore, no significant differences were observed with regards to Harris Hip Score (HHS), UCLA activity and SF-12 scores. The authors concluded that

conversion of a MoMHRA to a primary THA, due to a femoral side failure, appeared to be comparable to a primary THA in terms of surgical effort and clinical outcome.

However, to-date no studies have identified the outcome following revision due to all different modes of failure and more specifically for patients revised due to pseudotumour. Hence, the aim of the work reported in this chapter was to define the outcome of MoMHRA revision following any revision indication with particular attention to pseudotumour.

4.2 Null hypothesis

H_0: Patient-reported outcome following MoMHRA revision is independent of revision indication and is similar to the outcome following primary THA.

4.3 Materials and methods

4.3.1 Study design

A case-control study is an observational epidemiological study that compares subjects with a specific outcome (the cases – study group of interest) with subjects who do not have this outcome (the controls) with respect to attributes of interest. Therefore, in this study with an ethical committee waiver, the outcome of revised MoMHRAs (study group) was compared with the outcome of primary THAs

(control group) matched for gender, age and diagnosis leading to the primary procedure.

4.3.2 Patient groups and demographics

4.3.2.1 Study group

The first consecutive 53 failed MoMHRAs requiring revision, and conversion, to THA at the NOC were included in this study and formed the MoMHRA Group. Amongst those, 49 hips (47 patients) had their primary MoMHRA at the NOC. Two patients had conversion of bilateral hip resurfacing to bilateral THAs. Four revised MoMHRAs had the primary surgery at other centres. The study cohort had four different types of MoMHRAs (BHR, Conserve Plus, Recap and Cormet). The most common indication for the MoMHRA was primary osteoarthritis (40 hips, 75.5%) followed by osteoarthritis secondary to developmental dysplasia, slipped upper femoral epiphysis and avascular necrosis (AVN) (13 hips, 24.5%). One hip with developmental dysplasia had undergone a proximal femoral valgus osteotomy prior to MoMHRA. None of the other hips had had previous surgery. There were 33 hips in female patients (62%) (Table 4.1). The mean age at the time of MoMHRA was 53.7 years (range: 20 to 71 years). The extended posterior approach was used in all but one of the operations. The primary procedures were performed by 18 different surgeons.

The indication for revision surgery was pseudotumour in 16 hips (Pseudotumour Group), fracture of the femoral neck in 21 hips (Fracture Group) and other causes

including loosening, infection, AVN/collapse and recurrent dislocations in the remaining 16 hips (Other Group).

In all cases in the Pseudotumour Group, both components were revised and a conventional THA was implanted using either ceramic-on-ceramic (n=8), ceramic-on polyethylene (n=6) or metal-on-polyethylene (n=2) bearings. The mean femoral head size used at revision was 32.1 mm (range: 28 to 36 mm). In 13 of the Fracture Group, the femoral component was revised to a conventional stem with a large metal femoral head which matched the inner diameter of the retained acetabular component. In the remaining cases, both components were revised and ceramic-on-polyethylene (n=3) or metal-on-polyethylene (n=5) bearings were used. The mean femoral head size used at revision was 42.8 mm (range: 38 to 54 mm). In the Other Group, the acetabular components were retained in seven cases and in the remainder conventional THA was used with either ceramic-on-ceramic (n=4), metal-on-polyethylene (n=4) or ceramic-on-polyethylene (n=1) bearings. The mean femoral head size used at revision was 38.5 mm (range: 38 to 54 mm). The revisions were performed by 13 different surgeons. All cases in the Pseudotumour Group were performed by consultants. Nine cases in the Fracture Group and five in the Other Group were performed by trainees. The posterior approach was used in most of the revision cases (n=42, 80%). Eight were performed through the anterolateral approach and three through the Smith-Petersen approach[175]. The mean time between the initial MoMHRA and revision surgery was 1.6 years (0.0 to 6.7 years). The mean follow-up was three years (0.8 to 7.2 years).

4.3.2.2 Control group

For each of the subgroups (Pseudotumour, Fracture and Other) a Control group was established by matching each study case with two primary THA control cases. A ratio of 2:1 was aimed for in order to increase statistical power of the study. The control groups were matched for gender, age at primary surgery, pre-operative diagnosis and length of follow-up. The control cases were obtained from the Exeter Primary Outcome Study (EPOS). This is a multicentre, non-randomised prospective study which recruited more than 1,400 patients undergoing primary THA between January 1999 and July 2007 with all patients prospectively followed at yearly intervals by independent observers. In all control cases, a cemented Exeter femoral component (Stryker, Howmedica Osteonics, Newbury, UK) was implanted and a variety of cementless and cemented acetabular components were used. Forty-one THA patients were case-control matched for the fracture group, 32 for the pseudotumour group and 30 for the other group (Table 4.1).

Group	Number	M/F ratio	Age (years) at index surgery	
			Mean	SD
Fracture	21	13/8	57.9	8.5
Fracture Control	41	26/15	58.6	7.4
Pseudotumour	16	0/16	51.3	12.0
Pseudotumour Control	32	0/32	51.8	12.0
Other	16	6/10	50.5	13.2
Other Control	30	13/17	52.8	13.4

Table 4.1: Patient demographics (SD = standard deviation).

4.3.2.3 Parameters studied

Parameters studied included operating time, complications and patient reported outcome measures. Data was obtained via medical records and through questionnaires sent to patients. Complications were also identified from patient notes and patient correspondence. Functional outcome was measured by the OHS[169] and the UCLA activity score[49]. The OHS was measured as described by Murray with a maximum of 48 points (best outcome) and a minimum of 0 points (worst outcome)[139]. Unfortunately, the OHS measured before the primary MoMHRA was not available for many of the patients in the study group. The UCLA activity score was recorded for the study group, with a maximum of ten points (undertaking regular impact sports) and a minimum of one point (wholly inactive). No activity scores for the control THA groups were available. Two

patients in the Fracture Group did not return their OHS and UCLA forms, and three patients in the Other Group did not complete their UCLA activity form correctly.

4.3.2.4 Statistics

Statistical analysis was undertaken in two parts. First, the differences between the different groups of resurfacing revisions were analysed and then the differences between the MoMHRA revision groups and their respective matched primary THAs were examined. Non-parametric tests (Mann- Whitney *U,* Kruskal-Wallis) were used in order to analyse continuous, scale data (e.g. operating time, OHS, UCLA scores). The chi-squared test was used to compare rates of complications. Differences were considered to be significant when a p value ≤ 0.05 was obtained. All the statistical analyses were performed using SPSS version 18 software (SPSS Inc., Chicago, Illinois).

4.4 Results

4.4.1 Clinical summary of the various groups

Revision surgery in the Pseudotumour Group tended to be complex because of the associated massive soft-tissue destruction. In three cases the participation of a tumour and a plastic surgeon was required, in two for the exploration of vessels and nerves, and in one for a transverse rectus abdominis pedicle flap to cover a large defect anterior to the capsule after resection of a pseudotumour. In these

three cases the Smith-Petersen approach was used. In one case, because of the uncertainty of the diagnosis, the revision was carried out in two stages. Palsy of the femoral nerve was observed in three hips, which in one patient was associated with symptoms of intermittent claudication secondary to stenosis or fibrosis of the femoral artery which required an angioplasty. It is noteworthy that neurovascular symptoms were present prior to revision and persisted afterwards. Two hips had early loosening of the component and have been re-revised. Three hips required re-revision due to dislocation and one hip due to recurrence of pain. At revision, recurrent pseudotumour was detected. In the Fracture Group, three hips developed deep infection after the revision surgery and required further two-stage revisions. No infections recurred. In the Other group, one hip had a periprosthetic fracture requiring a further revision with change of the femoral component. Another patient developed a deep infection and had persistent infection, and a later periprosthetic fracture requiring a further staged procedure.

	Fracture Group (n=21)	Fracture Group Controls (n=41)	Pseudotumour Group (n=16)	Pseudotumour Group Controls (n=32)	Other Group (n=16)	Other Group Controls (n=30)
Blood Transfusion	7 (33%)	4 (10%)	12 (75%)	2 (6.2%)	7 (44%)	3 (10%)
Dislocation	-	4 (10%)	3 (2 recurrent) (19%)	2 (6.2%)	-	2 (6.7%)
Nerve Palsy	-	-	3 (1 partially resolved) (19%)	-	-	-
Component Loosening	-	-	2 (13%)	-	-	-
Infection	3 (14%)	-	-	-	1 (6%)	-
Peri-prosthetic Fracture	-	-	-	-	1 (6%)	-
Re-revision	3(14%)	-	6 (38%)	1 (3.1%)	2 (13%)	-

Table 4.2: Complication summary for each group.

4.4.2 Differences between the various groups of revised MoMHRA

The operating times for the different groups were significantly different ($p < 0.001$) with revisions for pseudotumours being the most protracted at a mean of 161.6 minutes (range: 120 to 200 minutes) followed by revisions for other causes at a mean of 129.4 minutes (range: 75 to 190 minutes). Revisions for fracture were the quickest at a mean of 99.6 minutes (range: 46 to 145 minutes). Major complications occurred in eight (50%) of the pseudotumour revisions, in three

(14%) of the fracture revisions and in two (13%) of the other revisions. Overall, the incidence of major complications was not significantly different in the three groups. It was, however, significantly (p=0.02) higher in the Pseudotumour Group compared with the combination of the other two Groups. The Pseudotumour Group had a significantly worse outcome compared to the Fracture and Other Groups as illustrated in Figures 4.1, 4.2 and Table 4.3. (p<0.001).

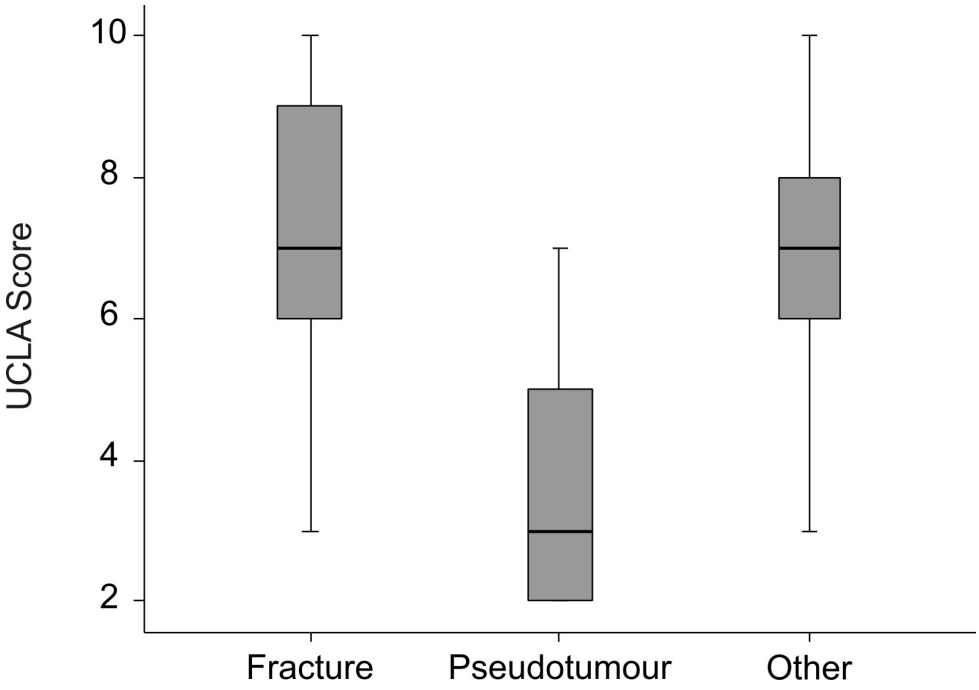


Figure 4.1: Differences in UCLA Activity Scores between the three MoMHRA revision groups.

Group	Oxford Hip Score		Operative Time (minutes)		UCLA Activity Score	
	Mean	SD	Mean	SD	Mean	SD
Fracture	40.2	9.2	99.6	30.4	7.0	2.0
Fracture Control	42.7	7.5	95.9	31.8	n/a	n/a
Pseudotumour	20.9	9.3	161.6	24.5	3.8	1.8
Pseudotumour Control	39.1	9.2	113.1	51.7	n/a	n/a
Other	37.8	9.4	129.4	36.7	6.7	2.1
Other Control	39.7	10.1	104.4	39.2	n/a	n/a

Table 4.3: Result summaries for each group (SD = standard deviation).

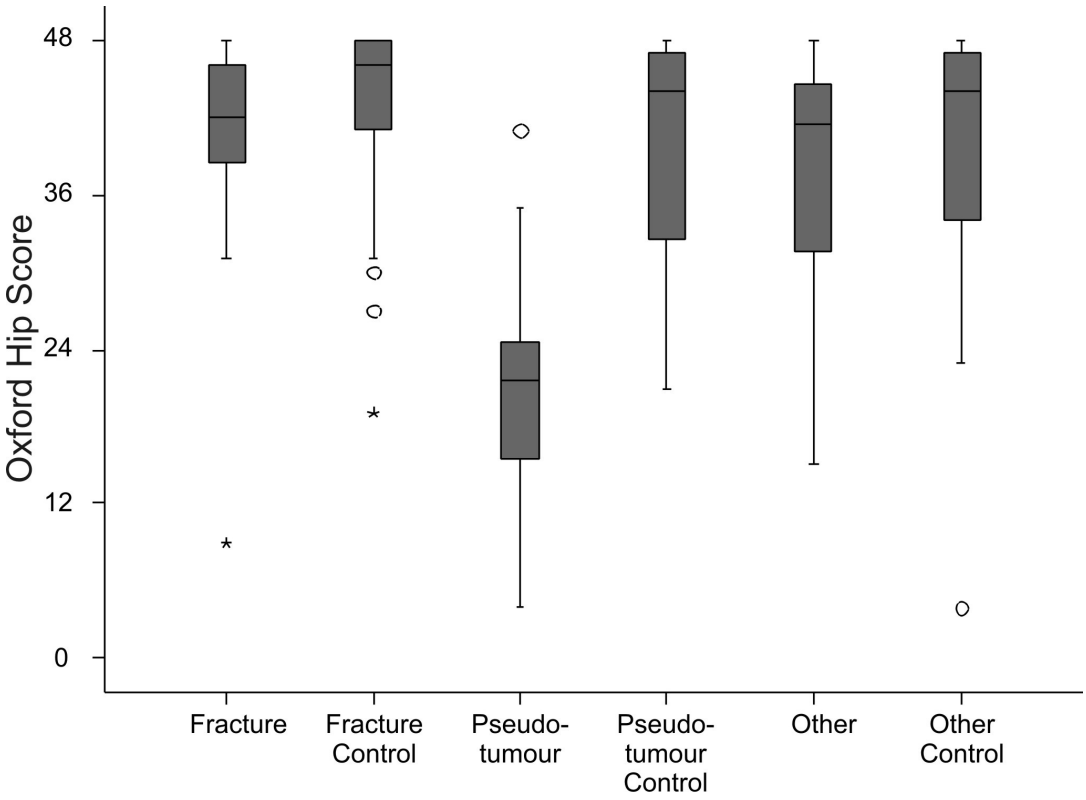


Figure 4.2: Differences in Oxford Hip Scores between the three MoMHRA revision groups and their controls.

4.4.3 Differences between revised MoMHRAs and primary THAs

The operating time for the Pseudotumour Group revisions was significantly longer than that for their matched THA controls ($p<0.001$, Table 4.3). The Pseudotumour Group had a significantly higher rate of major complications at 50% than their control group at 6.2% ($p<0.001$). This group also had a significantly worse outcome than their matched THA control group ($p<0.001$, Figure 4.2, Table 4.3). The mean OHS of the Pseudotumour Group after revision was 20.9 (4 to 41) which was within the range of scores for their THA control group before they had their primary THA with a mean OHS of 13.5 (4 to 28).

There was no significant difference in the mean operating time between the Fracture Group and their matched THA control group (Table 4.3) ($p=0.6$). Neither was there any significant difference in the mean OHS score between the fracture group and their THA group ($p=0.12$) (Figure 4.2, Table 4.3). Although there was no significant difference ($p=0.59$) between the major complication rates in the two groups, this may have been a function of the small numbers of patients.

There was no significant difference in the mean operating time between the Other Group and their matched THA controls ($p=0.07$, Table 4.3) or in the mean OHS between the Other Group and its control group ($p=0.26$; Figure 4.2, Table 4.3). Similarly, there was no significant difference in the major complication rate between the two groups ($p=0.50$), there may have been a real difference which was masked by the small numbers.

4.5 Discussion

The previous chapter identified the revision burden of failed MoMHRA and that of pseudotumour. The ten-year survival of MoMHRAs is 87.1%, the incidence of pseudotumour at ten years is 7.5% and the prevalence of pseudotumour amongst all failed MoMHRAs presenting to specialist centres is 47.5%. However, as evident with previous studies reviewing revision THA data, outcome is dependent on revision indication. Biring *et al* reviewed 222 revision THA patients and identified that aseptic loosening as a revision indication was a predictive factor of superior outcome[176].

Although case reports and series have described the occurrence of pseudotumour and have commented on the type of revision surgery performed, no study to-date has reviewed the outcome following revision. Similarly, there has been no study that describes outcome following revision for any failure mode other than femoral-side failures. In femoral side failures, only the femoral component is replaced in the majority of cases and may hence be considered a technically easier revision compared to one that involves exchange of both components. Hence, this case control study of the initial experience of revision of failed MoMHRA in a specialist centre aimed to identify the revision outcome following all different types of revision indication likely to be encountered, with particular attention to pseudotumour. In addition, it aimed to test the hypothesis, and proposed advantage, that regardless of revision indication, the outcome of a revised MoMHRA is similar to that of a primary THA.

The findings of this study suggest that outcome after revision of MoMHRA is dependent upon the revision indication and hence the null hypothesis is rejected. Furthermore, it is evident that pseudotumour is potentially a catastrophic complication following MoMHRA. In revisions for reasons other than pseudotumour the outcome was generally good and similar to that after primary THA.

The experience of inferior outcome following pseudotumour revision is probably explained by the intra-operative findings described in Chapter 2 and also identified in the revisions described in this chapter. The most prominent intra-operative finding was that of soft-tissue destruction and necrosis, with associated bone loss. Pseudotumours tended to pass through tissue planes. As evident by the intra-operative records, revision surgery was often difficult, particularly in cases with massive soft-tissue destruction or neurovascular involvement. The neurovascular involvement failed to fully resolve after surgery and hence patients had persistent neurological and claudication type of symptoms. The complexity associated with these revisions lead to all surgeries being performed by consultant hip surgeons and the involvement of tumour specialists and plastic surgeons in order to assist with appropriate excision of involved tissues and provision of soft-tissue coverage with necessary muscular flaps. All patients in the Pseudotumour Group required revision of both components. On the contrary, revisions in the Fracture or the Other Group, were not associated with the involvement of any other sub-specialist surgeons, neither was there any described extensive soft-tissue or bone involvement described at revision. Only eight hips in the Fracture Group (38%) and eight in the Other Group (50%) had revision of both components. It is

thus unsurprising, that revisions for pseudotumour tended to take longer and patients were more likely to require a blood transfusion compared to MoMHRA revisions undertaken for all other causes.

The outcome of pseudotumour revisions was poor, with the mean OHS at follow-up being inferior to the OHS's of the Fracture and Other Groups and the case matched THA group. The outcome after revision in the pseudotumour cases was of the same range to that of patients due to have a primary THA. Similarly, the post-revision activity levels in pseudotumour cases were inferior to the Fracture and Other Groups. Furthermore, nearly half of the revisions encountered major complications and a third required further revision within a few years. Three pseudotumours sustained dislocations and required re-revisions. The revision femoral head sizes in these three cases were 32 (n=2) and 28 mm (n=1). In order to reduce dislocation risk, it may be advisable for surgeons to consider as large a femoral head as possible without compromising polyethylene thickness and amount of bone being reamed. Recurrent pseudotumour has been found in all hips requiring further revision. Presumably, the reason why pseudotumours recur after revision is that a substantial amount of wear debris still remained after the first revision; hence a thorough debridement is probably necessary. Thus, the perceived advantage that MoMHRA revisions are simple to revise and that patients post revision function as well as those with primary THA could not be supported for the pseudotumour cases in this study.

However, this study provided evidence that the perceived advantage was correct for revisions performed for all other reasons, although significant complications

did occur. The operating time for revisions for fracture and the OHS after revision for fracture are similar to those for primary THA and hence confirm the findings of Ball *et al*[48]. This is not surprising since most of these cases, required only a conventional femoral component with a large metal head and did not have extensive soft-tissue and bone destruction. In this study, half of MoMHRAs for 'other' causes required revision of both components. Although the operating time was slightly longer and the OHS was slightly worse than for a matched THA control group, they were not significantly worse (p=0.07 and p=0.26, respectively).

The combined incidence of major complications after MoMHRA revision for fracture and other causes was significantly higher than that after primary THA. This is to be expected for the Other Group since it included complex problems such as infection. However, it is surprising for the Fracture Group since these revisions tended to be straightforward. The Fracture Group experienced a high rate of infection with 15% becoming infected and requiring further two-stage revisions. This may have been related to the soft-tissue damage and haematoma resulting from the fracture which increased the risk of infection.

The findings presented in this chapter strongly support the argument for revising any MoMHRA as soon as a pseudotumour is suspected so that revision occurs while soft-tissue damage is limited. This was also identified to be the case in a recently reported retrospective consecutive case series. De Smet *et al* reviewed the outcome of revision of failed MoMHRA and reported that mid-term outcome (Harris Hip Score, complication and re-revision rates) following MoMHRA

revision can be improved[177]. Factors that were identified to improve outcome included: increased awareness of the failure modes, the use of diagnostic aids such as metal ions, the use of femoral heads of greater diameter at revision and patient education. The improved outcome reported with increasing experience was also observed in cases with associated soft-tissue masses (pseudotumours). The authors noted that, with increased awareness, the pseudotumours revised were associated with less soft-tissue destruction, which probably contributed to improved outcome.

However, in order to achieve revision prior to extensive soft-tissue damage, surgeons should be aware of the condition, how to diagnose and what risk factors are associated with it. Patient and implant specific risk factors described previously (Chapter 2 and 3) are useful aids; however it is of importance to identify surgical factors that contribute to increased wear and pseudotumour development. This would further aid surgeons in identifying these masses earlier.

The likely contribution of surgical factors to failure of MoMHRA was first reported by De Haan *et al*[127]. In a series of 42 MoMHRA revisions, the most common reason for revision was a malpositioned component. Malposition of the acetabular component was evident in 27 cases and malposition of the femoral component was evident in 17 cases. This observation was made from intra-operative findings and a simplified method of determining cup orientation. De Haan *et al* had also reported on the association between of component orientation and increased *in vivo* wear[100]. These authors however had only considered for cup

inclination and reported the effect of cup inclination and size with variable resurfacing implants.

It is, therefore, of relevance to identify whether surgical factors identified *in vitro* to increase wear via edge loading and impingement (Chapter 2.2.2), could contribute to increased wear and pseudotumour development *in vivo*. Identification of any factors would help in identifying which hips are at risk of high wear and require further investigations in order to identify pseudotumours at an early stage. Furthermore, it would allow for the provision of evidence-based recommendation for surgical practice in order to minimise or eliminate pseudotumour risk.

There are several limitations to this case-control study. Firstly, the number of patients of the MoMHRA group is small. However, all patients that had undergone a revision during the study period were included in the study and hence there was no exclusion bias. Furthermore, in order to accommodate for the small number of patients, an effort was made to obtain a ratio of 2:1 for control THAs and hence improve statistical power. Secondly, the study involves the learning curve of the surgeons experience with pseudotumours and revisions associated therewith. Although, this can be considered a limitation, it may also be considered a strength of the study as it provides a realistic clinical picture of what different centres will encounter when revising their first pseudotumour cases, which are likely not to have been diagnosed, and hence revised in as timely a fashion as possible. Thirdly, the controls in the THA groups had received a cemented Exeter femoral stem with different types of cup fixation and bearing and femoral heads

varying between 26 and 32 mm. This may not be the universal choice of implant or size of bearing for this age group. However, it is the implant of choice that the patients in the study group would have received at the NOC if they had had a THA rather than a MoMHRA. Furthermore, it was the implant of choice used at 91% of revisions (n=42) and it was hence considered that patients from the EPOS group were the most appropriate controls. Lastly, the control THAs were obtained from different centres and could provide surgical biases. However, the number of surgeons involved with the primary and revision of the MoMHRA group is of similar number and experience as those surgeons that performed the THAs in the control group. In addition, the use of a multi-surgeon, multicentre data increases 'generalisability' of the study's findings.

4.6 Conclusion

The outcome after revision of MoMHRA is dependent upon the indications for revision. After revision for reasons other than pseudotumour the outcome was generally good and similar to that after primary THA. However, there was a high incidence of infection after revision for fracture. By contrast, the outcome after revision for pseudotumour was poor with major complications occurring in half of the patients. One third required a further revision and the overall pain and function status was as poor as it was before the primary surgery. There is a strong argument for revising any MoMHRA as soon as a pseudotumour is detected in a symptomatic patient so that treatment can be effected while soft-tissue damage is limited. Further understanding and identification of risk-factors, in particular surgical technique-related would aid reduction in incidence and recognition of patients at risk.

4.7 Summary

- Outcome of revision of a failed MoMHRA is dependent on revision indication. Outcome after revision for reasons other than pseudotumour is good and similar to that after a primary THA.
- In pseudotumour revisions, major complications occured in half of patients and a third required re-revision. The overall pain and function status of patients in the Pseudotumour Group was poor and inferior to other revised MoMHRAs and their primary THA controls.
- It is likely that early recognition of pseudotumour presence is necessary in order to prevent extensive soft-tissue damage and improve outcome. Although patient and implant factors have been identified, surgical risk factors increasing wear and pseudotumour risk remain to be characterised.

5 SURGICAL FACTORS ASSOCIATED WITH PSEUDOTUMOUR[§]

5.1 Introduction

The previous chapters highlighted the revision and disease burden of pseudotumour and identified gender and small femoral component size as important patient risk factors its development. Implant factors identified to have an effect were described in Chapter 2. However, surgical factors that may contribute to pseudotumour development are yet to be determined. This chapter investigates surgical factors and their possible association with pseudotumour. The aim of Study 5A, was to examine the association between component orientation and pseudotumour development. The aim of Study 5B was to investigate the association between head-neck ratio (HNR) alterations occuring secondary to the resurfacing procedure and subsequent risk of pseudotumour. By investigating the relationship between surgical factors and pseudotumour development, the findings may allow for provision of evidence-based surgical recommendations. These may be on both surgical technique and surveilance in order to reduce risk of pseudotumour development and aid recognition of

[§] Work in this chapter has been published as:

Grammatopoulos G, Pandit H, Glyn-Jones S, McLardy-Smith P, Gundle R, Whitwell D, Gill HS, Murray DW; Optimal acetabular orientation for hip resurfacing. J Bone Joint Surg Br, 2010: 92-B: 1072-1078.

Grammatopoulos G, Pandit H, The Oxford Hip and Knee Group, Murray DW, Gill HS. The relationship between head-neck ratio and pseudotumour formation in metal-on-metal resurfacing arthroplasty of the hip. J Bone Joint Surg Br 2010: 92-B, 1527-1534.

MoMHRA cases at risk of developing pseudotumour. Such recommendations may reduce both revision and disease burdens. Reducing risk of development would reduce incidence, whilst recognition of patients at risk may identify pseudotumours prior to extensive associated soft-tissue damage.

5.2 Null hypothesis

H_0: Surgical factors are not associated with risk of pseudotumour development.

5.3 Study 3A: Materials and methods

5.3.1 Study design

A retrospective case-control study is a type of study design described previously (Chapter 4). Case-control studies are used to identify factors that may contribute to a medical condition by comparing subjects who have that condition (the 'cases') with subjects who do not have the condition (the 'controls').

5.3.2 Patient groups and demographics

The first 31 consecutive MoMHRA (30 patients) revised for pseudotumour at the NOC that had adequate quality radiographs for radiological assessment post-resurfacing were identified and formed the Pseudotumour Group. The diagnosis of pseudotumour was made on the basis of clinical, radiological, intra-operative and histological findings as previously described (Chapter 2). Twenty-four

patients were females (mean age at primary surgery: 53 years, range 29 to 67 years) and six were males (mean age at primary surgery: 54 years, range: 40 to 54 years). One female patient had bilateral revisions for bilateral pseudotumours. Four different MoMHRA devices were involved; BHR (n=14), Conserve Plus (n=14), Cormet (n=2) and Recap (n=1). The average time to revision was 3.4 years (range: 0.7 to 8.3 years). The primary MoMHRA was performed at the NOC in the majority of cases (n=25), whilst the remaining six were performed in five different centres. Full patient details are given in Table 5.1.

Each patient in the Pseudotumour Group was matched with two control asymptomatic MoMHRA cases (Control Group) which were identified from the resurfacing database of the NOC. Aiming for a ratio of two controls for each pseudotumour patient, in order to increase the statistical power of the study, 58 control cases were identified as being eligible for inclusion. The controls were matched according to previously identified risk factors for pseudotumour development: gender, age at primary MoMHRA, pre-operative diagnosis, length of follow-up and component size. Details are provided in Table 5.1.

	Gender (n)	Age (years)		Diagnosis	Follow-up/revison time(years)	
		Mean (SD)	Range	OA/Dys.	Mean (SD)	Range
Pseudotumour	All (n=31)	53.5 (10.9)	28.7 to 67.9	27/4	3.4 (2.0)	0.7 to 8.3
	Male (n=6)	53.8 (9.6)	40.6 to 67.9	6/0	4.3 (2.7)	1.1 to 8.3
	Female (n=25)	53.5 (11.4)	28.7 to 67.1	21/4	3.2 (1.8)	0.7 to 6.6
Control	All (n=58)	54.0 (10.3)	29.9 to 68.1	50/8	3.7 (2.1)	0.6 to 7.9
	Male (n=10)	54.0 (10.1)	40.3 to 68.1	10/0	4.8 (1.8)	0.8 to 7.9
	Female (n=48)	54.0 (10.4)	29.9 to 67.4	40/8	3.4 (1.8)	0.6 to 7.9

Table 5.1: Pseudotumour and Control Group demographics, numbers are given per case basis, SD=standard deviation, OA=osteoarthritis and Dysp. = dysplasia.

5.3.3 Radiological assessments

5.3.3.1 Acetabular components orientation method – EBRA

Acetabular component orientation can be established with any of the three different definitions of orientation previously described (anatomical, radiographic and operative)[165]. Although CT with three-dimensional (3D) reconstruction is thought to be the most accurate method of assessing cup orientation in the anatomical reference plane, a number of limitations associated with its use limit its application. Firstly, CT exposes patients to a greater dose of radiation. Secondly, it is more expensive and time consuming. Thirdly, it is not readily

available and applicable to regular practice, as not all MoMHRA patients undergo CT investigation of their pelvis. In order, to make evidence-based recommendations on surgical practise, measurements that can be made from a readily available, commonly used investigation would be more relevant.

A recent study has provided evidence that the EBRA software (Einzel Bild Roentgen Analysis, University of Innsbruck, Austria) can be used reliably in assessing cup version and inclination in resurfaced cups from anteroposterior (AP) pelvic radiographs. Langton *et al*, established the reliability of EBRA by embedding acetabular components with varying inclination and versions in plasticine moulds with radio-opaque markers to simulate bone landmarks[178]. The authors placed the moulds on a radiolucent table and the horizontal grid was marked using the horizontal reference laser from the X-ray apparatus. Radiographs obtained included AP centred over the pubic symphysis and a lateral image captured with the x-ray beam directed perpendicular to the axis of the cup. From the lateral image, the version of the cup could be determined accurately by measuring the angle subtended at the intersection of the vertical and the cup rim. The angles measured from the lateral angles were compared againgst values measured from the anteroposterior (AP) radiograph using the EBRA software. The results showed that EBRA can reliably determine cup orientation to a clinically acceptable level of accuracy of ±5°. The accuracy of the measured cup inclination with the EBRA software is reported to be ±0.8°[179].

The above arguements and findings, coupled with the routine use of pelvic radiographs in clinical practice, making radiographic analysis more clinically relevant, led to the decision that the radiographic cup orientation should be the parameter studied and that the EBRA software would be the measuring instrument used.

The EBRA digital measurement system allows the user to input pelvic/spinal landmarks to compensate for changes in the position of the pelvis from AP pelvis radiographs. The user selects points along the cup and rim of the cup. The software, thereafter, creates a best-fit circle and a best-fit ellipse from the points selected (Figure 5.1). From the above it can reliably measure radiographic inclination and anteversion. A limitation of the software is the ability to distinguish between anteversion and retroversion of the component. It is hence dependent on the observer to decide whether a cup is anteverted or retroverted. A lateral radiograph can aid the observer reviewing the radiographs with this decision. It should be noted that the position of the patient's pelvis in terms of pelvic tilt, obliquity and rotation can lead to unacceptable degrees of inaccuracy if not taken into account. Although EBRA allows the user to place gridlines over various landmarks in order to compensate for pelvic obliquity; mal-rotated and mal-aligned films were excluded from analysis in order to exclude erroneous data entry and use.

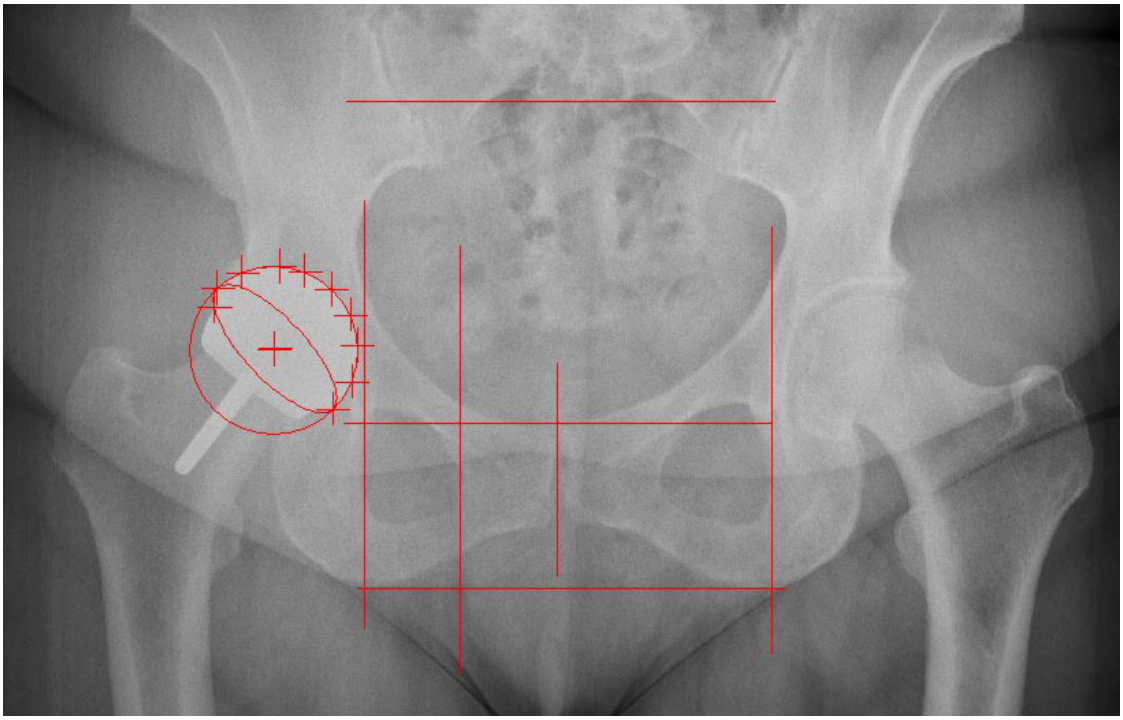


Figure 5.1: EBRA software analysis. Gridlines used for pelvic reference in red. Crosses along cup edge and rim represent points selected by reviewer. Best fit circle and rim for cup are drawn from the software and cup orientation is estimated representing radiographic cup inclination and anteversion.

5.3.3.2 Validity of EBRA measurements

Validity is evidence or justification that an instrument measures what it is intended to measure. Criterion validity relates to how the instrument compares with the established 'gold-standard' instrument. Currently, there is no established gold-standard method of measuring acetabular component orientation of MoMHRAs. Thus, in order to validate EBRA, the following study was undertaken.

A human 3-D pelvic model was obtained from an established, musculoskeletal modelling respository (AnyBody Modelling System™, Aalborg, Denmark). The

pelvic model was in a stereolithographic file (STL file) format. STL files describe the surface geometry of a 3-D object without any representation of colour or texture. The basic STL file format is to store a list of 3-D vertices, given by an index number and x,y,z co-ordinates, which are then linked in groups of three to define a face. The triangular faces can thus be used to describe a 3-D surface (Figure 5.2). A schematic representation of a 50 mm BHR acetabular component, based on known thickness and alpha angle, was virtually implanted in the left acetabulum. The cup was implanted in various acetabular orientations in the radiographic reference planes.

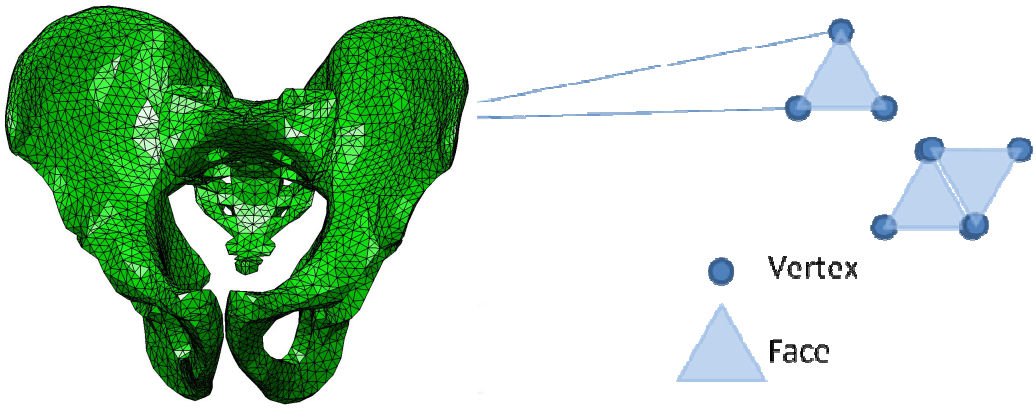


Figure 5.2: Pelvis and decomposition into vertices and faces. Source of image: Anybody Modelling System (Aalborg University. Denmark)

The 3-D pelvis and the implanted BHR assembly described by their faces and vertices was transformed using a projection matrix (process to determine the transformation between a 3-D co-ordinate to 2-D co-ordinate) into a virtual AP plane, hence creating a 2-D, AP radiograph. The radiographic effect was created using an attenuation algorithm. The algorithm simulated the effects of cortical bone, metal prosthesis and their associated scatter resulting in a grey-scale image replicating a pelvic radiograph that was saved as a jpeg file. The software to

perform the synthetic radiograph generation was written by an engineer (HSG). EBRA measurements were performed on the 2-D images produced (Figure 5.3).

The EBRA measured orientations were highly correlated with the applied cup orientations from the model with a Pearson's Correlation coefficient (r)=0.9 (p= <0.0001) for both inclination and anteversion. Intra- and inter-observer Correlations (κ) were established by two observers (GG & AP) measuring acetabular component orientation in 50 pelvic model generated images with different orientations and one observer (GG) repeating the measurements. There were high intra- and inter-class correlations coefficient (κ) in the orientations measured between the two observers (κ=0.99, p= <0.001).

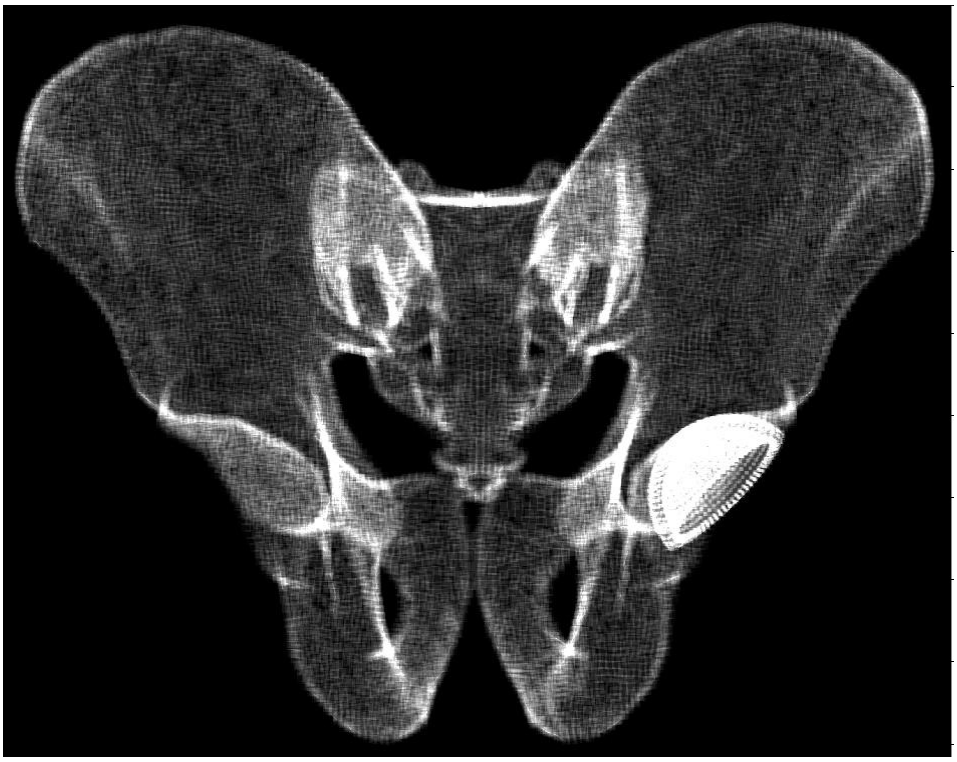


Figure 5.3: Synthetic 2-Dimentional (Xrays) produced of a BHR cup implanted in 45° of inclination and 15° of anteversion.

5.3.3.3 Reliability of measurements

Reliability refers to the consistency of a measure. A test is considered reliable if the same result is obtained repeatedly. 108 patients had EBRA analysis performed by two observers (GG, DL). The two observers were blinded to each other's measurements and outcome.

There was a highly significant inter-class correlation coefficient for absolute agreement in measurements of both inclination (coefficient: 0.99, $p<0.001$) and anteversion (coefficient 0.98, $p<0.001$). The mean difference in inclination and anteversion measurement was 0.08° and 0.18° respectively as illustrated in Figures 5.4 and 5.5 .

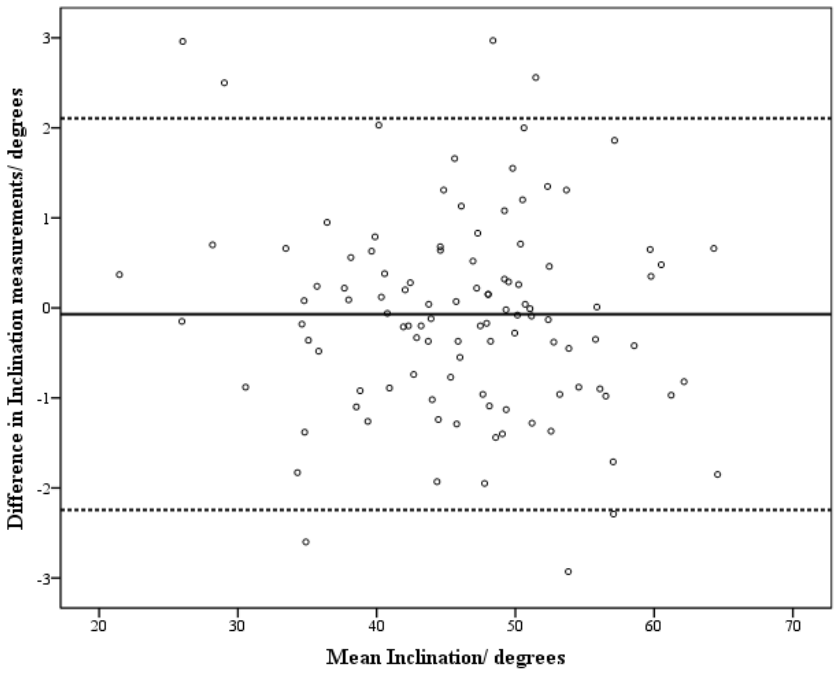


Figure 5.4: Bland Altman plot of the inter-observer measurement repeatability using EBRA for cup inclination. Horizontal solid line represents mean difference in measured inclination value (-0.07°), whilst horizontal broken lines denote overall mean difference ±1.96 x SD in difference (2.10° to -2.24°).

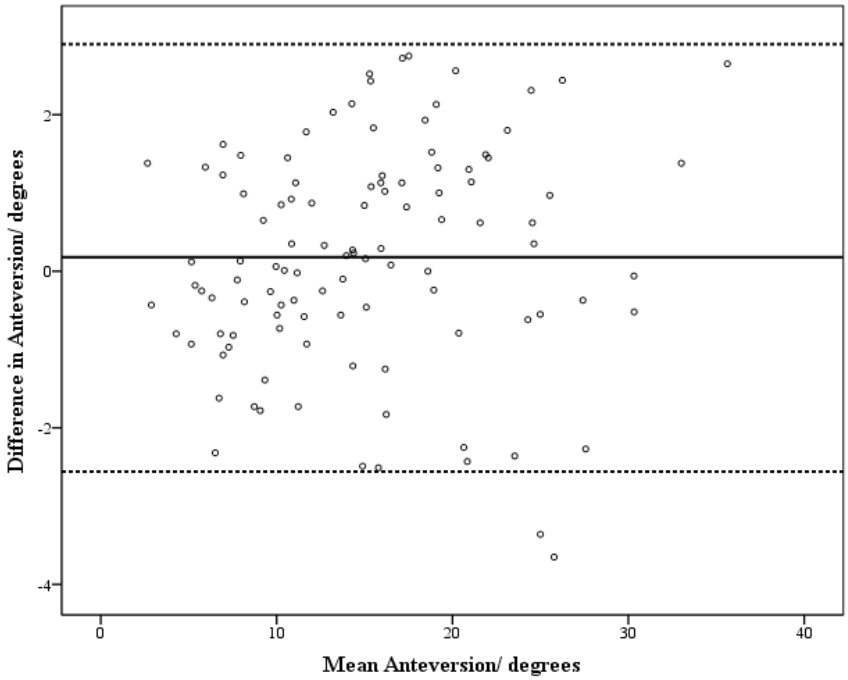


Figure 5.5: Bland Altman plot of the inter-observer measurement repeatability using EBRA for cup anteversion. Horizontal solid line represents mean difference in measured inclination value (-0.18°), whilst horizontal broken lines denote overall mean difference ±1.96 x SD in difference (2.9° to -2.56°).

5.3.3.4 Acetabular and femoral components' orientation measurements

Radiological measurements were obtained from digitised post-operative supine AP pelvis radiographs, which were taken following the standardised protocol at the NOC. The EBRA software was used for measurement of radiological acetabular component orientation [radiological anteversion (RCA) and radiological inclination (RCI)]. In addition, the neck-shaft angle (NSA) and the stem-shaft angle (SSA) were measured from the radiographs as previously defined by Beaule *et al* (Figure 5.6), which allowed for calculcation of the stem angle (SA) and hence determine the position of the femoral component in the coronal plane[180].

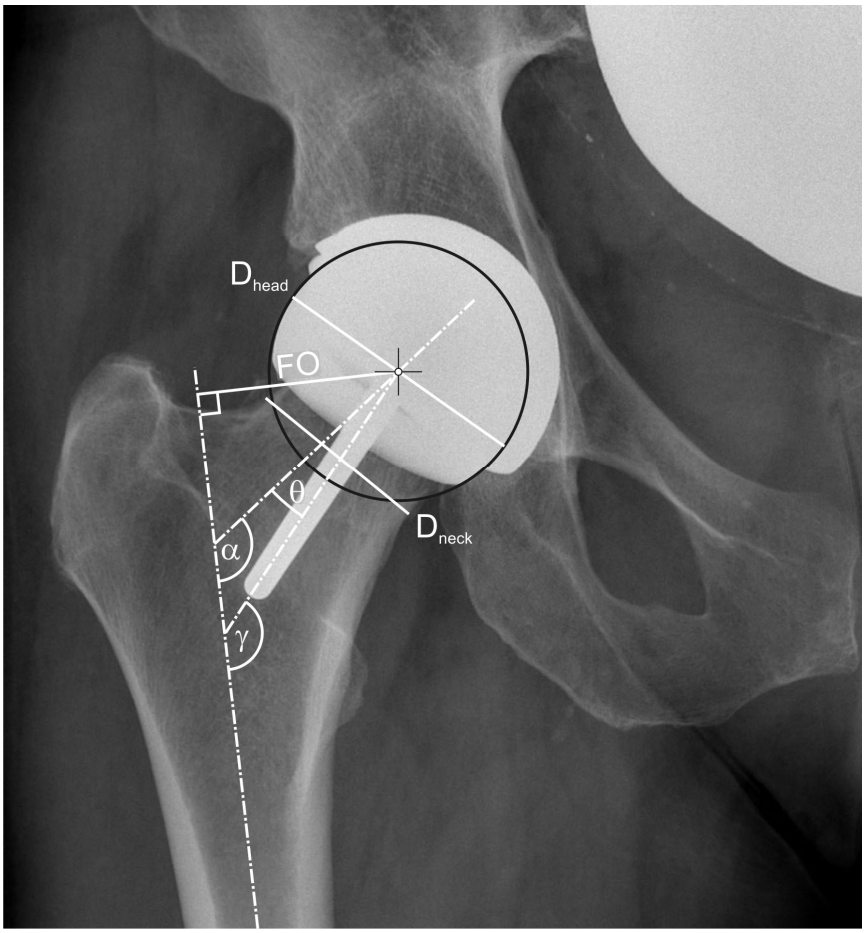


Figure 5.6: Antero-posterior hip radiograph illustrating measurments made in resurfaced and contra-lateral hips. FO = femoral offset, D_{head} = diameter of head at widest point, D_{neck} = diameter of neck at narrowest point, used to calculate head neck ratio, $HNR=D_{head}/D_{neck}$. Angles: α = neck shaft angle (NSA), γ = stem shaft angle (SSA), θ = stem angle (SA). NB difference between axis of neck and stem exaggerated for illustrative purposes.

All of the measurements were performed by two observers (GG and DL), and were found to have excellent inter-observer reliability; the interclass correlation co-efficients were 0.97 (95% CI: 0.96 to 0.99) for anteversion and 0.99 (95% CI: 0.98 to 0.99) for inclination. The values used in the study were the average of the measurements made by the two observers. For each case, adding the RCA and RCI values gave the combined inclination and anteversion (CIA).

$$CIA = RCA + RCI$$

SA was calculated as the difference between the SSA and the NSA.

$$SA = SSA - NSA$$

5.3.4 Analysis of data

5.3.4.1 Analyses for cup orientation measurements

The values of the RCA, RCI and CIA were compared between the Pseudotumour and Control Groups. In addition, the coverage arc and the CPR distance were calculated and compared between the two groups (Appendices 3, 4). The distance in the scatter plot degree space (*r*) of each acetabular component from the designer stated target orientation[25,26] of 40° inclination / 20° anteversion was calculated using the equation below and was compared for the two groups.

$$r = \sqrt{[(RCI - 40)^2 + (RCA - 20)^2]}$$

The orientation data were plotted on a scattergram, with RCA on the x-axis and RCI on the y-axis. From the scatter plot, the lower and upper bounds of RCI and RCA within which the majority of the data were contained were determined. Two different approaches were used to identify the optimal component orientation:

5.3.4.2 Optimal orientation based on degree space distance.

In similar way as described above for calculating distance (r) from the designer stated target orientation of RCA/RCI of 20°/40°, the distance from any point in the scatter plot can be calculated for each acetabular component, and then the mean distance from the pseudotumour cases ($\bar{r}_{PT}$) and the control cases ($\bar{r}_{CONTROL}$) could be separately calculated. The orientation furthest away from the pseudotumour cases and closest to the control cases will be the orientation with the maximum values of the ratio $\bar{r}_{PT} / \bar{r}_{CONTROL}$, which was termed the *distance ratio*. The distance ratio was calculated for every combination of each degree increment in RCI ranging from its lower to upper bound and each degree increment in RCA ranging from its lower to upper bound. This was then plotted as a contour plot, with RCA on the x-axis and RCI on the y-axis, allowing the orientation with the maximum value to be determined.

5.3.4.3 Optimal orientation based on the lowest incidence of pseudotumour

In order to establish the combination of RCI and RCA giving rise to the lowest incidence of pseudotumour, the following procedure was performed. For any given combination of RCI and RCA, a square zone extending ±10° centred on this location was established, and a 2x2 contingency table was constructed, consisting of:

	Number of pseudotumour (PT) cases	**Number of control cases**
Within zone	nPT	nControl
Outside zone	mPT	mControl

Fisher's Exact Test was then performed for the contingency table. This was repeated for every combination of each degree increment in RCI ranging from its lower to upper bound and each degree increment in RCA ranging from its lower to upper bound. A contour plot of the resulting probability values allowed the location of the zone with the lowest incidence of pseudotumour to be established. The use of a ±10° zone was based on the estimated achievable surgical accuracy in component placement as previously suggested by Lewinnek[160].

In addition, in a similar manner as described above, contingency tables were constructed for Lewinnek's Zone (LZ, inclination/anteversion: 30° to 50°/5° to 25°), a zone extending ±10° about the designer suggested operative target of 40° inclination and 20° anteversion [25,26] (Z1, inclination/anteversion: 30° to 50°/10° to 30°) and the optimal zone (Zopt) from the scatter plot analyses described above.

5.3.5 Statistics

Statistical analysis was performed using SPSS (version 18, SPSS Inc., Chicago, Illinois) and the Matlab Statistics Toolbox (version 7.1, The MathWorks Inc.,

Mass., USA). The dataset was assessed with non-parametric statistical tests. Inter-group comparisons of scale data were made with the use of non-parametric tests (Mann-Witney U). Cross-tabulation and the Fisher's exact test was used for categorical data. Fisher's exact test is a statistical significance test used in the analysis of contingency tables where sample sizes are small. It is one of a class of exact tests, so called because the significance of the deviation from a null hypothesis can be calculated exactly, rather than relying on an approximation that becomes exact in the limit as the sample size grows to infinity, as with many statistical tests. Significance was considered when p values of less than 0.05 were obtained.

5.4 Results

5.4.1 Cup orientation results

There was a wide scatter in the measured values of RCA and RCI (Figure 5.7); for the entire set of measurements (89 hips) the mean value of RCI was 46.6° (SD: 10.2°, range: 10.1° to 80.6°) and the mean value of RCA was 15.1° (SD: 7.6°, range: 4.1° to 33.6°). The mean acetabular inclination in the Pseudotumour Group was 47.5° (SD: 14.5°, range: 10.1° to 80.6°) and in the Control Group was 46.1° (SD: 7.1°, range: 28.7° to 59.8°). These were not statistically different (p=0.84). The mean acetabular anteversion in the Pseudotumour Group was 14.1° (SD: 8.4°, range: 4.1° to 33.6°) and in the Control Group was 15.6° (SD: 7.2°, range 4.3° to 32.9°). These were not statistically different (p=0.21). The mean combined radiographic orientation for the Pseudotumour Group was 61.6° (SD: 17.8°, range: 19.5° to 95.2°) and for the Control Group was 61.7° (SD: 10.2°, range: 40.3° to

90.0°). These were also not statistically different (p=0.72). The mean coverage arc in the Pseudotumour Group (13.3 mm, range: 0 to 31.4 mm) was not different to that in the Control Group (14.9 mm, range: 6.8 to 22.5 mm) (p=0.19). Similarly, the mean CPR distance was similar between Pseudotumour (14.6 mm, range: 0 to 29.5 mm) and Control (15.1 mm, range: 6.5 to 24.5 mm) Groups (p=0.85).

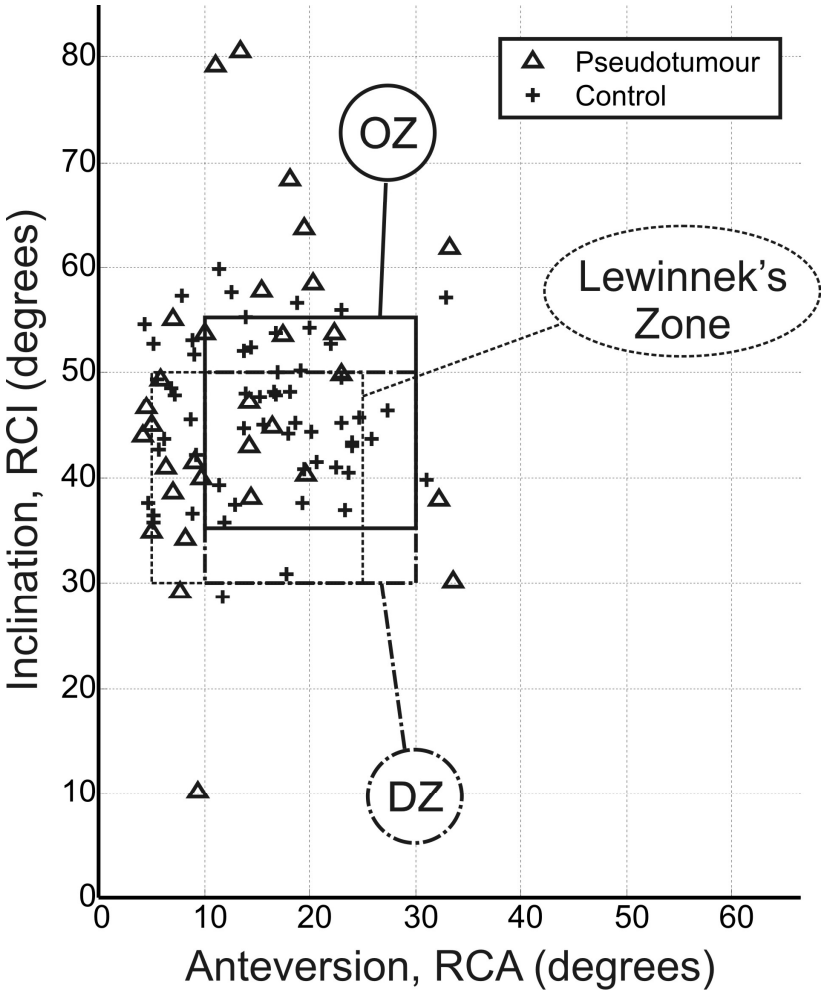


Figure 5.7: Scatter plot of measured acetabular radiographic component anteversion (RCA) versus radiographic component inclination (RCI) (Differently outlined boxes demonstrate the margins of the various cup orientation zones; Lewinnek's Zone, DZ: designer zone and OZ: optimal zone as per study).

Acetabular components in the Pseudotumour Group were positioned significantly (p=0.003) further away from the recommended orientation of 40°/20° than those

in the Control Group (Figure 5.7). The mean distance in degree space, *r*, from the designer target orientation of 40°/20° was 16.8° (SD: 9.1°, range: 0.5° to 41.1°) for the Pseudotumour Group and 11.3° (SD: 5.3°, range: 0.9° to 21.6°) for the Control Group.

The location with the maximum value of the distance ratio was an inclination of 45° and an anteversion of 19° (Figure 5.8); the maximum value of the distance ratio was 1.6, the minimum value was 1.0.

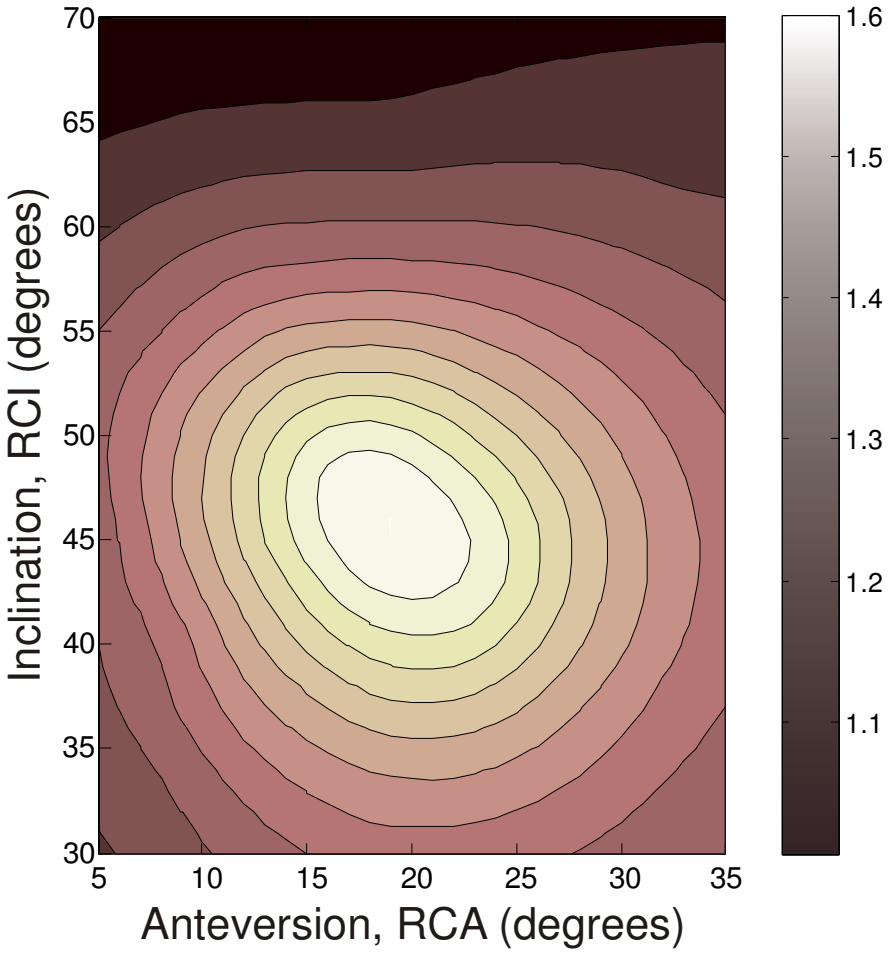


Figure 5.8: Contour plot displaying distance ratio values calculated for each combination of each degree interval in both anteversion and inclination (RCA, radiographic component anteversion; RCI, radiographic component inclination).

The location with the lowest risk of incidence of pseudotumour was an inclination of 43° and an anteversion of 21°, this was the centre of the contour plot corresponding to a p value of 0.0015 (Figure 5.9). As these two methods gave similar orientations, these were rounded to the nearest 5° giving the optimal zone (Zopt) to be a ±10° zone centred on 45°/20°.

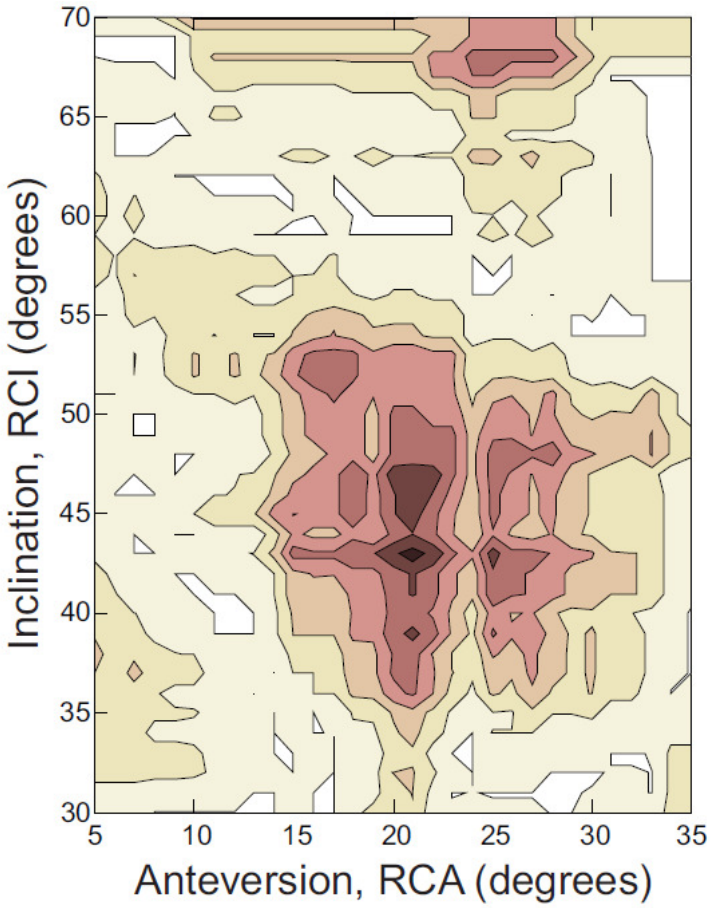


Figure 5.9: Contour plot displaying probability values produced by Fisher's exact test for pseudotumour incidence within a zone defined by ±10° centred on each combination of each degree interval in both anteversion and inclination. Probability values range from 0.0015 (darkest) to 1.0 (lightest).
(RCA, radiographic component anteversion; RCI, radiographic component inclination).

Thirteen pseudotumour cases were inside LZ, versus 18 outside this zone; there were 35 controls inside LZ and 23 outside. There was no difference in the probability of pseudotumour for components positioned within LZ compared to those positioned outside LZ (p=0.12). However, there was significantly (p=0.012)

lower probability of pseudotumour within a ±10° zone centred on 40°/20°. There were six pseudotumour cases inside Z1, versus 25 outside Z1; 27 controls were in Z1 versus 31 outside Z1. For Zopt the risk of pseudotumour was significantly (p=0.007) lower inside the zone versus outside the zone; there were eight pseudotumours inside the zone versus 23 outside and there were 33 controls inside Zopt versus 25 outside Zopt.

Zone	Group	Distance *r* Mean, SD	p-value, Mann-Whitney	Number inside zone	Number outside zone	p-value, Fisher's Exact
Lewinnek 40°/15°	PT	15.3, 9.9	0.055	13	18	0.120
	Control	10.9, 4.5		35	23	
Designer 40°/20°	PT	16.8, 9.1	0.003	6	25	0.012
	Control	11.3, 5.4		27	31	
Optimal 45°/20°	PT	15.6, 8.4	0.001	8	23	0.007
	Control	9.8, 5.0		33	25	

Table 5.2: Results of analysis for each zone, based on distance and 2x2 contingency tables. PT= Pseudotumour.

5.4.2 Femoral stem orientation results

There was no difference (p=0.29) in the NSA between the Pseudotumour, mean NSA 134° (SD: 5.5°, range: 126 to 144°), and the Control Groups, mean NSA 133° (SD: 5.3°, range: 122° to 146°). Similarly, there was no difference in the SSA between the two groups (p=0.579); the Pseudotumour Group had a mean of 137° (SD= 8.1°, range: 121° to 152°), whilst the controls had a mean of 138° (SD= 6.4°, range: 126° to 157°). Similarly, there was no difference in SA between

the two groups (p=0.06). Pseudotumours had a mean SA of 2.5° (SD: 5°, range: -12° to +13°), whilst Controls had a mean SA of 4.7° (SD: -12° to +18°).

5.5 Study 5B: Materials and methods

5.5.1 Study design

A retrospective case-control study was undertaken in order to study HNR changes in MoMHRA. This type of study has been described previously and was used in Study 5A.

5.5.2 Patient groups and demographics

The first 18 consecutive MoMHRAs (18 patients) revised for pseudotumour at the NOC that had adequate quality radiographs for radiological assessment pre- and post-resurfacing were identified and formed the Pseudotumour Group. The diagnosis of pseudotumour was made on the basis of clinical, radiological, intra-operative and histological findings (Chapter 2). Fourteen patients were females (mean age at primary surgery: 54 years, range 29 to 67 years) and four were males (mean age at primary surgery: 54 years, range: 41 to 54 years). Four different MoMHRA devices were involved; BHR (n=11), Conserve Plus (n=6), Recap (n=1) and Cormet (n=1). The average time to revision was 3.4 years (range: 0.7 to 8.3 years).

Each patient in the Pseudotumour Group was matched with two control asymptomatic MoMHRA cases (Control Group) which were identified from the resurfacing database of the NOC. Aiming for a ratio of two controls for each pseudotumour patients, in order to increase the statistical power of the study, 42 control cases were identified eligible for inclusion. The controls were matched according to previously identified risk factors for pseudotumour development: gender, age at primary MoMHRA, pre-operative diagnosis, length of follow-up and component size. Patient demographics are detailed in Table 5.3.

	Gender(n)	**Age (years)**		**Diagnosis**	**Follow-up/revison time (years)**	
		Mean (SD)	Range	OA/Dys.	Mean (SD)	Range
Pseudotumour	All (n=18)	53.0 (11.2)	28.7 to 67.1	16/2	3.6 (2.1)	0.9 to 8.3
	Male (n=4)	48.6 (6.1)	40.6 to 54.3	4/0	5.4 (2.6)	3.0 to 8.3
	Female (n=14)	54.2 (12.2)	28.7 to 67.1	12/2	3.1 (1.7)	0.9 to 6.6
Control	All (n=42)	55.1 (10.3)	29.9 to 68.1	36/6	2.8 (1.7)	0.6 to 7.3
	Male (n=5)	55.5 (8.8)	47.2 to 68.1	5/0	2.8 (1.2)	0.8 to 3.8
	Female (n=37)	55.0 (10.6)	29.9 to 67.4	31/6	2.9 (1.8)	0.6 to 7.3

Table 5.3: Pseudotumour and Control Group demographics, numbers are given per case basis, SD=standard deviation, OA=osteoarthritis and Dys. = dysplasia.

5.5.2.1 Head-Neck-Ratio measurements

Proximal femoral morphology was analysed using a Matlab based software package (Matlab R2009b, The MathWorks, Natick, MA, USA) named HipMorf 2.0. Nicholls *et al* validated the used of this software model for rapidly quantifying morphological parameters of the hip joint on an AP pelvis radiograph[181]. The software allowed the user to click on each of the constituent anatomical landmarks needed to measure several morphological parameters. Once all landmarks had been identified, the necessary angle, ratio and linear measurements were automatically calculated. Proximal femoral measurements were performed from AP pelvis radiographs and included: Head-Neck-Ratio (HNR), Neck-Shaft-Angle (α), Stem-Shaft-Angle (γ) and Stem Angle (θ).

HNR measurements were made as previously described by Doherty *et al*[182] (Figure 5.6). Femoral offset and stem orientation measurements were made as described by Beaule *et al*[180]. For patients with available pre- and post-operative radiographs, the difference between the native and the resurfaced hip HNR were defined as $\delta HNR_{pre \rightarrow post}$ and were calculated as:

$$\delta HNR_{pre \rightarrow post} = HNR_{pre} - HNR_{post}$$

Knowing femoral component size, native bony head diameter was calculated and assuming a 2 mm thick cartilage layer[183] (4 mm increase in diameter), the HNR ratio based on the diameter of the articular cartilage pre-operatively (HNR_{art}) was calculated. This allowed for estimation of the change in HNR between the

articular femoral head diameter (HNR_{art}) and the HNR of the resurfaced hip (HNR_{post}) as:

$$\delta HNR_{art \rightarrow post} = HNR_{art} - HNR_{post}$$

The stem angle (SA) was defined as the difference between stem-shaft angle (SSA) and neck-shaft angle (NSA) and was measured as:

$$SA = SSA - NSA$$

5.5.2.2 Reliability study

A reliability study was performed on anonymized AP pelvis radiographs. Intra-observer reliability was assessed by an investigator (GG) reading 50 randomly selected blinded radiographs on two occasions. Inter-observer reliability was assessed by a further observer (AC) reading the same 50 radiographs. Morphological measurements were compared using interclass correlation coefficients (ICC) for continuous data. Intra-observer correlation was highly significant and strong ($\kappa=0.98$, $p<0.001$). Similarly, there was a strong inter-observer correlation for both HNR measurements ($\kappa=0.96$, $p<0.001$), SSA ($\kappa=0.94$, $p<0.001$) and NSA/SA measurements ($\kappa=0.92$, $p<0.001$).

5.5.2.3 Analysis for Head-Neck-Ratio measurements

The immediate changes in HNR as a result of the operation can be expressed relative to either the bony or the articular cartilage HNR pre-operatively:

$$\Delta HNR_{pre \rightarrow post} = HNR_{post} - HNR_{pre}$$

$\Delta HNR_{art \rightarrow post} = HNR_{post} - HNR_{art}$

The correlations between changes in HNR and HNR_{pre} were examined. Changes in HNR were examined on a gender and group basis using non-parametric tests.

The power of HNR_{pre} and $\Delta HNR_{art \rightarrow post}$ for predicting pseudotumour development were examined by Receiver Operating Characteristic (ROC) analyses performed for the whole cohort and considering females only. ROC analyses allow for determination of sensitivity and specificy of a threshold value in predicting pseudotumour development. Sensitivity of a test refers to the probability that a person having a disease will be correctly identified by a clinical test; whilst specificity refers to the probability that a person who does not have a disease will be correctly identified by a clinical test. The area under the curve (AUC) of the ROC was evaluated as an indication of predictive power; a perfect predictor of pseudotumour would have an AUC of 1.0, whilst that no better than random chance would have an AUC of 0.5[184].

5.5.3 Statistics

Statistical analysis was performed using SPSS (version 18, SPSS Inc., Chicago, Illinois). The dataset was assessed with non-parametric statistical tests. Inter-group comparisons of scale data were made with the use of non-parametric tests (Mann-Witney U). Significance was considered when p values of less than 0.05 were obtained.

5.6 Study 5B: Results

5.6.1 Head-Neck-Ratio results

5.6.1.1 Entire cohort findings

Mean HNR_{pre} was 1.32 (SD:0.09, range: 1.09 to 1.37); this was significantly less ($p<0.001$) than mean HNR_{art}, 1.44 (SD:0.10, range: 1.19 to 1.65). The mean HNR_{post} was 1.33 (SD:0.07, range: 1.11 to 1.47), this was not different to HNR_{pre} ($p=0.494$), but was significantly ($p<0.001$) smaller than HNR_{art} (Table 5.4). Both pre-operative measures of HNR were significantly larger for the females compared to the males and the difference was maintained post-operatively.

HNR	Gender (n)	Mean (SD)	Range
$HNR_{articular}$	All (60)	1.44 (0.10)	1.19 to 1.65
	Male (9)	1.33 (0.09)	1.19 to 1.48
	Female (51)	1.46 (0.09)	1.26 to 1.65
HNR_{pre}	All (60)	1.32 (0.09)	1.09 to 1.51
	Male (9)	1.24 (0.09)	1.09 to 1.37
	Female (51)	1.33 (0.09)	1.13 to 1.51
HNR_{post}	All (60)	1.33 (0.07)	1.11 to 1.47
	Male (9)	1.26 (0.09)	1.11 to 1.41
	Female (51)	1.34 (0.06)	1.17 to 1.46

Table 5.4 Changes in HNR values for whole cohort. SD = standard deviation.

The changes in HNR were significantly ($p<0.001$) negatively correlated to HNR_{pre} (Figure 5.10), the correlation was stronger for $\Delta HNR_{art\rightarrow post}$ (r=-0.69) than for $\Delta HNR_{pre\rightarrow post}$ (r=-0.61).

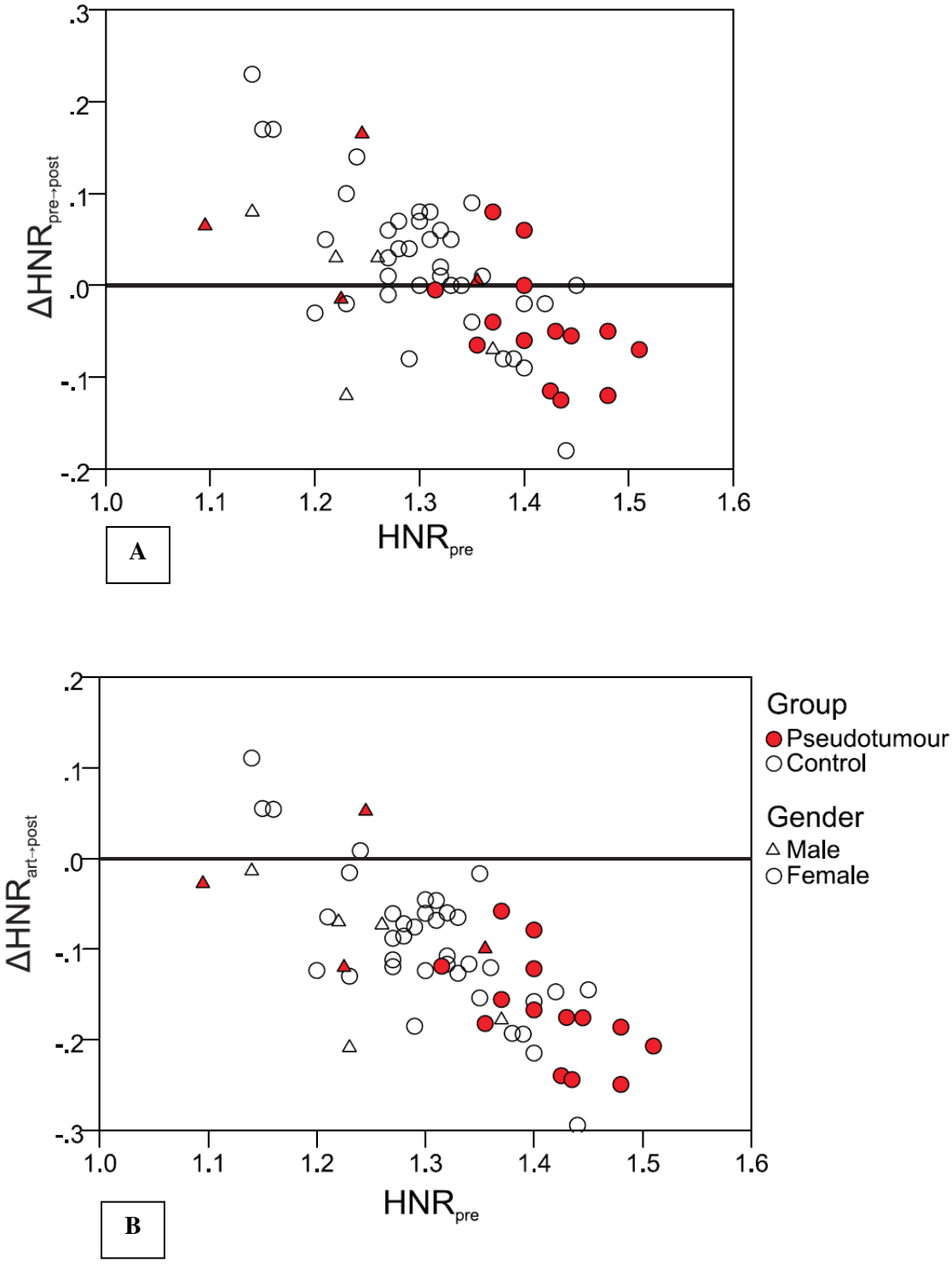


Figure 5.10: Scatter plots of HNR_{pre} versus $\Delta HNR_{pre\rightarrow post}$ (graph A) and $\Delta HNR_{art\rightarrow post}$ (graph B).

5.6.1.2 Pseudotumour Group versus Control Group

HNR_{pre} was significantly (p=0.001) larger for the Pseudotumour Group (mean 1.37 SD: 0.10) than for the Control Group (mean: 1.30 SD: 0.08) (Table 5.5, Figure 5.11). Similarly, HNR_{art} was also significantly (p=0.001) larger for the Pseudotumour Group (mean: 1.49, SD: 0.11) than for the Control Group (mean: 1.41, SD: 0.08). Post-operatively, there was no difference in HNR_{post} (p=0.069) between the two groups.

When the two groups were compared on a gender specific basis, the differences between them were found to be due to differences between females. There were no significant differences between males from the two groups for any of the HNR measures (Table 6.5). However, for the Pseudotumour females the HNR_{pre}, HNR_{art}, values were significantly higher than for the Control females (Table 5.5). There was no difference in HNR_{post} between females of the Pseudotumour and Control Groups.

Group		HNR_{art}		HNR_{pre}		HNR_{post}	
	(n)	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
PT	All (18)	1.49 (0.11)	1.19 to 1.65	1.37 (0.10)	1.10 to 1.51	1.35 (0.08)	1.16 to 1.46
	Male (4)	1.33 (0.11)	1.19 to 1.46	1.23 (0.11)	1.10 to 1.36	1.29 (0.12)	1.16 to 1.41
	Female (14)	1.54 (0.06)	1.43 to 1.65	1.42 (0.05)	1.32 to 1.51	1.37 (0.06)	1.29 to 1.46
Controls	All (42)	1.41 (0.08)	1.23 to 1.60	1.3 (0.08)	1.14 to 1.45	1.32 (0.08)	1.11 to 1.30
	Male (5)	1.34 (0.09)	1.23 to 1.48	1.24 (0.08)	1.14 to 1.37	1.23 (0.08)	1.11 to 1.30
	Female (37)	1.42 (0.08)	1.26 to 1.60	1.3 (0.08)	1.14 to 1.45	1.33 (0.06)	1.17 to 1.45

Table 5.5: Comparison of changes in HNR values between Pseudotumour (PT) and Control Groups. SD = Standard Deviation.

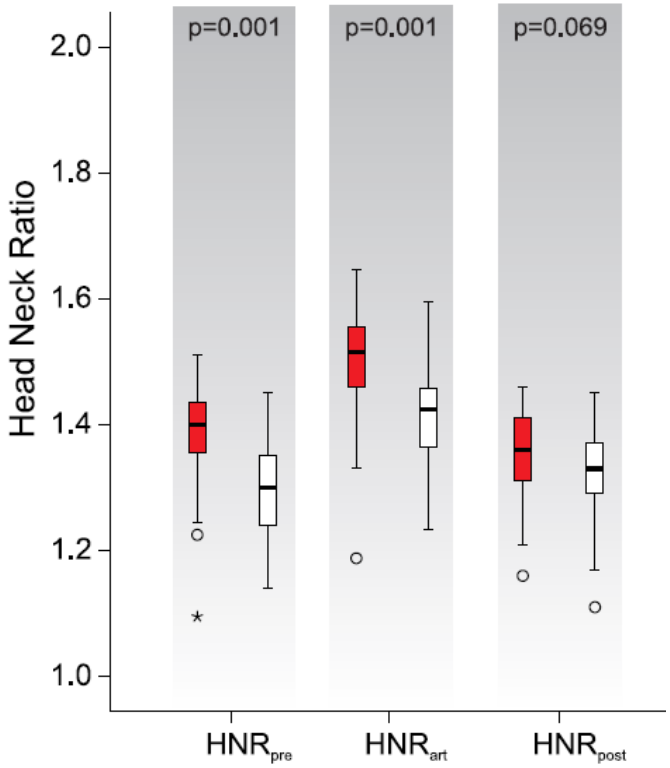


Figure 5.11: Differences in HNR between Pseudotumour and Control Groups colour coded as per group (red = Pseudotumour, white = Control).

5.6.1.3 ROC Analyses for prediction of pseudotumour (Table 5.6)

Considering the whole cohort, HNR_{pre} was significantly (p=0.001) more predictive than chance (AUC=0.77, 95%CI: 0.62 to 0.92 versus AUC=0.5 for chance) for predicting pseudotumour development. Performing the same analysis for females only, the AUC for HNR_{pre} was 0.89 (95%CI: 0.80 to 0.98, p<0.001, Figure 5.12). A threshold value of 1.35 for HNR_{pre} gave 92.9% sensitivity and 78.4% specificity in predicting pseudotumour in females (Table 5.6). Females with HNR_{pre} above 1.35 had a 3.4-fold higher risk of developing pseudotumour following MoMHRA compared to those with HNR_{pre} <1.35 (p<0.001).

For the whole cohort, $\Delta HNR_{art \rightarrow post}$, was more accurate than chance (AUC=0.68, 95%CI: 0.52 to 0.83, p=0.032) for predicting pseudotumour development; considering females only, the predictive power of $\Delta HNR_{art \rightarrow post}$ was improved (AUC=0.782, 95%CI:0.64 to 0.92, p=0.002). A threshold value of -0.15 (equivalent to 5.3 mm head downsizing) for females gave 71% sensitivity and 81% specificity. Female patients in whom the articular head diameter was downsized more than 5.3 mm had a 4.4-fold higher risk of developing pseudotumour than those downsized less than 5.3 mm (p<0.001).

Parameter		Value	Sensitivity	Specificity	Risk Ratio	Odds Ratio	p value (Fishers Exact)
Females Only							
HNR_{pre}	ROC threshold	1.35	92.9%	78.4%	3.43	35.1	<0.001
	Clinically optimal threshold	1.3	100%	52.5%	1.77	Infinity	0.002
$\Delta HNR_{art \rightarrow post}$	ROC threshold	-0.15	71.4%	81.1%	3.78	10.71	<0.001

Table 5.6: Threshold values derived from ROC analysis examining the power of HNR_{pre} and $\Delta HNR_{art \rightarrow post}$ in females in predicting pseudotumour.

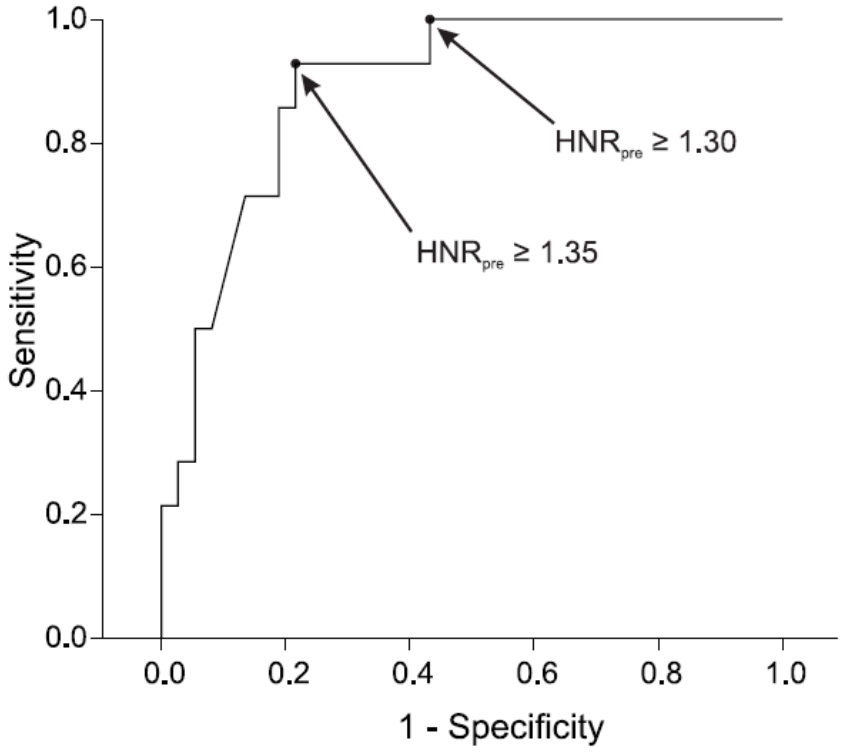


Figure 5.12: ROC curve for females only, examining the power of HNR_{pre} in predicting pseudotumour.

5.7 Discussion

The findings of this chapter allow for the rejection of the null hypothesis set out at the beginning of this chapter. Sugical factors were identified to have an effect on risk of forming a pseudotumour. Surgeons can reduce the risk of pseudotumour by implanting the acetabular component within the defined optimum zone and appropriately sizing components based on the articular HNR of the native hip. Furthermore, surgeons should be aware that MoMHRA with mal-positioned components and/or females with $HNR_{pre} > 1.35$ that have been downsized during operation are at increased risk of pseudotumour.

There was a great variability in the orientation of the implanted acetabular components as evident in Figure 5.6. Following review of cup orientations, mean acetabular inclination and anteversion were the same for pseudotumour patients and controls. In addition, the combined inclination and anteversion, coverage arc and CPR distances were similar for both groups. Hence, a simple analysis of cup orientation does not help explain the possible association between component orientation and pseudotumour development. However, the variability of cup inclination and anteversion was larger in the pseudotumour patients than in the control patients. This suggests that there may be an optimal orientation for acetabular components and that the outliers may be more likely to develop pseudotumour. Based on this suggestion, and an assumption that a surgeon can at best implant an acetabular component within ±10° of inclination and anteversion of a desired target, the data was re-analysed in order to determine the optimal position for a surgeon to aim for in order to minimise the risk of pseudotumour.

The optimal position was found to be 43° of inclination and 21° of anteversion. A separate analysis based on the distance the pseudotumour and control cases were from any given orientation, confirmed that this was optimal.

The incidence of pseudotumour occurring when the acetabular component was optimally positioned (45°±10° inclination and 20°±10°anteversion) was approximately four times lower, and this was significantly (p=0.007) lower, than when it was not optimally positioned. Unfortunately, this optimal position does not represent a "safe zone" as eight pseudotumours occurred despite optimal positioning of the acetabulum. Although the pseudotumours occurring with optimal position tended to be in females with small components, there was no real difference in the incidence of these risk factors (Fisher's Exact Test p=0.31 for gender and p=0.60 for size) in optimally and non-optimally positioned pseudotumour patients, suggesting that there is no direct linkage with these risk factors. Similarly, there was no difference in length of interval (survival time) between primary MoMHRA and revision between pseudotumours occuring in well and mal-orientated cups (p=0.9). Hence, it would appear that although acetabular component orientation is important, other factors also contribute to pseudotumour development. All pseudotumours with well-postioned cups had pre-operative HNR> 1.30. However, these patients were not downsized further in comparison to other pseudotumour cases (p=0.7).

Although it is generally accepted that appropriate acetabular component positioning is essential for long-term success of total hip arthroplasty, there have been relatively few studies to determine what the most appropriate orientation is.

The most quoted study is that of Lewinnek who defined a safe zone of 40°±10° inclination and 15°±10° anteversion, in order to reduce dislocation risk. In this study, the incidence of pseudotumour was the same inside and outside Lewinnek's Zone, so the Lewinnek Zone cannot be recommend for resurfacing. When resurfacing became popular, it was generally perceived that acetabular component orientation was not as important as with conventional THA because the large head virtually eliminated the risk of dislocation. The concern at that stage was femoral component positioning, which was linked with femoral neck fracture[6]. However, it has become apparent that acetabular orientation is more critical with resurfacing because of the severe consequence of excess metal wear debris released as a result of impingement and/or edge loading. The main focus has been inclination, with a number of studies showing that that steep acetabular components are associated with high ion levels. To-date, no previous study has defined an optimal zone for resurfacing acetabular orientation. The optimal zone described in this study was selected to minimise the risk of pseudotumour, which is the most serious complication of resurfacing as shown previously in Chapters 2 and 3.

The designers currently recommend that the MoMHRA acetabular components should be positioned at 40° inclination and 20° anteversion[25,26]. However, there is no evidence in the literature to justify this recommendation. Implantation of a socket within a ±10° zone around 40°/20° does decrease the risk of pseudotumour significantly, but the decrease was not as significant as it was placing it in the optimal zone described above.

The majority of patients in this cohort had either BHR (38/89) or Conserve Plus (45/89) components, although four different implants designs were used in total. Patients in the two groups were matched as best as possible for implant design and component size to account for this limitation. Furthermore, all four devices in this study have been shown to have acceptable and similar α angles (Chapter 2). The importance of individual cup design should not be underestimated. At any given inclination, devices with smaller acetabular α angle have a greater effective inclination in comparison to devices with greater α angle and are hence more prone to edge loading. This would hence translate to a different, narrower, safe zone in order to reduce pseudotumour risk for smaller α angle devices (e.g. ASR) in comparison to devices with greater α angle, such as the BHR and the Conserve Plus described in this study. Langton *et al* recently described a narrower area of inclination and anteversion associated with reduced ion levels with the ASR compared to the BHR[99].

Similar wide ranges in cup orientation following hip resurfacing to the one presented in this study have been observed in other studies from different centres[34,129,185]. The wide variation in cup orientation in this study is thought to be due to multiple factors. In three of the pseudotumour cases with extreme mal-position, there is radiographic evidence that the socket was loose and had moved from a position that was initially satisfactory. Furthemore, it is important to note that early on with the resurfacing procedure, there was no consensus as to the optimal orientation of the socket, nor the importance of cup orientation. It was, for example, not clear if it should have the same or different orientation from a conventional THA socket, or if the orientation should be different with different

degrees of valgus or anteversion of the femoral neck. In addition, before it was appreciated how critical socket position was, in cases of acetabular dysplasia a certain amount of increased inclination and anteversion was accepted so as to gain good fixation. A further problem is that with resurfacing it is difficult to implant a component precisely. The reasons for this difficulty include the fact that acetabular visualisation may be compromised, heavy retraction may tilt the pelvis, bone or soft tissue may force an introducer out of place, and the introducers often did not have adequate mechanical alignment guides.

A complex interaction exists between acetabular component inclination and anteversion, femoral neck anteversion, femoral offset, head-neck ratio, bony anatomy and range of movement (ROM). The reduced head-neck ratio of MoMHRAs, relative to conventional THAs, coupled with the younger patient with greater range of movement during normal activities render acetabular component position of great importance to avoid impingement and edge loading. Too much inclination leads to superior edge loading and too little leads to superior impingement and medial edge loading. Too little anteversion leads to anterior impingement and posterior edge loading in flexion, whilst too much anteversion leads to posterior impingement or anterior edge loading during extension. Another important factor influencing when impingement occurs is HNR. Impingement occurs earlier as the size of the head decreases and as that of the neck increases, both of which are associated with a decrease in HNR. There is a trigonometrical relationship between HNR and the angle at which impingement occurs (Figure 5.13). For a normal hip or a resurfaced hip an increase in HNR of 0.01 results in

impingement occurring about 0.5° later, or increases the ROM without impingement by about 1°.

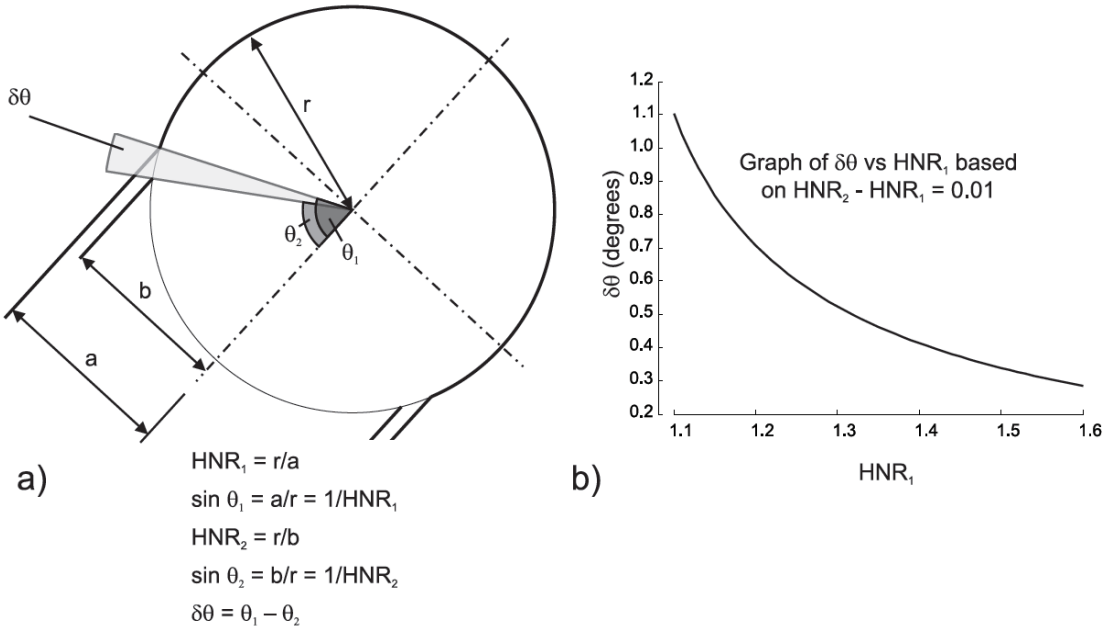


Figure 5.13: a. Relationship between HNR and ROM. δθ is the increase in angle before impingement occurs for HNR_1 cf. HNR_2 b. Plot of change in δθ for 0.01 change in HNR.

Prior to hip resurfacing, women had a larger HNR than men (HNR_{pre}=1.33 and 1.24 respectively, HNR_{art}=1.46 and 1.33 respectively). This would, on average allow women to have an 11° greater ROM compared to men without impingement between the edge of the acetabulum (assuming a spherical shape) and the femoral neck. Following hip resurfacing HNR, measured using the standard technique that does not account for articular cartilage, was unaltered for both men and women. However, if the cartilage layer is included, then the procedure significantly reduced the HNR. As the neck size does not change during the operation, the decrease in HNR is a manifestation of decreasing the size of the head. On average resurfacing decreased the size of the head by 3.7 mm, taking account of the

cartilage thickness. The reason why the head size was smaller after hip resurfacing than before was probably that the surgeon aimed both to preserve acetabular bone and to avoid neck notching. The surgeon, therefore, reamed the acetabulum until there was a good bony bed, and then selected the appropriate acetabular component provided the associated head fitted over the neck. The greater the pre-operative HNR, the more the head size can be decreased without notching the neck. Therefore, in order to preserve acetabular bone, there was a tendency to decrease the HNR more if the pre-operative HNR was high, as is demonstrated by Figure 5.10. The differences were particularly marked and were statistically significant in women, whereas in men they were not significant. This may be because the numbers of men with pseudotumour are small or because the significance and consequences of HNR changes are different between men and women.

The data suggests that an important patient risk factor associated with pseudotumour is very high head-neck ratios pre-operatively. This may in part explain why women are more likely to have pseudotumour than men: Women tend to have higher HNR_{pre} than men and therefore are more likely to have the very high HNR_{pre} that increase the chance of pseudotumour. The main surgical risk factor is downsizing of the head in these patients with high HNR_{pre}. In patients with high HNR_{pre} it is easy to downsize the head when retaining acetabular bone stock, as there is very little risk of notching the neck. The average decrease in HNR, including the cartilage layer, ($\Delta HNR_{art \rightarrow post}$) at the time of operation in women with pseudotumour was about 0.17 (11%) and the maximum was about 0.25 (16%). This would decrease the range of movement in the hip

without impingement by on average 13° and by a maximum of 21°. Furthermore, a smaller femoral component would have an effect on α angle and effective inclination of the acetabular component. This would increase the risk of edge loading further. Therefore, the chance of these patients impinging and edge-loading their metal bearings is substantially increased. Edge-loading causes a large release of metal wear debris and probably explains why very high HNR and downsizing the head increase the risk of pseudotumour.

The ROC analysis suggests that a useful threshold for predicting whether patients will develop a pseudotumour is a pre-operative HNR of 1.35. The incidence of pseudotumour in patients with HNR_{pre} less than 1.35 was 3.5 times lower than patient with HNR_{pre} more than 1.35. However, pseudotumours still occur with HNR less than 1.35. A safer cut off to use clinically may be 1.30, as in this study no woman with a HNR of 1.30 or less developed a pseudotumour. To minimise the risk of pseudotumour, resurfacing should be avoided in women with HNR >1.30. Furthermore, increasing the size of the femoral component as much as possible, without compromising acetabular bone, would have an effect on coverage angle and effective inclination of the acetabular component.

Downsizing the femoral head at operation was found to increase the risk of pseudotumour. Patients, of both genders, downsized by more than 5.3 mm had a 2.9 times increased risk of developing pseudotumour. Sizing of resurfacing components requires consideration of many factors. Amongst those, include femoral neck width (prevent notching), articulating femoral head diameter (restore

HNR), diameter of acetabular inlet (adequate 'seating' of implant and prevention of soft-tissue irritation) and width of acetabular floor and rim (preservation of acetabular bone stock). Thus, respecting all above factors as much as possible, resurfacing head size should be selected to be as similar as possible to the size of the articulating native femoral head and should not be more than 5 mm smaller.

Unfortunately, there is no data to show whether retaining the head size will prevent pseudotumours from occurring in patients with very high pre-operative HNR, who are at high risk for developing pseudotumour. The reason for this is that in this study all patients with $HNR_{pre} > 1.35$ had downsized heads. A recent study identified that preservation of the HNR was associated with low ions even in cases with high HNR_{pre}, whilst downsizing was associated with high metal ion levels[186]. However, until it is known what happens to pseudotumour risk with $HNR_{pre} > 1.35$ and preservation of head size no firm surgical recommendations can be provided for this sub-group of patients.

It is of interest that pseudotumours also occured in a subset of patients with well-orientated acetabular components and without overt femoral head downsize, in comparison to other pseudotumour cases. This finding may explain the previous observation that some pseudotumours are associated with little wear concluding that they may be a result of a 'metal sensitivity' (Chapter 2). Pseudotumours have been shown to have great heterogeneity in appearance, radiology and histology (Chapter 2). It may be that pseudotumours around well-orientated implants are of a different nature to those around mal-orientated components. Pseudotumours

around well-orientated components may have little associated component wear, may have different nature (type of mass) and may have different histological features in comparison to pseudotumour patients with mal-orientated cups. On the contrary, it may be that the pseudotumours with well-positioned cups are associated with similarly increased wear compared to mal-orientated implants. Further studies are needed in order to test whether cup orientation has an effect on amount of wear and whether the variability of cup orientation seen in this chapter may explain the variability in pseudotumour presentation and nature described in Chapter 2.

The studies described in this chapter have a number of limitations: Firstly, the small number of subjects, particularly males, which was further reduced in study 5B. However, all patients that were revised due to pseudotumour during the study period were included in the studies and every possible effort was made in order to obtain their radiographs. Transition of hospital's radiographs from hard to electronic copies during the study period contributed greatly to the unavailability of radiographs, through misplacement of the hard copies during transfer from the hospital to the storage site. Secondly, other surgical parameters such as femoral anteversion and combined anteversion were not studied. It has previously been suggested that a combined anteversion (anteversion of femoral and acetabular component) greater than 45° is a risk factor for posterior impingement, secondary edge loading and pseudotumour development[172]. The unavailability of axial imaging, the only validated method of accurately assessing femoral component anteversion, prevented such analysis in this cohort. An additional limitation is that all radiographs were performed in the supine position as per hospital protocol. The

pelvic tilt in the supine orientation is not zero and is different to the pelvic tilt in different body positions, e.g standing, weight bearing conditions. As wear is more likely to occur in weight bearing condition rather than the supine position, it would probably have been preferable to obtain AP weight bearing radiographs. However, a recent study identified the difference in radiographic MoMHRA cup orientation between supine and standing radiographs to be a mean of 1.5° for inclination and 4.5° for anteversion[187]. These small differences allow for a significant correlation between supine and standing radiographic measurements for both inclination (ICC:0.9, $p<0.001$) and anteversion (ICC:0.8, $p<0.001$). Lastly, measurements of the HNR on standardised lateral radiographs and being able to calculate anterior offset of the femoral head on the anterior neck may have provided additional information of the plane where flexion occurs. However, such standardised radiographs were unavailable. Furthermore, Doherty *et al* have shown a significant correlation between HNR measurements made from AP and lateral radiographs[182].

The findings of these studies allow for surgical recommendations to be made regarding cup orientation and component sizing. Surgeons should aim for a radiographic cup orientation within the optimum zone. During surgery, different measures of anteversion and inclination are used from when radiographs are analysed; the relationship between these measurements have been defined by Murray[165]. Based on these previously defined relationships and assuming an identical pelvic position at the times of impaction and measurement, in order to achieve an optimal radiographic orientation of 45°/20°, a surgeon should aim for an operative inclination about 3° less (i.e. 42°) than the required radiographic

inclination and an operative anteversion about 7° more (i.e. 27°) than the required radiographic anteversion. Hence, for simplicity purpose it is recommended that surgeons should aim for an operative inclination/anteversion of 40°/25°. Provided the pelvis is not tilted, this would implant the cup in an acceptable orientation. However, further work is needed in order to assess various parameters during surgery and their effect on subsequent cup orientation.

Optimal sizing of components is also crucial. Surgeons should aim to use as large of a component as possible, considering acetabular anatomy and acetabular bone preservation. In order to achieve this, after surgical dislocation of the femoral head, surgeons should use a femoral sizing ring placed over the articular surface, similar to that in Figure 5.14, and make a note of the femoral head size. Implanting as large of a component as possible, i.e. one as similar as possible to native femoral head diameter, would decrease impingement risk and improve effective orientation which would in turn reduce risk of edge loading and increased wear.

Lastly, radiographic evidence of acetabular component mal-orientation and/or evidence of high HNR_{pre} and femoral head downsize at surgery in symptomatic patients should alert surgeons of the need for further investigation. These radiographic features should aid surgeons in identifying MoMHRA hips at risk and diagnosing pseudotumour prior to extensive soft-tissue and/or bony destruction.

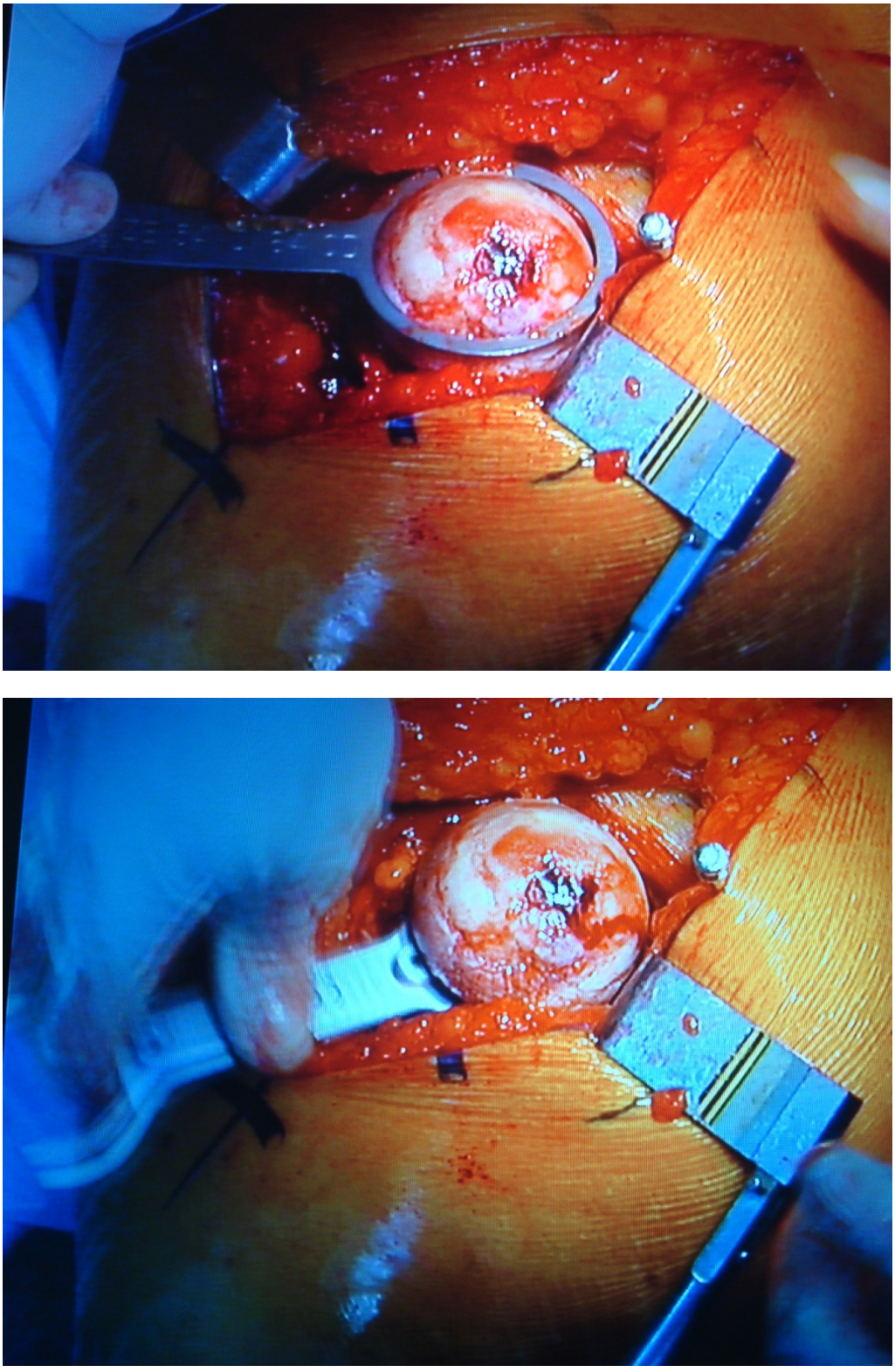


Figure 5.14: Different sizing keys available. Sizing of the femoral head articular surface a size 54 mm was the corresponding diameter (top figure). Sizing of the femoral neck, a size 48 mm could be placed over the femoral neck. Having respected acetabular bone stock, prosthesis inserted had a femoral component size of 52 mm and an acetabular size of 58 mm.

5.8 Conclusion

In conclusion, this study has identified surgical risk factors for the development of pseudotumour and has provided recommendations in surgical practice both during surgery and at clinical review.

Acetabular component mal-orientation was one of the identified contributing factors to pseudotumour development. The optimal radiological acetabular component orientation that surgeons should aim for in order to reduce risk of pseudotumour development is around an inclination/anteversion of 45°±10°/20°±10°. This would reduce risk of pseudotumour by four-fold.

HNR changes were also identified to be a contributing risk factor for pseudotumour development. Patients who have very high pre-operative HNR and who have a marked decrease in HNR as a result of the resurfacing are at high risk of developing a pseudotumour. This study suggests that it is safe to resurface women if the pre-operative head-neck ratio is 1.3 or less. Preservation of head size at resurfacing, provided no excess acetabular bone is removed, seems sensible as it may decrease the risk of pseudotumour.

5.9 Summary

- Surgical factors (acetabular component orientation, HNR changes) were identified that can reduce the revision-, and hence, disease- burden of pseudotumour.

- A wide scatter of cup orientation was detected. There was no difference in cup inclination and anteversion between pseudotumour and controls, although pseudotumour cups had a greater scatter. An optimum zone of acetabular componenent orientation was identified. Cups orientated within inclination of 45° ± 10° and anteversion of 20° ± 10°, were associated with a 4-fold decrease in risk of pseudotumour. However, pseudotumours were detected in well-orientated implants.

- During the resurfacing procedure HNR changes occured that correlated with native anatomy (HNR_{pre}). Such cases are a reflection of surgical practice and principles. HNR changes during the operation were more pronounced in pseudotumour cases. High pre-operative HNR and a greater change in HNR was detected in pseudotumour cases. Such changes would theoretically have an effect on impingement risk and increase wear.

- High HNR_{pre} and $\Delta HNR_{art \rightarrow post}$ were statistically significant predictors of pseudotumour development.

6 CHARACTERISING PSEUDOTUMOURS

6.1 Introduction

In the previous chapters, the burden of pseudotumour as a clinical condition was defined and surgical technique-related risk factors contributing to pseudotumour development were identified. These surgical factors complement the previously defined patient[153] and implant related[27,99] risk factors to pseudotumour development. The high prevalence of MoMHRA revisions secondary to pseudotumour performed in tertiary referral centres such as the NOC, provides a unique opportunity to study these cases further in order to gain a greater understanding in the pathoaetiology. The study described in this chapter aims to answer the following questions that remain unanswered from the literature and findings of previous chapters.

1. *Does the amount of prosthesis wear correlate with the histological findings in peri-prosthetic tissues?*

As described in Chapter 2, although pseudotumours are usually associated with a highly worn prosthesis[11,129] a few studies have suggested that pseudotumour formation is not always associated with increased wear[10,12,152]. This has led to the suggestion that the extensive necrosis and tissue destruction seen in MoMHRA-associated pseudotumours results not from a cytotoxic effect of the large number of metal particles on macrophages, which have phagocytosed these wear particles[105], but from a hypersensitivity response to one or more components of

metal wear particles[128]. In keeping with this hypothesis, a prominent perivascular lymphoid infiltrate termed ALVAL, is commonly seen in MoMHRA periprosthetic tissues[9,10,131,149,151,152]. Whether the inflammatory changes and tissue necrosis seen in peri-prosthetic tissues of failed MoMHRAs are due to cytotoxicity or hypersensitivity is essential to the understanding of pseudotumour pathogenesis. If cytotoxicity related to the amount of wear has a dominant role in pseudotumour development, reducing amount of wear would decrease pseudotumour incidence. On the contrary, if hypersensitivity has the dominant role in pseudotumour development and is not dose dependent, reducing the amount of wear would have little effect on reducing pseudotumour incidence.

2. *Can pseudotumours be categorised based on macroscopic appearance?*

As previously described in Chapter 2, a great variability has been described in radiological assessment, histological characteristics and bearing wear findings. This great variability may be due to the fact that different types of pseudotumour exist, for example solid masses may be associated with well-orientated acetabular components, have different histological features and are associated with minimal wear amounts, hence represent the 'metal sensitivity' group. Alternatively, the great variability may be due to the wide spectrum of the clinical entity of pseudotumour and no differences between pseudotumour cases can be elicited when reviewing different parameters collectively.

3. *Do cups orientated within the previously defined optimal zone have smaller amount of prosthesis wear in comparison to cups orientated outside this zone?*

In Chapter 5, an optimum zone of acetabular component orientation was identified that was associated with a reduced pseudotumour risk. However, some pseudotumours occur even with optimally orientated cups. This zone was determined by various statistical evaluations based on pseudotumour prevalence per zone in a case-control study. Work on serum metal ions, as surrogate markers of *in vivo* wear, has shown that patients with orientated acetabular components within this zone have smaller amount of metal ions in their serum[101]. However, whether components orientated within this defined zone are associated with less bearing wear remains to be determined.

6.2 Null hypotheses

H_0: There is no correlation between prosthesis wear and histogical features in MoMHRA peri-prosthetic tissues.

H_0: Pseudotumours can be categorised into different types with distinguishable (radiological, histological and wear) features.

H_0: Acetabular component orientation has no effect on the amount of wear of retrieved prostheses.

6.3 Materials and methods

6.3.1 Study design

A retrospective study was undertaken. Such study has been described previously (study 3B).

6.3.2 Ethical approval

According to the Human Tissue Act 2004, there are no statutory requirements to the need for consent to the storage and use of tissue from existing holdings for research. However, this study adhered to the Human Tissue Authority's (Department of Health, United Kingdom) (HTA 12217) recommended practice code by formally seeking and obtaining institutional review board (BioBank, Nuffield Orthopaedic Centre, Oxford, UK) approval prior to accessing patient records, imaging, histology slides and implants from the existing holdings (Ethical Approval Number: REC C9 H0606/11).

6.3.3 Patient selection

Although pseudotumour cases were of primary interest for this study, a group of controls as a means of comparison was also included. The study's cohort was,

therefore, made up of two groups. Group 1 was MoMHRA implants retrieved from patients who underwent revision due to the presence of a symptomatic pseudotumour. Group 2 was the control group, which included MoMHRA implants retrieved from patients who underwent revision due to other causes of failure. In order to minimise selection bias, the following criteria had to be fullfilled for inclusion in the study:

Inclusion criteria:

1. Obtained patient consent as per BioBank regulations for use of medical records, tissue and explants for further study.
2. Availability of explanted prostheses for wear analysis measurement. Available, explanted MoMHRAs implants were deposited at the BioBank unit at the Nuffield Orthopaedic Centre and the Histopatholgy Department, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS).
3. Availability of tissue for histological examination, archived at the Histopatholgy Department, NDROMS.
4. Availability of MRI scan of the MoMHRA hip prior to revision for all patients except those revised due to femoral neck fracture.
5. Detailed clinical, radiological and histological findings in order to determine revision mode classification.

Exclusion criteria:

1. Implants damaged during revision were excluded from analysis, as they would lead to unreliable wear estimation.

2. Patients that showed any discrepancy between clinical indication, radiological and operative findings and histology reports were also excluded.

6.3.4 Patient demographics

Fifty-six patients fulfilled the above criteria and were included in this study. 46 of them had their index procedure at the NOC. The majority of patients were female (n=38, 68%) and had a mean age at primary MoMHRA of 56 years (range: 29 to 77 years). All cases underwent arthroplasty for osteoarthritis. The mean implant survival was 4.7 years (0.8 to 9.8 years). The majority of failures were in patients with a unilateral MoMHRA (n=34), 16 failures were in patients that had received bilateral MoMHRAs and one side had failed; six failures were in (three) patients with bilateral MoMHRAs that required bilateral revisions and fulfilled all above five criteria for inclusion of both sides in the study. The majority of implants retrieved were BHR (Smith & Nephew, UK) and Conserve Plus (Wright Medical Technology, USA). The majority of cases were performed via the posterior approach (n=48). Detailed cohort demographics are given in Table 6.1.

The commonest cause of revision was the presence of a symptomatic pseudotumour (n=45). Other modes of failure included periprosthetic femoral neck fracture (n=5), impingement (n=2), unexplained pain (n=2), heterotopic ossification (Brooker III[188]) (n=1) and acetabular component loosening (n=1).

		Cohort Mean (SD) Range	Group		p-value
			Pseudotumour (n=45) Mean (SD) Range	Control (n=11) Mean (SD) Range	
Age at primary/ years		55.7 (10) 28.7 to 71.8	54.9 (9.6) 28.7 to 71.8	59.4 (12.2) 32.6 to 70.9	0.1
Gender	Male	18	12	6	0.07
	Female	38	33	5	
Approach	Lateral	8	7	1	0.58
	Posterior	48	38	10	
Implant Survival/ years		4.7 (2.5) 0.8 to 9.8	5.0 (2.5) 0.8 to 9.8	3.6 (2.3) 1.2 to 7.9	0.1
Implant Type	BHR	31	27	4	0.4
	C+	22	16	6	
	Cormet	2	1	1	
	Recap	1	1	0	
Femoral head size/ mm		46 (4) 36 to 54	46 (3.5) 36 to 52	47.5 (5) 40 to 54	0.1

Table 6.1: Cohort demographics, including analysis for the Pseudotumour and Control Groups. (C+ : Conserve Plus)

6.3.5 Power of the study

Due to the limited number of available retrieved implants that met all of the above criteria, it was important to estimate the power of the study. The power of a statistical test is the probability that the test will reject the null hypothesis when the null hypothesis is actually false (i.e. the probability of not committing a Type

II error, or making a false negative decision)[132]. Power of the study was determined using Altman's nomogram[189]. The nomogram incorporates three variables into the calculations (sample size, significance level and standardised difference). Standardised difference is defined as the ratio of the difference of interest divided by the standard deviations of the observations[189].

For linear wear rate, a significant difference of interest is 8 µm/year. This difference represents a two-fold increase from the previously reported steady-state of 4 µm/year for MoM implants[190,191]. Previous studies have reported on a standard deviation of 8 µm[12]. Hence, a standardised difference of 1.0 was calculated. Based on this standardised difference, a sample size of 54 patients for the whole cohort and 45 for the pseudotumour cases, the estimated power of the study for the whole cohort was 0.97 and for the pseudotumour cases was 0.95. This implied that the study had 97% probability of correctly concluding that a 8 µm/year difference between the pseudotumours and controls exists. Similarly, the study had 95% probability in correctly concluding such a difference between pseudotumour cases. However, power study calculation is not a precise method because certain parameters used for calculation are not precisely estimated. Furthermore, the nomograms used for calculations of sample size assume equal sized groups. Strict inclusion criteria and inherent variability in revision burden and pseudotumour presentation did not allow for equal size groups to be obtained, hence reducing the power of the study. Despite these limitations, it was concluded that the current study had sufficient power to detect wear rate difference between the groups tested.

6.3.6 Parameters studied

6.3.6.1 Histological assessment

Histological analysis of tissues retrieved at revision is an important component of diagnosis and therefore management in many aspects of revision hip arthroplasty. It has been previously suggested that some of the pseudotumour cases, may be associated with a peri-prosthetic infection[192]. In order to exclude such cases, histological and microbiological findings were reviewed to rule out any possibility of infection as previously characterised by Pandey *et al*[193].

In all cases, specimens submitted included capsule/synovium, femoral and acetabular membrane, pseudomembrane; the numbers of specimens submitted varied from case to case but at least two specimens were submitted from each case.

Retrieved tissues were prepared in 5 μm thick tissue sections and were examined and scored for a number of parameters by a histopathologist fellow (FM) and a consultant musculoskeletal histopathologist (NA) blinded to mode of failure, radiological findings and wear analysis results. Review of the specimens by histopathologists was deemed necessary in order to avoid erroneous assessments of the histological features. Histological assessment of peri-prosthetic tissues is a highly specialised field that requires specific expertise.

All cases were scored using the ALVAL scoring system described by Campbell *et al* (Campbell-ALVAL)[10]. In this system, a score less than 4 is defined as low, a score between 5 and 8 as moderate and scores 9 – 10 as high. In addition, as in Mahendra *et al*[150], the extent of tissue necrosis and the nature and degree of the inflammatory cell infiltrate in MoM periprosthetic tissues was analysed. The presence of specific inflammatory cells (macrophages, lymphocytes, plasma cells, eosinophil polymorphs) was noted and the presence or absence of an ALVAL response was also assessed semi-quantitatively as previously described; in this scoring system, necrosis and the number of specific inflammatory cells are scored as 0 (absent) 1, (few) 2, (many) and 3 (abundant). The ALVAL response was also assessed semi-quantitatively as 0 (absent) 1, (relatively little evidence of a perivascular lymphocytic infiltrate with lymphocyte cuffing of blood vessels being less than five cells in thickness), 2, (numerous perivascular lymphoid aggregates and lymphocyte cuffing of vessels being 5-10 cells in thickness), and 3, (abundant with numerous large perivascular lymphoid aggregates with lymphocyte cuffing around vessels being more than ten cells in thickness) (figure 6.1). This scoring system was termed the Oxford-ALVAL score and was designed to provide a more quantitative measure of the ALVAL response. As the inflammatory infiltrate varied between different specimens, the specimens showing the maximum inflammatory response was scored; at least 20 fields per specimen magnification (100 x) were examined.

All cases were scored independently by both reviewers (NA, FM). Repeatability testing demonstrated highly significant intra- ($k=0.86$, $p<0.001$) and inter- ($k=0.74$, $p<0.001$) observer (intra-class) correlation coefficient (k).

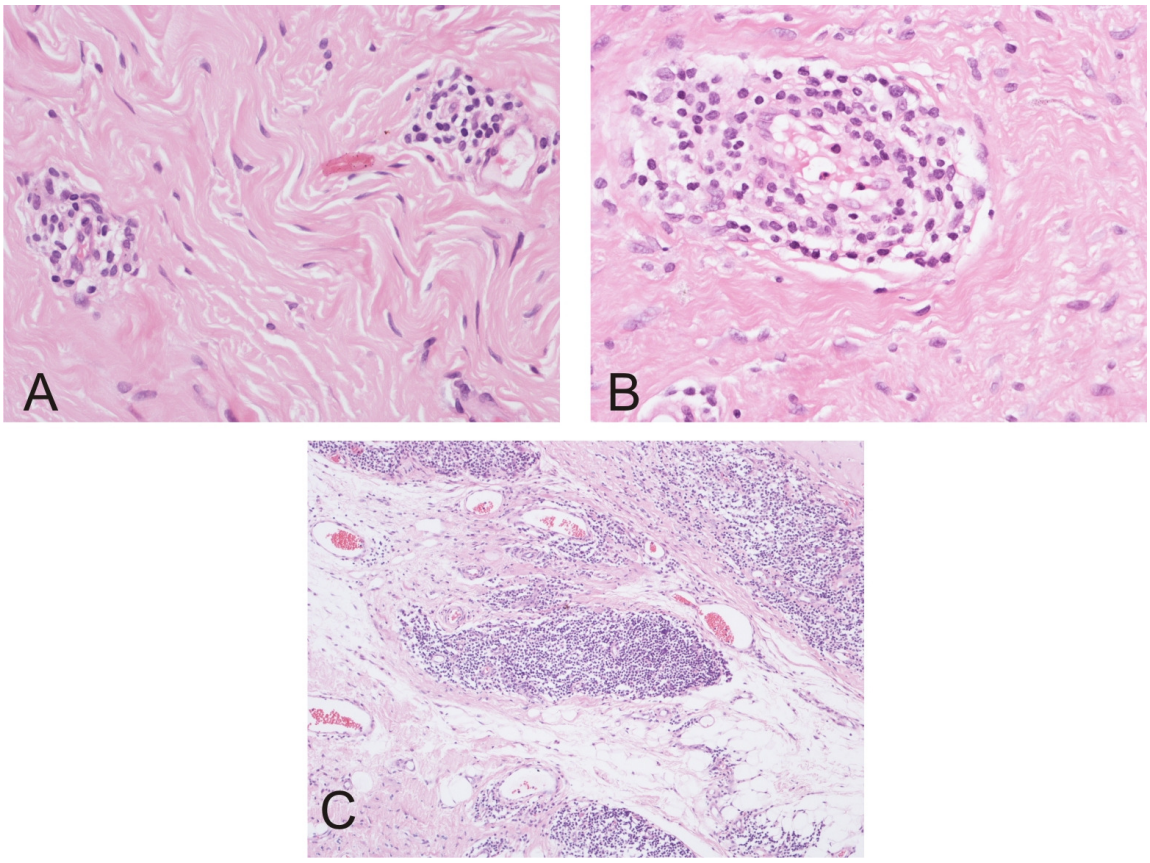


Figure 6.1: The Oxford ALVAL scoring system: A. Grade 1; B. Grade 2; C. Grade 3; showing respectively fewer than 5, 5-10, and more than 10 lymphocytes around vessels. Magnification power: 100x for Figures A/B and 40x for Figure C.

6.3.6.2 MoMHRA implant wear measurement

All implants were catalogued by an identification number to ensure patient anonymity. Bearing surface wear was assessed using an Artificial Hip Profilometer (AHP, Redlux, Southampton, UK) in a blinded fashion at the Smith and Nephew Implant Development Centre (IDC) (Leamington Spa, United Kingdom). The Redlux technique and measuring system used was previously described in Chapter 2 and is a validated, highly accurate method in determining linear, volumetric wear and local radius[95,98].

Acetabular component wear measurements were obtained up to the edge of the acetabular component. The presence or absence of edge wear was determined visually after inspection of the wear contours produced.

6.3.6.2.1 Estimation of linear wear and linear wear rate

The linear wear depth was defined as the maximal distance between the wear profile and an ideal hemisphere, recorded in micrometer (µm). Linear wear measurements of both the femoral and the acetabular components allowed for calculation of the Total Linear Wear (TLW):

TLW (µm)= Linear Wear (Femur) (µm) + Linear Wear (Cup) (µm)

The total linear wear rate (TLWR) was defined as the maximum TLW divided by the *in vivo* duration (i.e. survival) of the MoMHRA in years (µm/yr):

TLWR (µm/yr) = TLW (µm) / Implant survival (yrs)

Schmalzried *et al* measured the linear wear rate of retrieved large head metal-on-metal devices with good outcome and reported a TLWR of 4 µm/yr[190]. Similar observations were reported by Tuke *et al*. Hips were defined to be highly worn if

the TLWR $\geq$ 4 µm/yr[191]. On the contrary, hips with TLWR < 4 µm/yr were considered to be associated with low/expected prosthesis wear.

6.3.6.2.2 Estimation of volumetric wear and volumetric wear rate

The volumetric wear depth was defined as the volume of deviation between the wear profile and an ideal hemisphere, recorded in cubic millimetres (mm^3). Volumetric wear measurements of both the femoral and the acetabular components allowed for calculation of the Total Volumetric Wear (TVW):

TVW (mm^3)= Volumetric Wear (Femur) (mm^3) + Volumetric Wear (Cup) (mm^3)

The volumetric wear rate (TVWR) was defined as the maximum volumetric wear divided by the *in vivo* duration (i.e. survival) of the MoMHRA in years (mm^3/yr):

TVWR (mm^3/yr) = TVW (mm^3) / Implant survival (yrs)

6.3.6.2.3 Edge loading definition

The presence or absence of edge wear was determined visually after inspection of the wear contours produced. If the wear scar on the acetabular component transversed the edge, edge wear had occurred, which was usually accompanied with a corresponding flattened stripe on the femoral head (Figure 6.2). Such

components were categorised as having edge wear. Components with no such wear features and with the wear patch detected within the sub-hemispherical surface were categorised as having non-edge wear.

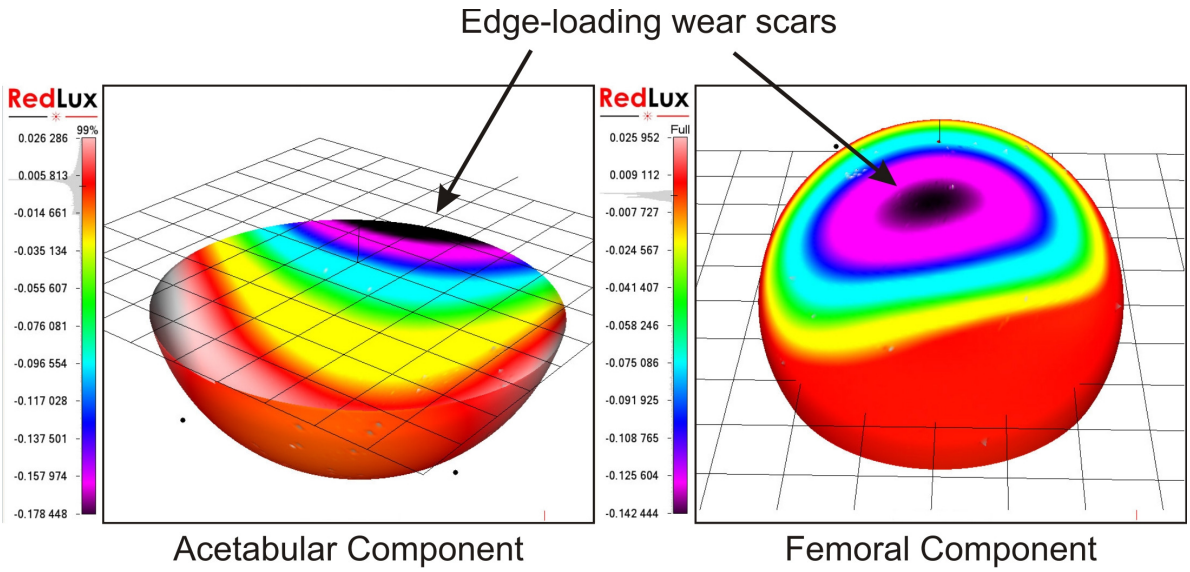


Figure 6.2: Figures produced following RedLux wear analysis. Note edge loading scar on acetabular component with associated pole scar on the femoral head. Amount of wear of each component is colour coded with a bar on the left of each component for reference. Images obtained are courtesy of Amir Kamali, Smith & Nephew, Leamington Spa, UK

6.3.6.3 Radiological assessment

Assessments were performed both on pre-revision radiographs and MRIs.

6.3.6.3.1 Radiographic assessment

Radiographic assessments were independently performed by two observers (GG, AC). Radiographs were scored for the presence of any abnormal findings

including: lytic lines, osteolysis, impingement signs and neck narrowing. In addition, the radiographic acetabular component orientation was determined using the EBRA software. Assessments showed a high an inter-observer reliability (κ) coefficient of >0.9 ($p< 0.001$).

6.3.6.3.2 MRI assessment

All patients were imaged on a 1.5 T magnet MRI scanner (Symphony, Siemens, Erlangen, Germany). A standard MRI imaging protocol for MoMHRA pelvic imaging was employed (Chapter 2). Interpretation of MRI scans of the hip is a skill routinely employed by radiologists. In order to avoid bias resulting from erroneous assessment of MRI scan, a consultant musculoskeletal radiologist with an interest in hip pathology (SO) participated in this study. The principal investigator (GG) and SO reviewed and graded all scans. Pseudotumours were classified based on the MRI classification system described by Hauptfleisch *et al*[145], dividing them into three types: Types I, II and III (Chapter 2).

6.3.7 Analyses

The possible correlation between histological findings (quantitative analyses, Campbell-ALVAL and Oxford-ALVAL Scores) and amount of wear detected was tested. The amount of wear and TLWR and the incidence of histological findings for different revision Groups were assessed. The determined ALVAL scores (Campbell-ALVAL and Oxford-ALVAL) were tested for correlation with TLWR. Further analyses on histological differences were performed for different

subgroups based on revision indication and TLWR findings.

In addition, the association between type of pseudotumour and location as per MRI was determined. The association between radiological findings, histological assessments and wear measurements was tested.

Lastly, the incidence of radiological findings was determined for the whole cohort and for the two groups (Pseudotumour and Control Groups). The amount of wear was compared between patients with acetabular components within the previously defined optimum zone for MoMHRA (of inclination 45° ± 10° and anteversion of 20° ± 10°) and patients with acetabular components outside the optimum zone.

6.3.8 Statistics

The distribution of data was assessed for normality. The Mann Whitney *U* and Kruskal Wallis, non-parametric tests were used to calculate level of statistical significance in the non-normally distributed linear and volumetric wear amounts between different radiological and histological findings. Cross-tabulated data was compared using the chi-square (χ^2) test. Spearman's (rho) correlation coefficient was used to assess correlation between histological features and amount of wear detected. Statistical analysis was performed with the SPSS statistical programme version 18.0.

6.4 Control measurements

The reliability of the Redlux optical profilometry method to estimate linear wear was tested against a roundness machine. Five femoral heads were measured with both the Redlux and a roundness machine (Talyrond 290, Talyrond-Hobson Ltd., Leicester, UK). The average difference between the two methods was 0.08 μm (SD: 0.43 μm). Similarly, the reliability of the Redlux to estimate volumetric wear was compared with a gravimetric method using a precision balance (Mettler Toledo 500, Mettler Toledo Ltd, Leicester, UK). Wear scratches of various sizes and depths were generated on the surfaces of four CoCrMo femoral heads. The Redlux estimated wear volume was compared with the measured wear volume; the average difference was 0.01 mm^3 (SD: 0.01 mm^3). The results of these reliability tests provide evidence that Redlux is a reliable method of measuring both linear and volumetric wear.

6.5 Results

As noted in previous studies, there was a wide spectrum of histological findings (Table 6.2) (Figure 6.3) . Necrosis was seen in all pseudotumour cases, the majority of patients showing 2+ (n=13) or 3+ (n=35) necrosis. These necrotic areas were composed of necrotic connective tissue and often contained numerous macrophages which had undergone necrosis. A heavy [2+ (n=9) or 3+ (n=38)] macrophage infiltrate was noted in most cases. The lymphocyte response was more variable with most cases containing 1+ (n=17) or 3+ lymphocytes (n=25), although some cases contained 2+ lymphocytes (n=9) and a few cases contained

none (n=5). The amount of necrosis, moderately correlated with both the grades of macrophage (rho=0.6, $p<0.001$) and lymphocytic (rho=0.5, $p<0.001$) infiltration. The lymphocyte infiltrate was mainly perivascular in distribution and it was found that the lymphocyte score closely mirrored the Oxford-ALVAL score (rho=0.73, $p<0.001$). A prominent plasma cell infiltrate was seen in eight cases. Eosinophil polymorphs were only seen in four cases. Specific analysis of the ALVAL response showed that application of the previously described Campbell-ALVAL scoring system on the current case series resulted in a mean score of 7.5 (range: 3 to 9). The majority of patients (n= 51, 91%) had an ALVAL score of six or more. The Oxford-ALVAL score was also high (≥ 2) in most cases (n=38, 68%).

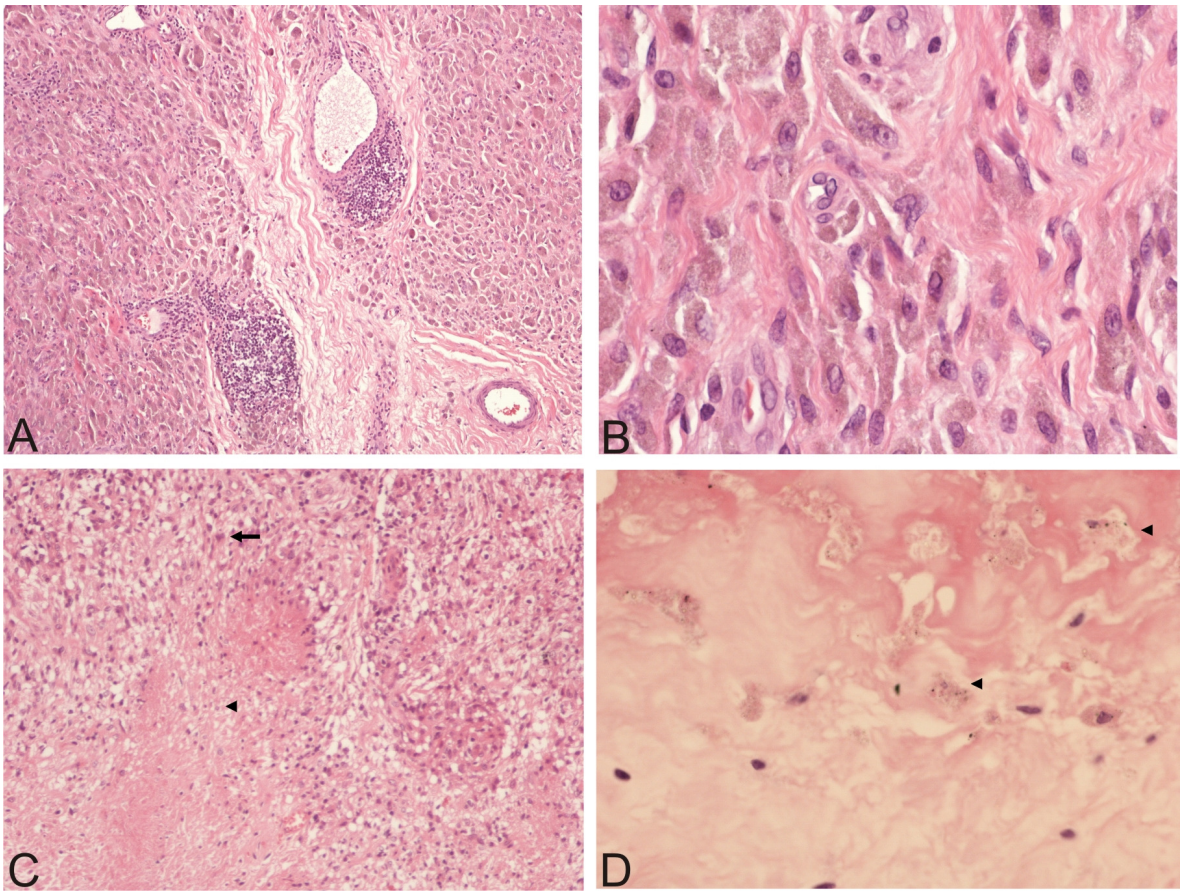


Figure 6.3: Photomicrographs showing the variable cell and tissue response to Co-Cr particles (A) A heavy (3+) infiltrate of wear particle-containing macrophages and perivascular lymphocytes in periprosthetic tissues; (B) High-power view of viable macrophages containing Co-Cr particles; (C) A cystic pseudotumour containing viable wear particle-containing macrophages (arrowed) in the wall with necrotic macrophages (arrowhead) on the surface; (D) High-power view of the surface of a pseudotumour showing macrophages, some of which are necrotic but still contain Co-Cr particles (arrowhead).

Histological Feature	Score	Cohort	Group		p-value	TLWR > 4 µm/yr		p-value
			PT (n=45)	Control (n=11)		Yes (n=39)	No (n=17)	
Necrosis	**0 – 1**	8	3	5	<0.001	1	7	0.001
	2 – 3	48	42	6		38	10	
Macrophage	**0 – 1**	9	1	8	<0.001	2	7	0.006
	2 – 3	47	44	3		37	10	
Lymphocytes	**0 – 1**	22	13	9	0.001	14	8	0.04
	2 – 3	34	32	2		25	9	
Campbell-ALVAL	**0 – 4**	7	1	6	<0.001	1	6	0.003
	5 – 8	33	29	4		26	7	
	9 – 10	16	15	1		12	4	
Oxford-ALVAL	**0**	10	2	8	<0.001	2	8	0.002
	1	8	6	2		7	1	
	2	13	12	1		10	3	
	3	25	25	0		20	5	

Table 6.2: Histological findings for the whole cohort, per diagnosis group and per prosthesis wear group. TLWR: Total Linear Wear Rate, PT= Pseudotumour Group.

The mean linear wear for the femoral component was 36 µm (SD: 54, range: 0 to 283 µm) and the mean acetabular component linear wear was 87 µm (SD: 197, range: 0 to 949 µm) (Table 6.3). The mean femoral component volumetric wear was 15.6 mm^3 (SD: 36, range: 0 to 198 mm^3) and the mean acetabular component volumetric wear was 11.3 mm^3 (SD: 27, range: 0 to 150 mm^3). Linear and volumetric wear parameters of both components correlated significantly with implant survival (rho=0.44 to 0.66, $p<0.001$). The TLWR was 21.8 µm/yr (SD: 37.3, range: 0 to 202 µm/yr). The majority of prostheses had TLWR above 4

µm/yr (n=39, 70%). Edge loading was detected in the majority of the components (n=41, 73%).

	Cohort Mean (SD) Range	Group		p-value
		PT Mean (SD) Range	Control Mean (SD) Range	
Linear Wear Femur (µm)	36.0/ 54.5 0.0 to 283.1	43.3/ 58.5 0.0 to 283.1	6.4/ 8.6 0.0 to 23.5	<0.001
Linear Wear Cup (µm)	86.8/ 196.6 0.0 to 948.9	97.7/ 207.8 0.0 to 948.9	9.2/ 14.1 0.0 to 60.7	0.02
Total Linear Wear (µm)	125.5/ 231.7 0.0 – 987.41	140.9/ 243.5 0.0 to 987.4	14.8/ 23.4 0.0 to 60.7	0.004
Volumetric Wear Femur/ (mm^3)	15.6/ 35.9 0.0 to 197.8	19.1/ 39.4 0.0 to 197.8	1.7/ 2.3 0.0 to 5.9	<0.001
Volumetric Wear Cup/ (mm^3)	11.3/ 27.4 0.0 to 149.9	12.8/ 29.1 0.0 to 149.9	1.0/ 1.3 0.0 to 2.7	0.03
Total Volumetric Wear/ (mm^3)	28.4/ 65.9 0.0 to 347.7	32.4/ 69.9 0.0 to 347.7	2.3/ 3.5 0.0 to 8.6	0.007
Total Linear Wear Rate (TLWR)/ (µm/yr)	21.8/ 37.3 0.0 to 201.5	26.4/ 40.3 0.0 to 201.5	2.9/ 4.3 0.0 to 12.8	<0.001
No. of hips with TLWR > 4 µm/yr (%)	39 (70%)	37 (82%)	2 (18%)	<0.001
Total Volumetric Wear Rate (mm^3/yr)	4.8/ 9.9 0.0 to 48.3	5.5/ 10.4 0.0 to 48.3	0.4/ 0.5 0.0 to 1.4	0.002
No. of hips with edge-loaded scars (%)	41 (73%)	37 (82%)	4 (36%)	0.002

Table 6.3: Wear findings for the whole cohort and per group. PT = Pseudotumour Group, TLWR: Total Linear Wear Rate.

The majority of pseudotumour patients had a Type II mass (n=28). There was a similar distribution of Types I (n=8) and III (n=9) amongst the remaining cases. The majority of the cases were located along all compartments of the hip joint (n=22), some were posterio-laterally (n=16), whilst the remaining were located anteriorly (n=9).

Positive radiographic findings were detected in 26 (46%) of the revisions. In seven hips, more than one finding was present. The type of radiographic changes detected are detailed in Table 6.4.

Radiographic Sign	Number of cases
Fracture	5
Loosening	10
Osteolysis	9
Neck narrowing > 10%	8
Heterotopic ossification	1
Impingement sign	5

Table 6.4: Radiological findings detected on radiographs for the whole group.

The mean acetabular component orientation had a radiographic inclination of 48.5° (SD: 10.8°, range: 27.3° to 86.2°) and anteversion of 17.3° (SD: 10.1°,

range: -14.1° to 38.7°). The scatter of the acetabular component orientation is illustrated in Figure 6.4. The majority of cups were outside the previously defined optimum acetabular orientation (n=29, 52%).

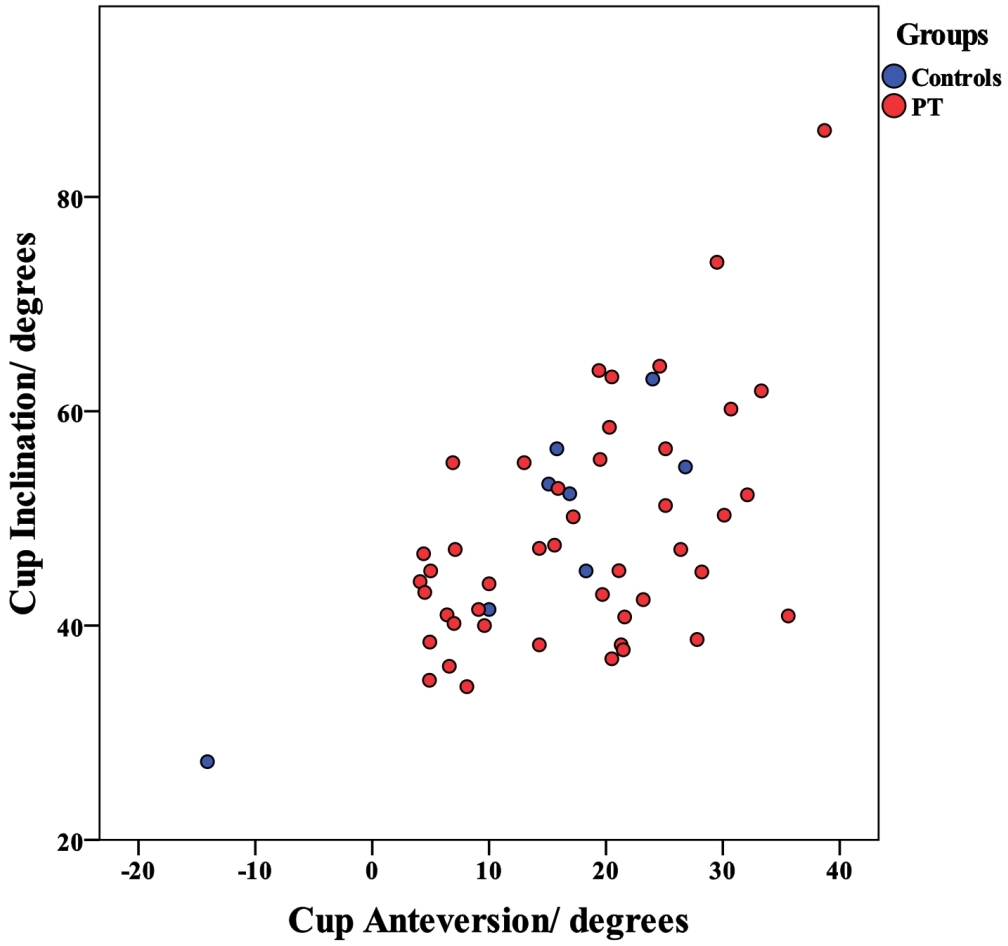


Figure 6.4: Scatter diagram of acetabular component orientations for the whole cohort. Graph is colour-coded for the two Groups. PT: Pseudotumour.

6.5.1 Group analysis

The presence of positive radiographic signs was less prevalent amongst revisions for pseudotumour. Only 18 of the 45 pseudotumour revisions (40%) had positive radiographic findings, compared to nine out of 11 for the controls (82%). The most common radiographic findings in the Pseudotumour Group were osteolysis

(n=9) and neck narrowing (n=8). The majority of cups in the Pseudotumour Group (26/46) were orientated outside the previously defined Optimum Zone.

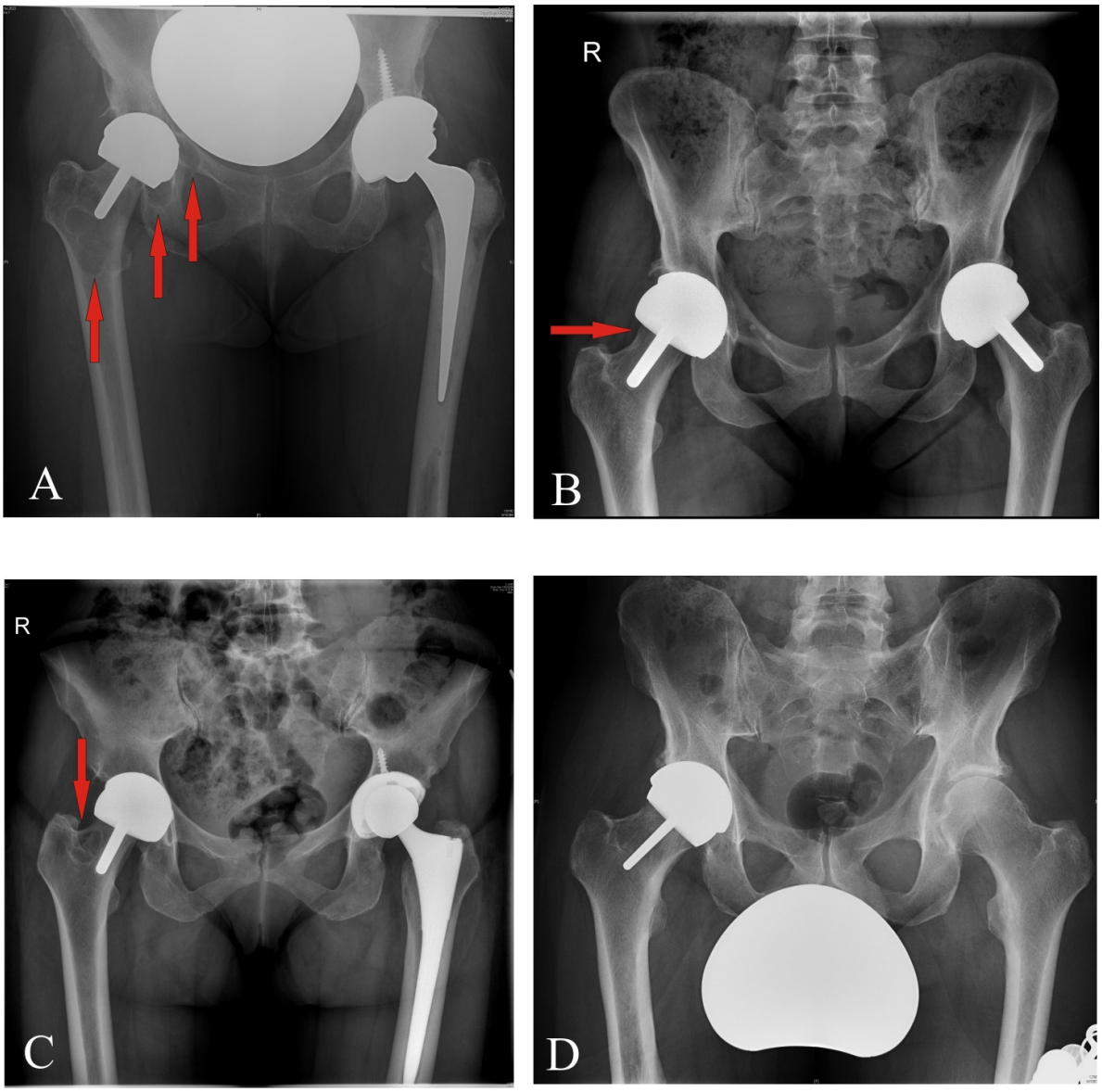


Figure 6.5: Radiographic features of four pseudotumour cases pre-revision. Red arrows pointing at most prominent pathological features on radiographs. X-ray A demonstrating osteolytic lesions on proximal femur and pelvis. X-ray B demonstarting neck narrowing . X-ray C demonstrating osteolytic area over proximal femur. No pathological features were detected in case D; however a Type II pseudotumour was detected on MRI with mixed macroscopic features (cystic and solid components) intra-operatively.

All histological features including extent of necrosis, macrophage and lymphocytic infiltration, Campbell-ALVAL and the Oxford-ALVAL scores were

scored significantly higher in the Pseudotumour Group in comparison to the controls ($p<0.001$) (Table 6.2). Amongst the pseudotumours there was a moderate or strong presence of both necrosis (n=42) and macrophage (n=44) infiltration in the great majority of cases. However, the extent of lymphocytic infiltration varied, although the majority had moderate or strong lymphocytic presence (n=32, 71%), none or scattered lymphocytic presence was detected in 13 cases (29%). There were no differences in any of the histological features between unilateral and bilateral MoMHRAs revised for pseudotumour ($p=0.2$ to 0.8).

Components that were revised due to pseudotumour had significantly higher wear compared to components revised for other modes of failure ($p<0.001$). The majority of pseudotumours had high TLWR (n=37, 82%), whilst only 2 of the controls had high TLWR (Table 6.3). There was no difference in wear measurements between pseudotumours identified in unilateral or bilateral MoMHRA ($p=0.7$).

6.5.2 Correlation between amount of wear and histology

Histological findings correlated moderately with wear measurements (Table 6.5). The amount of necrosis and the extent of macrophage infiltration were associated with TLWR. Patients with abundant presence of necrosis and macrophage infiltration were associated with the greatest amount of TLWR (Figures 6.6 & 6.7). However, there were some patients (n=10) with low TLWR and moderate/strong necrosis and macrophage presence (scores: 2 and 3). The majority of these patients (n=8) were in the Pseudotumour Group.

Correlations (rho/p-value)	**Necrosis**	**Macrophages**	**Lymphocytes**	**Campbell-ALVAL**	**Oxford-ALVAL**
TLWR/ (µm/yr)	0.45 <0.001	0.43 <0.001	0.33 0.13	0.16 0.26	0.41 0.002
TLW/ (µm)	0.54 <0.001	0.42 0.003	0.25 0.09	0.28 0.06	0.37 0.009
TVWR/ (mm^3/yr)	0.44 0.002	0.32 0.03	0.2 0.2	0.42 0.1	0.46 0.001
TVW/ (mm^3)	0.51 <0.001	0.33 0.02	0.2 0.1	0.39 0.009	0.44 0.002

Table 6.5: Correlations of TLWR, TLW, TVWR and TVW with histological features. rho= Spearman's rho coefficient.

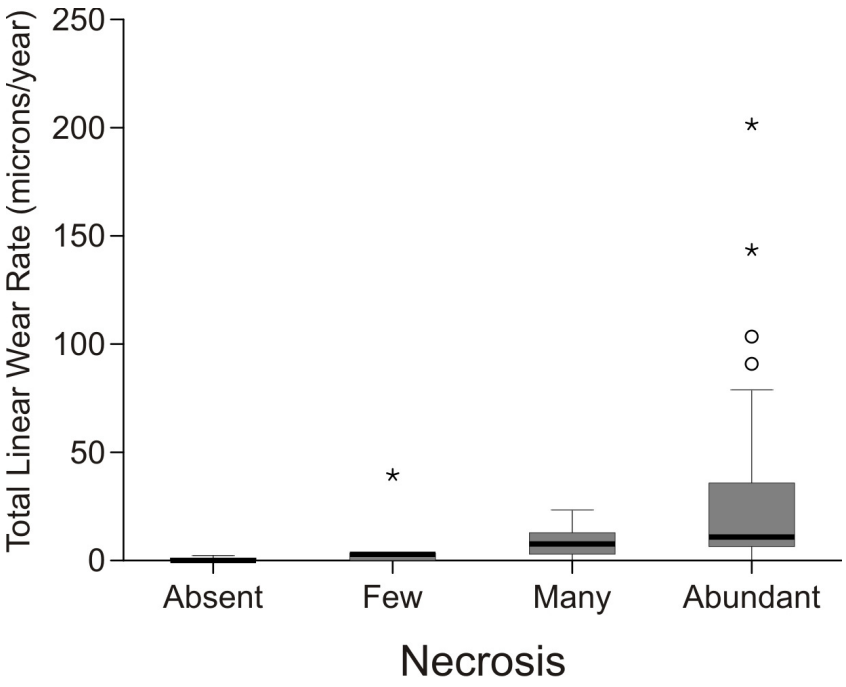


Figure 6.6: Box-plot of the amount of TLWR for the different grades of necrosis seen in the whole cohort.

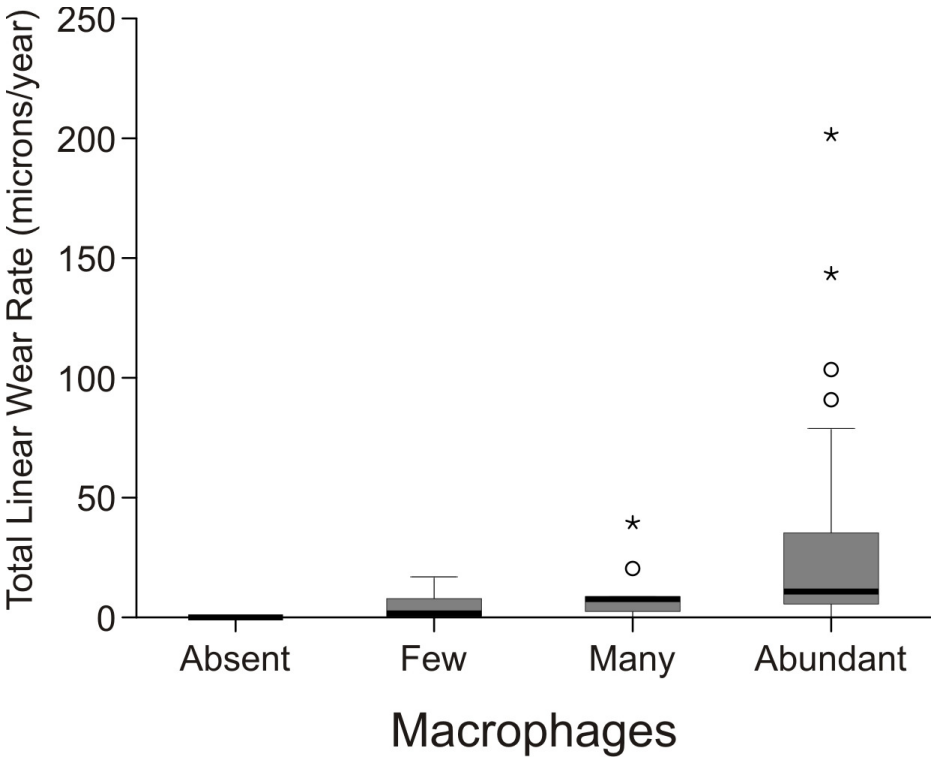


Figure 6.7: Box-plot of the amount of TLWR for the different grades of macrophage infiltration seen in the whole cohort.

The presence of lymphocytes was associated with significantly greater TLWR (Figure 6.8). However, there were some patients with low TLWR and moderate or strong lymphocytic presence (n=9). Eight of these were patients in the Pseudotumour Group (Figure 6.9).

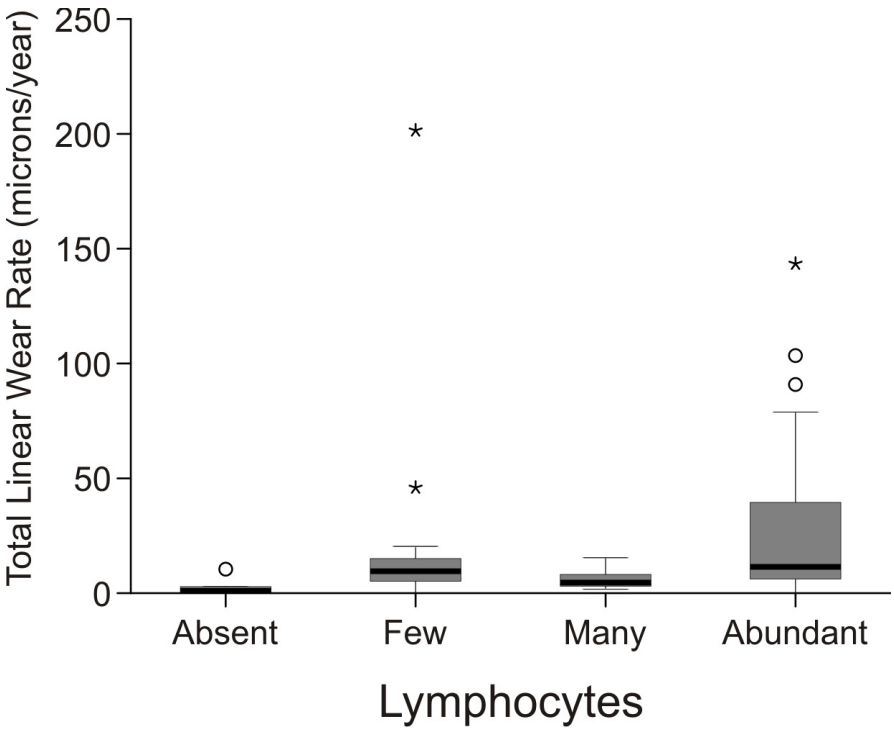


Figure 6.8: Box-plot of the amount of TLWR for the different grades of lymphocyte infiltration seen in the whole cohort.

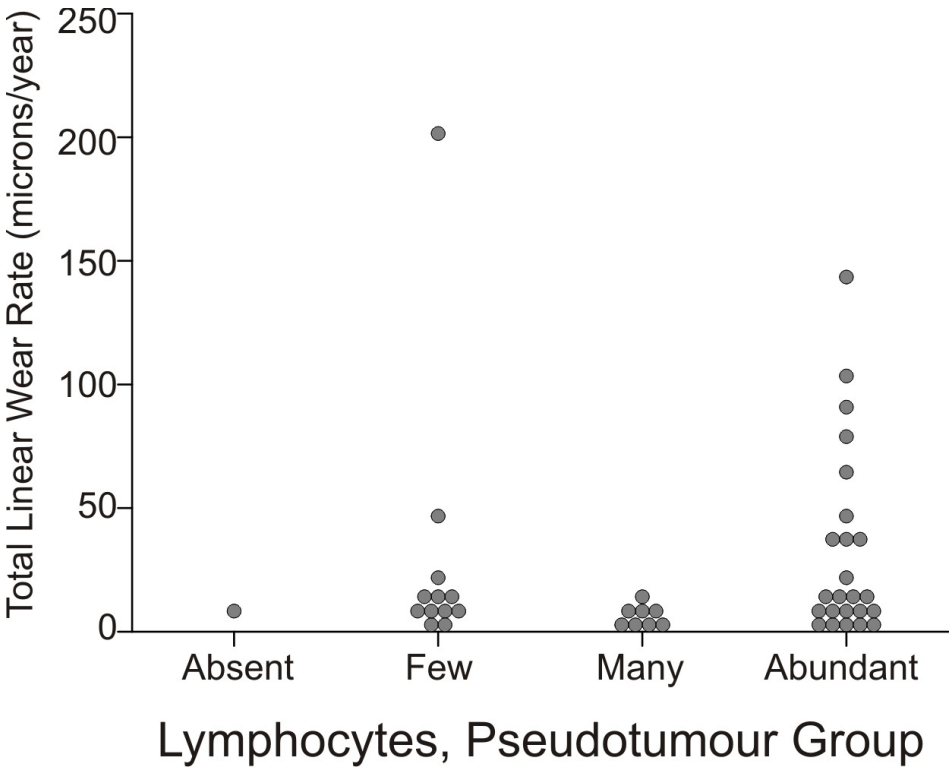


Figure 6.9: Two dimensional dot-plot of the amount of TLWR detected for the different grades of lymphocyte infiltration in the Pseudotumour Group.

The previously described Campbell-ALVAL score did not correlate with TLWR (p=0.1) (Figure 6.10). Patients with low Campbell-ALVAL score had significantly less wear in comparison to both moderate (p=0.002) and high score (p=0.008) groups. On the contrary, the Oxford-ALVAL score weakly correlated with TLWR (rho=0.4, p=0.002) (Figure 6.11). However, there were still some patients (n=8) with a high Oxford-ALVAL score with low TLWR; all of which were in the Pseudotumour Group.

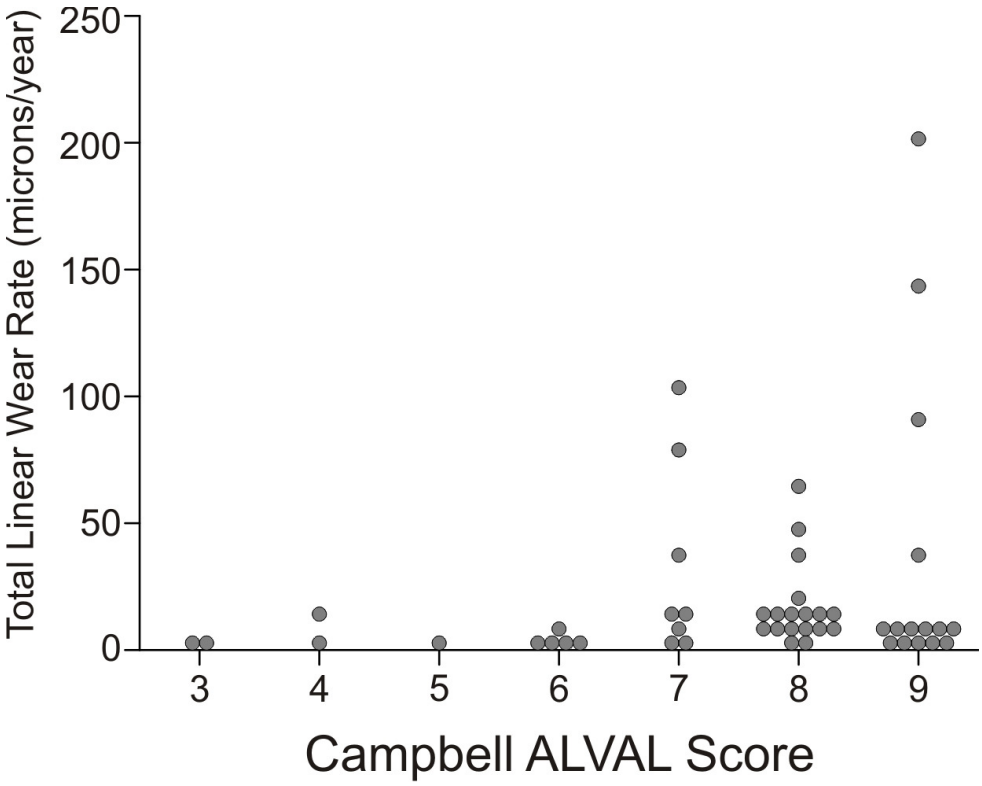


Figure 6.10: Amount of TLWR for the different grades of Campbell's ALVAL score.

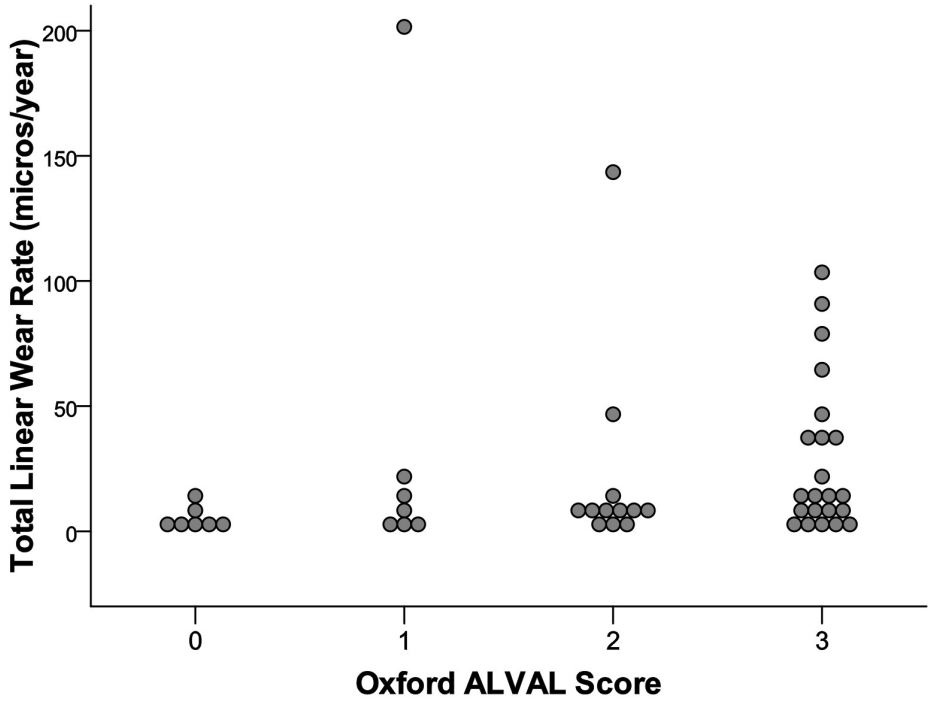


Figure 6.11: Amount of TLWR for the different grades of Oxford's ALVAL score.

6.5.3 Pseudotumour sub-analysis

Location of pseudotumour mass was significantly different for the different classification types ($p<0.001$) (Table 6.6). There was no difference in location of pseudotumour for the different approaches ($p=0.6$). There were no differences in the incidence and type of radiographic findings between the different MRI types of pseudotumour ($p=0.5$). There was no difference in acetabular component inclination ($p=0.6$) or anteversion ($p=0.2$) between the different types (Figure 6.12). Accordingly, the incidence of cups within the optimum zone was similar for the three types ($p=0.11$).

Location	**MRI Classification**		
	Type I (n)	**Type II (n)**	**Type III (n)**
Anterior	0	1	6
Postero-lateral	6	10	0
Anterior & Postero-lateral	2	17	3

Table 6.6: The location of the three different pseudotumour types as classified by MRI. Anterior reflects the anterior compartment of the hip joint (anterior to the neck and involving the psoas and adjacent tissues anteriorly), postero-lateral reflects the postero-lateral compartment which involves the postero-lateral hip joint capsule, including the gluteal bursa and adjacent tissue.

Histological features were similar amongst the three MRI types of pseudotumour. There were similar amounts of necrosis (p=0.17), macrophage (p=0.76) and lymphocyte (p=0.61) infiltration between the three types. Similarly, the Campbell- and Oxford-ALVAL scores were not different (p=0.78 and p=0.83 respectively) for the three types. In addition, there were no differences in the wear measurements for the different types of pseudotumours (p=0.1 to 0.7).

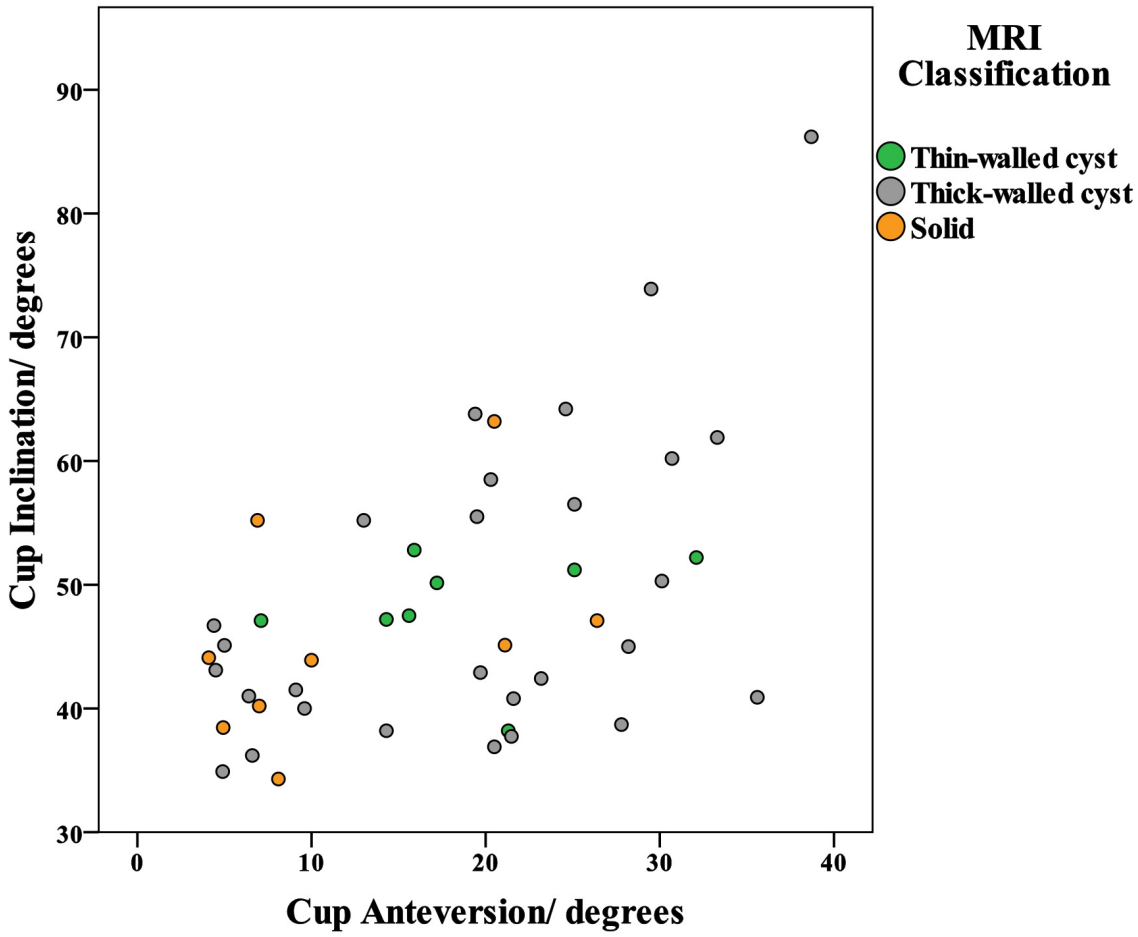


Figure 6.12: Scatter diagram of the acetabular component orientation for the different Psuedotumour types as per MRI findings.

6.5.4 Acetabular component orientation

Acetabular component orientation varied widely. Acetabular component inclination did not correlate with any wear parameter (p=0.58 to 0.97). Acetabular component anteversion only weakly correlated with TLWR (rho=0.35, p=0.01).

There was significantly less wear detected in the implants of patients with cups orientated within the previously defined optimum zone compared to those with cups orientated outside the optimum zone (p=0.001 to 0.08) (Table 6.7).

	Linear wear femur/ µm	**Linear wear cup/ µm**	**TLWR µm/year**	**Volumetric wear femur/ mm^3**	**Volumetric wear cup/ mm^3**	**TVWR mm^3/year**
Within optimum zone	22.4/25.4 0 to 96.4	23.3/ 36.6 0 to 144.5	11.8/ 19.1 0 to 78.9	6.5/ 8.6 0 to 31.8	4.0/ 8.5 0 to 39.1	2.3/ 3.2 0 to 14.3
Outside optimum zone	50.4/ 69.5 0 to 283.1	143.0/ 257.0 0 to 948.9	35.1/ 48.9 1.7 to 201.5	24.2/ 47.5 0.1 to 197.8	36.1/ 17.9 0 to 149.9	7.2/ 13.0 0.1 to 48.3
p-value	0.01	0.004	0.003	0.04	0.03	0.08

Table 6.7: Wear measurements for revised MoMHRAs analysed as per cup orientations within or outside the previously defined optimum zone.

6.6 Discussion

The findings of this study allow for rejection of two out of the three null hypotheses set out at the end of the introduction. A correlation between histological and wear measurements was identified. Furthermore, cups within the previously identified optimum zone were found to be associated with reduced wear. However, pseudotumours could not be sub-categorised into different types with distinct histological and wear findings.

Histological findings of this study demonstrate that necrotic and inflammatory changes are commonly seen in MoMHRA peri-implant tissues and that both necrosis and the extent of the macrophage infiltrate correlate strongly with the extent of prosthesis wear. In addition, it was evident that although the extent of perivascular lymphocyte infiltration correlated with the amount of wear; a heavy perivascular lymphocyte infiltrate could be detected in a small number of cases revised for pseudotumour with low or the expected amount of wear. Hence, this provides insight that in the majority of pseudotumours (80% in this study) the increased wear debris production results in macrophage infiltration and necrosis with a variable amount of immune response (lymphocytic infiltration); whilst in the minority of pseudotumours (20%) the small/expected amount of wear leads to a heavy lymphocytic presence with the subsequent macrophage recruitment and associated necrosis.

The tissue changes and inflammatory features in MoMHRA peri-implant tissues are well recognised. These include extensive necrosis, loss of the synovial lining, a heavy macrophage response to metal wear particles, and a pronounced perivascular lymphoid infiltrate composed mainly of lymphocytes; plasma cells and eosinophil polymorphs are also observed in some cases. Considerable necrosis was seen in revised MoMHRA periprosthetic tissues and this was invariably associated with a heavy macrophage infiltrate. Both the amount of necrosis and the extent of the macrophage infiltrate correlated most strongly with the amount of prosthesis wear. These findings suggest that the extent of the non-specific foreign body macrophage response is related to the amount of prosthesis wear. It is very likely that MoMHRA-derived metal wear particles, in particular cobalt, have a cytotoxic effect on phagocytic macrophages[105,194,195]. This would lead to a vicious circle, whereby metal wear particle generation leads to a foreign body macrophage response with inability of macrophages to process the phagocytosed particles, resulting in cell death and re-release of the metal wear particles leading to further macrophage recruitment and continuation of the cycle. Release of lysosomal enzymes from this necrotic macrophage component is likely to contribute to the extensive connective tissue destruction seen in pseudotumours[194]. Surface ulceration of the pseudocapsule and pseudomembrane around MoMHRA is also likely to be a reflection of this process as the cells that line the surface of periprosthetic tissues are mainly macrophages in phenotype. It has been shown that exposure of articular synovial tissues to CoCr debris can lead to surface ulceration in the absence of a loose prosthesis[196].

A perivascular lymphocyte reaction has been noted in periprosthetic tissues of failed MoMHRA arthroplasties; this is considered to develop as a result of a hypersensitivity response to Co-Cr metal wear debris. A major finding of this study is that the extent of the perivascular lymphocyte reaction correlated with the amount of wear in most MoMHRAs. An ALVAL response was seen in both low wear (n=8) and high wear MoMHRA periprosthetic tissues but most cases with a 2+ and 3+ Oxford ALVAL score were seen with highly worn MoMHRAs. The perivascular lymphocyte reaction that characterises ALVAL is thought to represent part of a specific immune response. Taken with other pathological changes in MoMHRA peri-implant tissues of a heavy macrophage infiltrate, granuloma formation and tissue necrosis this is thought to be indicative of a delayed hypersensitivity (Type IV) reaction. The lymphocyte population in a failed surface arthroplasty is mainly composed of CD3+ T lymphocytes and comprises a mixture of CD4+ and CD8+ cells[131,150]. As in other delayed hypersensitivity reactions, these cells play a role in the recruitment of macrophages; the extent of the lymphocyte response (and consequent macrophage infiltration and tissue necrosis) has been shown to be antigen dependent[197,198]. As not all pseudotumours were associated with high wear (n=8), these findings suggest that the specific immune response to wear particles plays an important role in this MoMHRA complication. As individual immunogenicity is known to vary[199], it is possible that some patients develop a specific immune response to metal particles at low/expected levels of wear. When the amount of wear increases, the risk of exceeding the immune threshold and hence evoking a specific immune response is correspondingly increased. As shown in Figure 6.13

the non-specific and specific response to wear particles should not be regarded as mutually exclusive in the pathogenesis of pseudotumour formation.

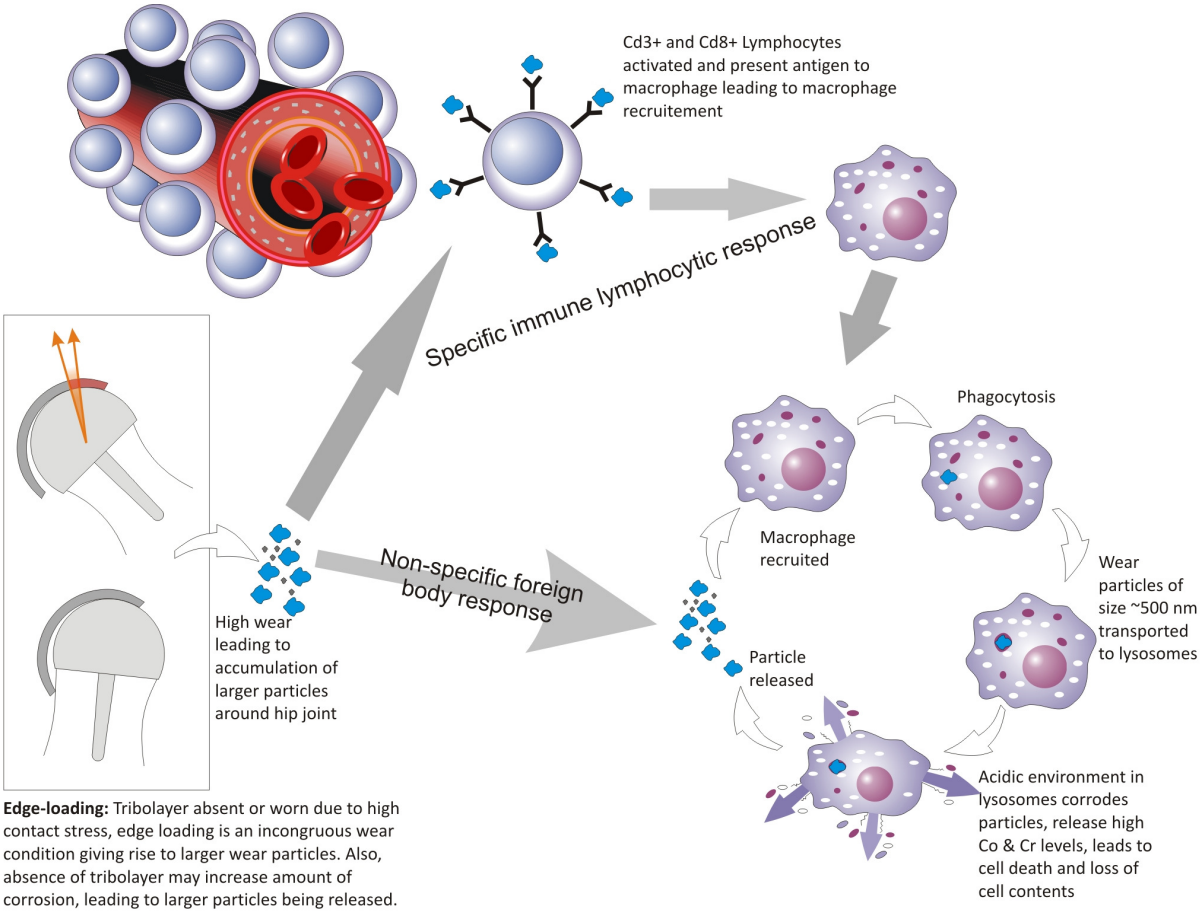


Figure 6.13: Schematic of the possible patho-mechanism involved in pseudotumour development. During conditions of increased wear, particles produced can lead to stimulation of either and/or both the innate and the humoral response. The innate response involves the recruitment of macrophages to the area of wear-particle deposition with associated phagocytosis with subsequent inability to process the particles (especially cobalt) and resulting cell death and release of particles and lysosomal enzymes. The release of particles in tissues leads to subsequent further macrophage recruitment and a vicious cycle of cell death. The immune response, involves activation of CD4+ and CD8+ lymphocytes upon exposure of tissues to metal particles with subsequent presentation of antigen and macrophage recruitment resulting in a similar cycle of cell death and macrophage recruitment.

Amongst the 45 pseudotumours, eight (18%) pseudotumours had minimal Oxford-ALVAL score values, high TLWR, necrosis and macrophage response indicating a predominant non-specific immune response; eight (18%) had high (2+/3+) Oxford-ALVAL score values and low TLWR indicating a predominant immune response; and the remaining (n= 29, 64%) had a combined picture of high TLWR, necrosis and a 2+ or 3+ macrophage and perivascular lymphocytic response indicating the presence of both the innate and immune responses. This would suggest that reducing the amount of wear from MoM components lowers the frequency of these pathological changes and hence the risk of pseudotumour. This does not, however, entirely eliminate this possibility as individual differences in immunogenicity may trigger a specific response at lower particle levels than in most cases. Further research is needed in order to pre-operatively identify those patients who are likely to develop a pronounced immune reaction to MoMHRA. Failed implants from patients with bilateral MoMHRA had similar wear and histology findings to failed unilateral MoMHRAs. This would indicate that in the majority of these cases, the pathogenesis of failure was increased wear stimulating the innate response with or without an associated immune response.

Similar findings of a variability in the individual response to arthroplasty bearing wear products has previously been reported[200,201]. The variability of the inflammatory response to polyethylene (PE) wear products has led authors to search for genetic markers that may predict increased susceptibility to PE wear-induced osteolysis[202]. Wilkinson *et al* in a cohort of 481 caucasians with cemented metal-on-polyethylene THAs, noted that the carriage of a specific allele (TNF – 238A) was associated with an increased risk of osteolysis versus non-carriage,

which was independent of other risks[202]. Differences in genetic composition could lead to assorted cellular mechanisms involved in the inflammatory response. Sabokbar *et al*[203] described two distinct cellular mechanisms involved in the process of osteolysis. These observations hence raise the possibility that the variability of psedotumour reported in multiple different series is in part a consequence of individual response. Further research is needed in order to pre-operatively identify patients that are likely to develop immunological reactions to MoMHRA.

Although it has previously been suggested that in patients with bilateral MoMHRAs the immune response has a predominant role in failure, findings of this study are in contrast to this observation for the majority of cases. Failed implants from patients with bilateral MoMHRAs had similar wear and histology findings to failed unilateral MoMHRAs. This suggests that in the majority of cases, the failure pathogenesis is increased wear stimulating the innate response with or without an associated immune response.

This study's findings contrast to those of Langton *et al* who reviewed the histology of 17 ASR MoM prostheses which failed due to an adverse reaction to metal wear debris (ARMD) where an association between the lymphocyte infiltrate and wear volume was not established, however the number of cases in their study is a limiting factor[129]. The morphological findings were similar to those of Campbell *et al*[10] but the ALVAL scoring system they employed did not provide sufficiently discriminatory criteria to permit distinction between high-wear and low-wear MoMHRA. Two of the main criteria of this scoring system

are the status of the synovial lining and tissue organisation. Loss of the synovial lining was commonly found in both low and high wear MoMHRA periprosthetic tissues and a marked loss of normal arrangement (score 2) with perivascular lymphocyte aggregates (score 3) was detected in most specimens. The latter overlaps with another major criterion of this scoring system i.e. the extent of the macrophage and lymphocyte infiltrate. Evaluation of the relative proportion of these inflammatory cells is used effectively to reflect the non-specific and specific response to wear particles respectively. However, as the findings of the present and previous studies indicate, both these two inflammatory components are commonly found in MoMHRA periprosthetic tissues. The Oxford ALVAL score, which measures a single histological feature (i.e. the extent of lymphocyte cuffing around vessels), provides a more specific semi-quantitative measure of the immune response; it is much easier to evaluate and in effect combines the second and third criteria of the Campbell ALVAL system.

On further characterisation of pseudotumours, it was evident that macroscopic appearance of pseudotumour only correlated with location. The majority of pseudotumours were located throughout the joint and were of mixed nature (Type II). Solid masses (Type III) were more commonly found anterior to the hip joint, whilst purely cystic masses (Type I) were found postero-laterally. It has previously been postulated that these masses develop along the pathways of least resistance[141]. Those are either anterior to the hip into the iliopsoas region, or laterally into the bursa of the greater trochanter, or along new pathways created by the surgery. Although the latter has not been seen to occur in all cases, MRI findings show this to be the case in some pseudotumours (Figure 6.14).

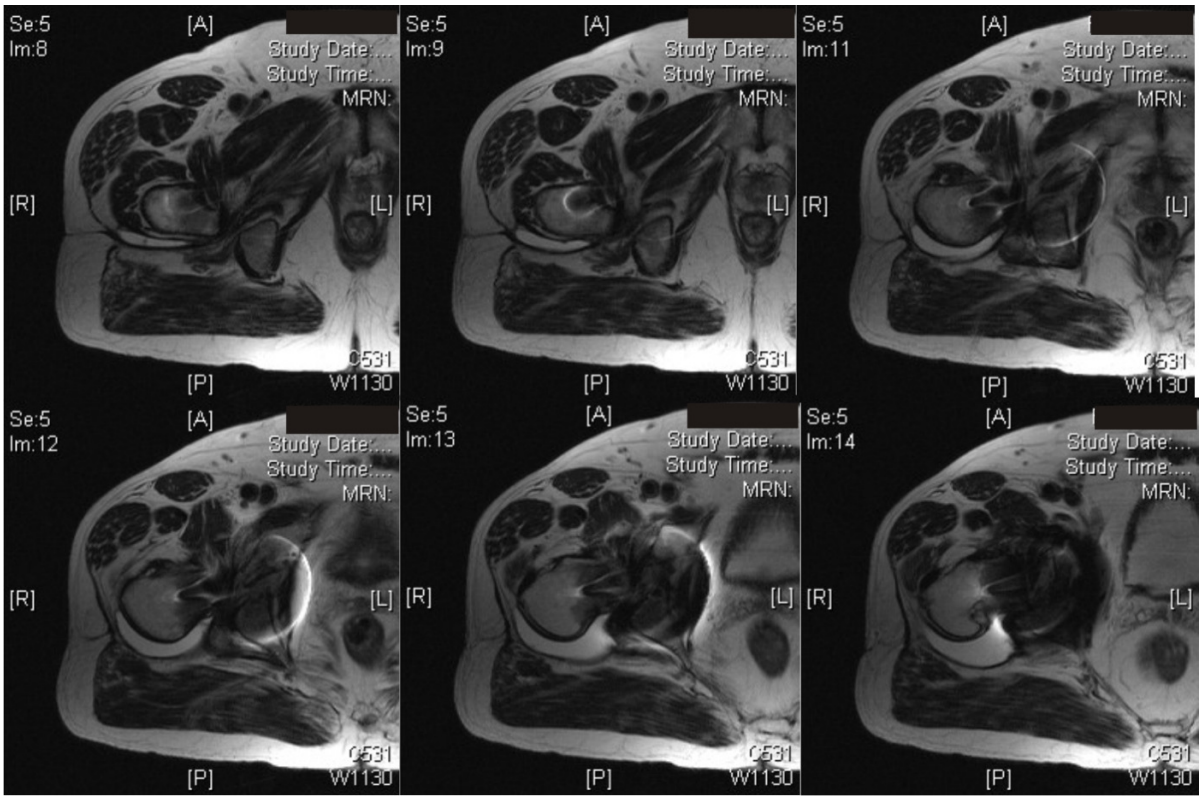


Figure 6.14: Figure illustrating the presence of a pseudotumour along the surgical pathway in a MoMHRA implanted via the posterior approach.

Communication of the lesion with the joint has been found in all pseudotumours. An anterior capsulotomy or a capsulectomy during surgery creates a connection between the iliopsoas tendon, its bursa and the hip joint anteriorly. Similarly, a posterior capsulotomy creates a communication with the posterior structures. In addition, with a lateral approach, dehiscence of the gluteus medius tendon from the greater trochanter may occur creating a void or a communication with the trochanteric bursa. When the hip's external rotators and the gluteus maximus tendon are incised with the posterior approach, the integrity of the compartment may be compromised by inadequate repair or healing and sinuses may be created followed by the formation of fluid collections.

It may be that pseudotumours occur along the path of least resistance as previously suggested[141]. Alternatively, it may be that pseudotumour location is determined by the location of debris deposition. The latter may be influenced by many factors including component orientation, proximal femoral and pelvic anatomy and individual activity pattern governing the 3-D interaction of the components. The 3-D interaction of the components has been shown to vary greatly between individuals during functional activities[59], but could not be determined in this cohort. Nevertheless, acetabular component orientation was tested as a contributing factor influencing location of a pseudotumour; without a correlation between cup orientation and pseudotumour location being found.

As no difference in histology assessments or wear measurements were determined for the different type of masses, a possible hypothesis is that location influences the type of mass. Pathology studies have shown that bursae type of structures form along planes of increased movement[204]. A possible hypothesis is that posterolateral masses are usually cystic due to the fact that increased movement occurs along this compartment of hip and furthermore, there is greater space potential in the subcutaneous tissues. However, findings of this study cannot provide any evidence for or against this hypothesis.

Similarly to Study 5A (section 5.4.1), a wide scatter of cup orientation was also detected in this study. Patients with acetabular components within the previously described zone had significantly reduced wear in comparison to those with cups

orientated outside this zone. However, as previously described (Chapter 5) placement of a cup within this zone does not exclude pseudotumour development.

Although the majority of pseudotumours had cups outside the zone, a significant proportion of cases had well-orientated components. Of interest, six out of the eight pseudotumours associated with low/expected amount of wear had well-orientated acetabular components. Thirteen patients with well-orientated cups had high wear; other factors may be related to the increased wear. These include patient and surgery specific factors. Patient-specific factors have previously been described to influence amount of wear by influencing the 3-D interaction of the components[59]. In addition, it should be noted that the radiographic evaluation performed represents a static evaluation. However, findings from static evaluations may not necessarily apply in the dynamic situation during the wear process. Other surgery related factors contributing to wear would include HNR alteration as previously described (Chapter 5).

Radiographic assessment of the pseudotumour cases provides evidence that X-ray assessment is not a sensitive enough marker of a problematic hip. Only 46% of the whole cohort had positive radiographic changes and this percentage dropped to 40% on reviewing pseudotumour cases only. It is, therefore, evident that additional investigations, both serum metal ions and USS/MRI as per local protocol and MHRA guidelines[137,138], are necessary in order to aid clinicians with the diagnosis.

The study described in this chapter has certain limitations. Firstly, its nature of a retrospective retrieval study. Such studies present selection bias as only failed implants and tissues can be studied; however such studies provide important facts in the understanding of the failing mechanism and have been used extensively in the literature of MoM prostheses[13,190,191]. In order to prevent any additional bias associated with the retrospective nature of the study, all assessments were performed prospectively and previous histological and radiological assessments, performed at the time of revision, were not included in the analysis. In addition, all assessments were performed in a blinded fashion to exclude any biases. Secondly, a number of different implants were included in the study. Although wear rates are sensitive to material, design and manufacturing parameters (Chapter 2), a number of different implants were included in the study so that an adequate study power was achieved. The prosthetic designs included were of designs currently in the market and with no design fault described. Thirdly, the measurements were performed in a laboratory associated with the manufacturing of a prosthesis which could have created a potential conflict of interest. In order to minimise this, all assessments were performed blindly to mode of failure and time *in-situ*. Furthermore, no prosthesis design was associated with greater TLWR or TVWR in the cohort in comparison to others ($p=0.4$ and 0.3 respectively). Lastly, wear measurement analysis using TLWR has certain inherent limitations. As it is a measure of linear wear, it is limited to estimating the local deepest scar (worst case) and not the mean amount of wear. In addition, although MoM wear has a biphasic rate (run-in and steady state)[53], the calculation of TLWR determines a mean value not accounting for the difference in the two phases. In order to overcome these limitations, wear analyses in this study included additional

parameters of wear other than TLWR, such as TLW, VW and VWR. The findings were similar regardless of wear parameter used.

6.7 Conclusion

In conclusion, this study provided insight into the response to metal wear following MoMHRA and the patho-mechanisms of pseudotumour development. The majority of pseudotumours are associated with increased wear. In these cases, the increased wear is associated with necrosis due to the increased innate response coupled with a variable immune-response. A minority of pseudotumours are associated with low wear and a predominant immune response resulting in necrosis. Surgeons should aim to minimise wear of MoMHRA with appropriate patient, implant selection and surgical technique. This would lead to a reduction in pseudotumour incidence. However, some pseudotumours would still occur even in low-wearing prostheses due to the variability in the immune response between patients.

Pseudotumour type is associated with location of lesion. No difference in histology findings or wear measurements could be elicited for the different types of pseudotumour. A wide scatter of acetabular component orientation was seen. Acetabular component orientation within the previously defined optimal zone (Chapter 5) is associated with decreased amount of wear.

6.8 Summary

- The majority of pseudotumours are associated with highly worn prostheses (80%), whilst the remaining are associated with low/expected amount of prosthesis wear. However, not all patients with higher than expected wear develop a pseudotumour. This highlights the possible influence of host-specific factors.

- Histological findings confirm that both necrosis and the extent of the macrophage infiltrate correlate with the extent of prosthesis wear. In addition, although the extent of perivascular lymphocyte infiltration correlated with the amount of wear; a heavy perivascular lymphocyte infiltrate could be detected in a small number of cases revised for pseudotumour with low/expected wear in their prostheses. In the majority of pseudotumours (80%) the increased wear debris production results in macrophage infiltration and necrosis with a variable amount of immune response (lymphocytic infiltration); whilst in the minority of pseudotumours (20%) the small/expected amount of wear leads to a heavy lymphocytic presence with the subsequent macrophage recruitment and associated necrosis.

- Pseudotumour type is only associated with, and may be influenced by, location.

- Acetabular component orientation within the previously defined optimum zone is associated with significantly lower wear in comparison to cups orientated outside the optimum zone.

- The findings of this chapter provide evidence that if the amount of wear following MoMHRA is reduced to within the expected limit of 4 µm/year, the incidence of pseudotumour will significantly reduce. However, even under optimal tribological conditions some pseudotumours will occur in cases with evidence of exacerbated immune response on histology. Appropriate implant and patient selection would reduce amount of wear. Optimal surgical technique with appropriate implant size selection and acetabular orientation is also necessary. Further work is necessary to aid surgeons with acetabular component placement during MoMHRA surgery. This is described in the next chapter.

7 HOW TO IMPROVE CUP ORIENTATION

7.1 Introduction

The findings of the previous chapters (Chapters 5 and 6) provide evidence that reducing the amount of wear following MoMHRA would significantly reduce the incidence of pseudotumour development. Furthermore, the studies provided evidence that if surgeons orientate the acetabular component within the defined optimal zone, the risk of pseudotumour development will be reduced because of a reduction in wear.

As described in Chapter 2, acetabular orientation is defined in terms of inclination and anteversion[99,165,205]. Recommendations for optimal inclination and anteversion are usually based on measurements made on post-operative supine pelvic radiographs[158,160]. The inclination and anteversion measured in this manner is different from that measured at operation. There are two reasons for this: firstly, the angles of inclination and anteversion measured relative to the pelvis are defined differently in various situations[165] and secondly, the positions of the pelvis relative to the measurement reference frame are disparate.

Murray in 1993 defined the cup inclination/anteversion angles measured in the various situations (operative, radiographic and anatomical)[165](Chapter 2, section 2.4.9.4). These orientation angles are measured relative to the pelvis and are

different due to the distinct reference planes used for their calculation. However, they are interrelated in a non-linear manner and hence nomograms have been produced that quantify the differences (Appendix 6). Murray's nomograms were calculated for a neutral alignment of the pelvis assuming that no pelvic obliquity, rotation or tilt is present; the differences due to the assorted definitions are usually about 5° but can be as large as 15°[165].

In clinical situations the body fixed co-ordinate system of the pelvis is not usually the same as the co-ordinate system used for taking measurements. In geometry, a coordinate system is a method that uses spatial locations along defined axes, to uniquely determine the position of a point. A Cartesian coordinate system for a three-dimensional space means choosing an ordered triplet of mutually perpendicular lines (axes), a single unit of length and an orientation for each axis. Each reference line is called a coordinate axis (x, y or z) or just an axis of the system, and the point where they meet is its origin, usually at the ordered triple (0,0,0). The cup is ideally defined relative to the neutral pelvis as described by Murray. In such situations, the transverse axis of the pelvis is usually defined as the line between the anterior superior iliac spines and the longitudinal axis is the perpendicular to this passing between the pubic tubercles. At radiographic assessment, measurements are made relative to the X-ray film and the axes of the pelvis are usually not parallel to this, with the pelvis being commonly extended[206]. During surgery, at the time of cup impaction, the majority of surgeons take into account the perceived orientation of the pelvis relative to the operating theatre reference frame and orientate the cup accordingly. For the operation, the surgeon

attempts to position the pelvis in a neutral position relative to the operating table (neutral meaning that the reference plane of the pelvis is aligned to the reference plane of the table) and provides adequate support in order for the neutral orientation to be maintained during surgery. In such a condition, the operative cup orientation as per Murray (i.e. orientation of the cup relative to the pelvis) is the same as the intra-operative cup orientation (i.e. orientation of the cup relative to the operating table in the same reference planes as Murray's operative orientation). However, the pelvis may not be neutrally positioned at set-up and/or may move considerably following retraction of soft/bony tissues during surgery. Thus, the pelvis may not be in neutral position relative to the table at the time of cup-impaction. In such a condition, intra-operative cup orientation would be different from operative cup orientation as per Murray.

Most, recommendations on cup orientation in hip arthroplasty made to date have described the target radiographic orientation and do not provide surgeons with recommendations as to how to achieve this intra-operatively[61,158,160]. Hill *et al*[207], photographed the cup introducer following impaction and compared the cup inclination measured from the photograph with the radiographic inclination. The authors noted a mean difference of 13° in inclination and recommended considerably less operative inclination to achieve the radiographic inclination target.

Amongst studies of radiographic cup orientation, similar to the findings of Chapter 5, a wide scatter of orientation is reported even in the hands of

experienced hip surgeons, suggesting failure to achieve a specific orientation target in a high proportion of cases[129,158,160,185]. Factors such as patient's body habitus, patient/pelvic position on the operating table, pelvic movement during surgery and different reference systems used by surgeons may contribute to the difficulty in reliably achieving optimal cup orientation. A recent study identified minimally invasive surgery, low-volume surgeons and obese patients as factors increasing the risk of radiographic cup mal-orientation[185]. However, it remains unknown if radiographic cup mal-orientation is a consequence of intra-operative cup mal-orientation in a well-aligned pelvis or of surgeons orientating the cup in a pre-set acceptable orientation without considering the exact orientation of the pelvis at impaction, or whether it is a combination of both.

The primary aim of this prospective, *in vivo* study was to measure cup orientation at the time of surgery (intra-operative orientation) and to determine how this relates to the cup orientation measured on the post-operative X-ray (radiographic orientation). On the basis of this relationship, recommendations can be developed as to how the surgeon should implant the component so as to achieve the target orientation on post-operative radiographs that he/she is aiming to achieve.

7.2 Null hypothesis

Ho: Cup orientation at surgery is an accurate predictor of the radiographic cup orientation.

7.3 Materials and methods

This study used the principles of stereo-photogrammetry (SPG) to measure the intra-operative orientation of the cup immediately after impaction.

7.3.1 Photogrammetry

Photogrammetry provides a method of obtaining quantitative data and can be defined as 'the science of measuring in photos'[51]. Stereophotogrammetry allows the spatial measurement of three-dimensional (3-D) objects from a stereo-pair of images and has been used in different fields, such as meteorology and geology[208-210]. Common points are identified on each image and if the location of each camera relative to the image plane is known, the 3-D coordinates, and hence location and orientation of the object of interest can be determined.

7.3.2 Study protocol

This study was given approcal by the local ethics committee (REC No: 10/H0505/45) (Appendix 10). An information leaflet was provided to each patient prior to the surgery, allowing them enough time in order to decide whether they wanted to participate. Informed consent for participation in the study was

obtained. Inclusion criteria were primary arthroplasty surgery for primary osteoarthritis and American Society of Anaesthesiologist (ASA) grades (I – II) (Appendix 11). This study was performed at two different sites and involves a collaboration between two centres (the Nuffield Orthopaedic Centre, Oxford, UK and the ANCA Medical Centre, Ghent, Belgium).

7.3.3 Photogrammetric technique development

A custom application, Fotop™, written in Matlab (R2011, The MathWorks, Natick, MA, USA) was developed by an engineer (HSG) to capture the data and perform the measurements. The object of interest in this study was the cup introducer. The 3-D orientation of the cup introducer after impaction was measured; as the impactor is rigidly attached to the cup during impaction, the cup orientation could therefore be deduced.

7.3.3.1 Software considerations and design

In order to obtain 3-D coordinates of any object in space using photogrammetry at least two images of the object of interest are required. Two factors important for the calculations are the relative position of the two cameras to each other and the internal parameters of camera, most importantly the focal length during image capture. As a number of different surgeons were included in this study, all

operating in different theatres, it was important to have a portable stereophotogrammetric method. A calibration object was used to determine the relative locations of the cameras and the internal camera parameters for each case. The calibration object consisted of 12 easily identifiable markers whose relative positions were known having been measured accurately using the Vicon system (section 7.3.3.2). Capturing a stereo-pair of images of the calibration object prior to commencement of the case allowed the software to determine the positions of the cameras relative to each other and the camera parameters. Once the cameras were calibrated, further stereo-pair images could then be used to measure 3-D data in the volume in view of both cameras as long as the cameras were not moved and the focus of the cameras not altered. For all the stereo-photogrammetric measurements the autofocus feature of the cameras was turned off to ensure focal length did not change.

In order to ensure that the stereo-pairs of images were correctly identified for each case, and that the calibration images were distinct from the measurement images, a custom software application, Fotop^{TM}, was developed (by HSG). The Fotop software incorporated a database, electronically controlled the simultaneous image capture from the two cameras, stored the images in the database and performed the stereophotogrammatic calibrations and measurements on the images. Prior to each case, the investigator (GG) entered the case (using anonymised codes to identify subjects), surgeon and operative details. The subsequent calibration and measurement stereo-pairs of images were then stored in the database, the Fotop software ensuring that images were correctly associated with the appropriate case.

After the measurements were taken, the Fotop software was then used to process the images. This consisted of digitisation, which provided the location of points of interest in each image, calibration calculations and 3-D reconstruction of data From the 3-D reconstruction of the impactor, the orientation of the acetabular cup was calculated by the Fotop software using the various reference systems described by Murray[165].

7.3.3.2 Calibration object

A calibration object (CO) was constructed by the Department of Engineering Science (University of Oxford) workshop with specific characteristics and dimensions. The CO had to be of specific dimensions that allowed positioning on top of a patient (CO leg height = 50 cm) on the operating theatre (CO frame width = 40 cm). In order to perform the spatial calibration, each leg had a specific number of phenolac balls at given distances from the base (Figure 7.1). Phenolac balls were used as they are both bright and retro-reflective, and hence can easily be detected both by photography and by the infra-red cameras at the Oxford Gait Laboratory.

Following manufacturing, the calibration object was measured using the Vicon Nexus Motion Analysis System (Vicon Motion Systems, Oxford, UK), a method previously demonstrated to have accuracy better than 1 mm[211] at the Oxford Gait

Laboratory. The co-ordinates obtained from the Vicon system were incorporated in the Fotop^{TM} software and were used for any calculations subsequently made.

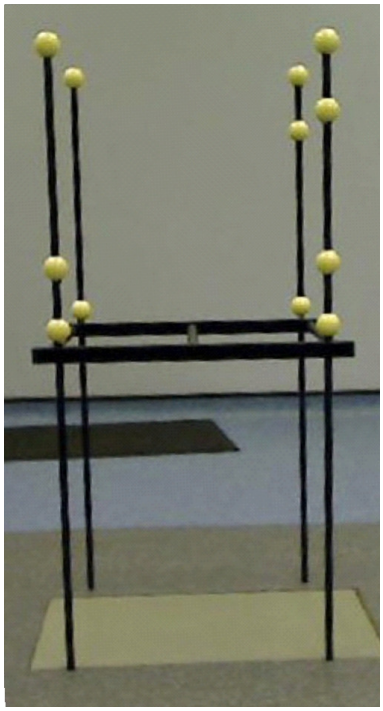


Figure 7.1: Schematic of the calibration object used for the manufacturing process and photograph of the object during maesurements performed at the Oxford Gait Laboratory.

7.3.3.3 Technique validation

The validity of the SPG technique described above was tested at the Oxford Gait Laboratory. The laboratory is equipped with a 12-camera Vicon Nexus Motion Analysis System, which captures video data at a rate of 100 Hz (Figure 7.2). Following static and dynamic laboratory calibration, the error of the motion analysis system (average error between constructed and actual marker positions) on the day of validity testing was 0.66 mm. Each of the 12 markers of the

calibration object was reconstructed in both the gait laboratory and in the photogrammetry co-ordinate frames. Transposition of the two co-ordinate frames demonstrated that the SPG method was accurate within 0.1 mm (range: ±2 mm). In addition, a wand with three retro-reflective markers was placed within the calibration volume simulating a possible orientation and location of a cup impactor. The location and orientation of the wand was captured by both the Vicon system and the SPG technique. Transposition of the two co-ordinates frames demonstrated that the SPG technique had a mean accuracy of 0.1 mm (range: ±2 mm) in terms of translation and 0.03° (range: ±1.6°) in terms of rotation. These provided validity that the SPG method accurately measured the 3-D co-ordinates of the objects of interest in this study.

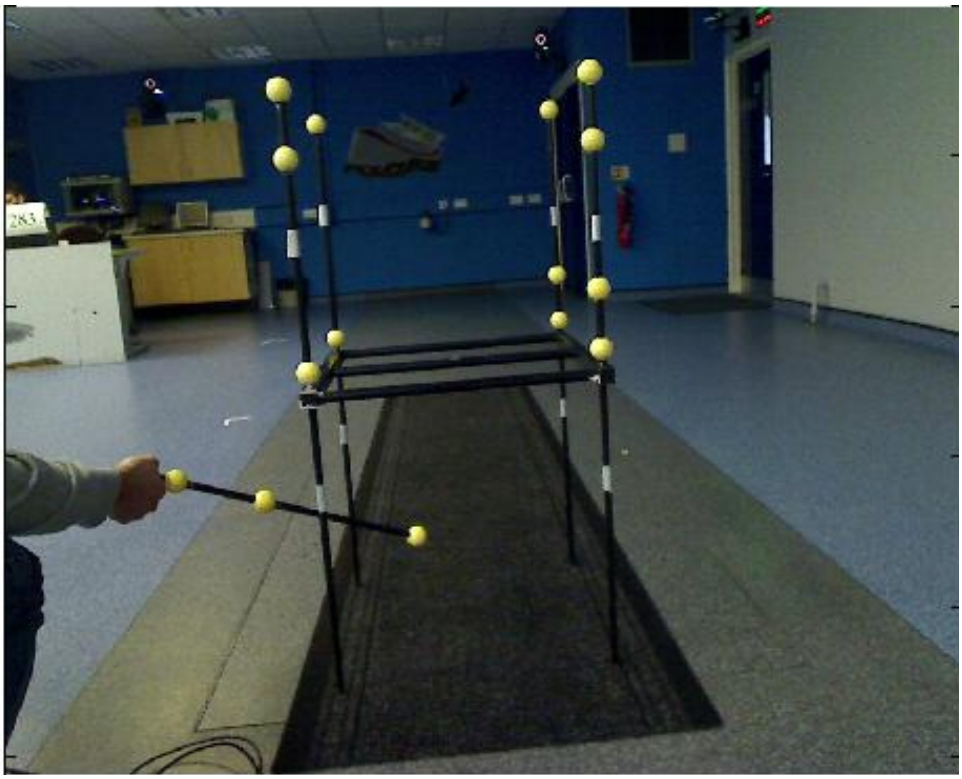


Figure 7.2: Photograph captured during technique validation demonstarting the calibration object and the testing wand in the Oxford Gait Laboratory.

7.3.4 Power of the study

Power of study was estimated using Altman's nomogram[189] as previously described (Chapter 6). The statistical significance was set at $p \leq 0.05$. Hill *et al* identified variation in radiographic inclination angle to have a standard deviation (SD) of 6.0°[207]. As previously mentioned in Section 7.1, the differences due to the different definitions are usually about 5°[165], this was therefore used as the difference of interest giving a standardised difference of 0.83. Using Altman's nomogram[189] for the power calculation, it was determined that a sample size of 50 patients was required for detecting a difference (85% power at 5% significance).

7.3.5 Patient demographics

Seventy-one patients were recruited. Patient demographics and anthropometric parameters (weight, height and BMI) were recorded prospectively. The majority of patients were female (n=46, 65%), mean age at surgery was 66 years (range: 41 to 87) and the mean BMI was 32.6 (range: 17.5 to 38.6) (Table 7.1).

The majority of patients (n=55, 77%) underwent THA, whilst the remaining 16 (23%) underwent MoMHRA. Thirty-eight (69%) of the THAs were done through a posterior approach[25] the remaining (n=17, 31%) were performed by the antero-

lateral approach as described by Hardinge[212]. All MoMHRAs were implanted through the posterior approach. Therefore, 54 (76%) of all cases were performed via the posterior approach. The procedures were performed by six different surgeons; four consultant hip surgeons and two senior fellows with an interest in hip arthroplasty. All patients were operated in the lateral decubitus position. Three surgeons (A, B and C) performed the majority of cases (n=67, 94%). Surgeon A is a senior clinical fellow, has completed his training and has performed 300 hip arthroplasties; he performs his arthroplasties via the posterior approach and his target cup inclination/anteversion is 40°/20°. Surgeon B is a specialist hip surgeon, who has performed over 7,000 hip arthroplasties, including over 3,500 MoMHRAs; his routine hip arthroplasty practice is via the posterior approach and his target cup inclination/anteversion is 45°/20°. Surgeon C is a specialist hip surgeon, having performed over 13,000 hip arthroplasties; he operates routinely via the lateral approach and his target zone cup inclination/anteversion is 40°/15°. Details of surgical practice, including prostheses used, pelvic supports and cup size implanted are included in Table 7.1.

The choise of pelvic support was made as per surgeon's preference reflecting their practice. All surgeons used the same support posteriorly over the sacrum. Surgeon B routinely uses a single support over the pubic symphysis, Surgeons A and C use a support over the operated anterior superior iliac spine (ASIS) and the Other Surgeons used a single ASIS support or a roll over both ASIS's. Surgeons A and C were invited to place an additional support over the contra-lateral ASIS in the

latter 12 cases enrolled in the study. Different types of pelvic supports used are illustrated in Figure 7.3.

		Cohort (n=71)	Arthroplasty		
			THA (n=55)	HRA (n=16)	p-value
Gender	Male (n)	25	16	9	0.04
	Female (n)	46	39	7	
Age/ years Mean (range)		66.4 (41.4 to 86.8)	69.2 (46.2 to 86.8)	56. 4 (41.4 to 69.1)	<0.001
Height/ m Mean (range)		1.7 (1.3 to 1.9)	1.7 (1.5 to 1.9)	1.8 (1.7 to 1.9)	0.004
Weight/ Kg Mean (range)		72.7 (47.1 to 123.6)	72.3 (47.1 to 123.6)	74.1 (50.0 to 97.0)	0.47
BMI/ Kg/m^2 Mean (range)		32.6 (17.5 to 38.6)	26.1 (17.3 to 38.6)	23.5 (17.9 to 28.0)	0.10
Cup size/ mm Mean (range)		53.5 (46 to 60)	52.6 (46 to 60)	56.5 (52 to 60)	<0.001
Supports	Pubis (n)	31	16	15	<0.001
	Cylinder (n)	3	2	1	
	ASIS x 1 (n)	25	25	-	
	ASIS x 2 (n)	12	12	-	
Approach	Lateral (n)	17	17	-	0.01
	Posterior (n)	54	38	16	

Table 7.1: Cohort demographics and surgical details.

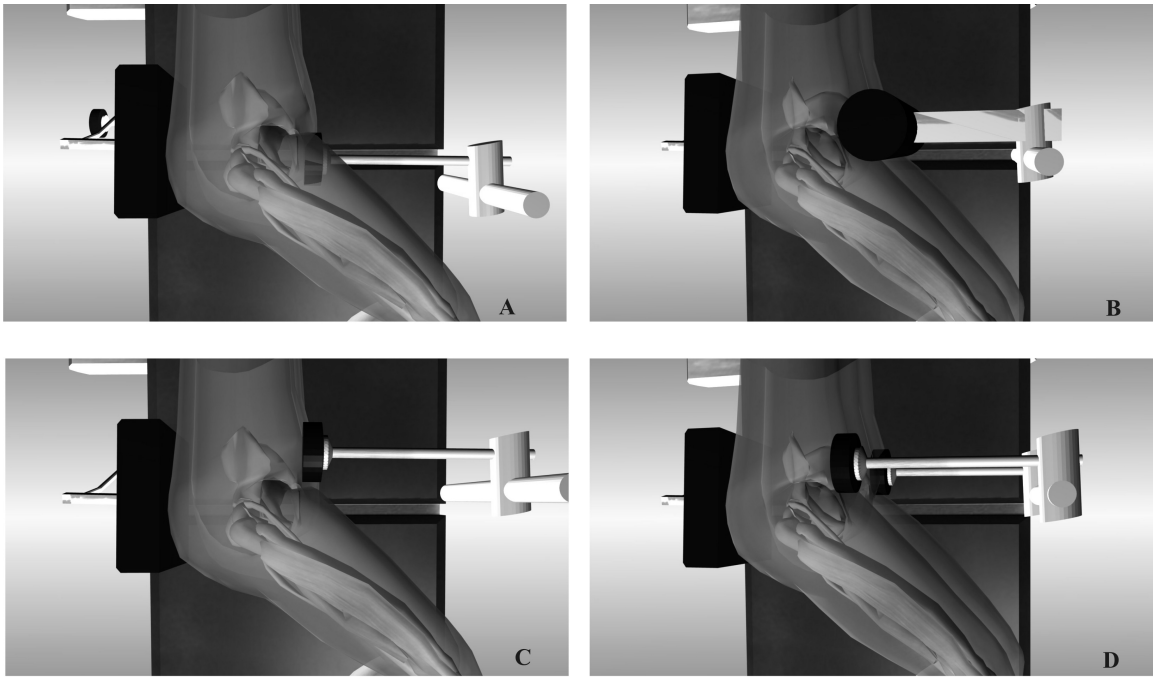


Figure 7.3: Different types of supports used in this study. Support A: Support placed over the pubic symphysis (Surgeon A). Support B: Support cylinder placed over the pelvis at the level of the ASIS's (Other surgeons). Support C: Support placed over the operated ASIS (Surgeons A, C, Other). Support D: Support placed over both ASIS's (Surgeons A, C).

7.3.6 Intra-operative orientation measurements – Photogrammetric technique used

Two cameras (Webcam Pro 9000 HD, Logitech, Morges, Switzerland) were mounted on the theatre's laminar air flow hoods orientated at approximately 90° to each other and arranged so that the operating field was fully captured. The surgeon positioned the patient on the operating table as per routine practice. The table was set in the middle of the theatre space as defined by the laminar flow hood. The calibration object was aligned to the theatre space, i.e. parallel to the

walls and the floor, and placed over the patient, then a stereopair of images was captured (Figure 7.4). The calibration object was removed, surgery was carried out as normal and a second stereo-pair of images was captured immediately after cup implantation with the introducer still attached and retractors in place in order to measure the 3-D location of the cup introducer and therefore of the cup (Figure 7.5). All surgeons used the supplied orientation guides for each impactor used. Knowledge of the 3-D location of the cup introducer relative to theatre table allowed for calculation of the intra-operative cup inclination (IOI)/ intra-operative cup anteversion (IOA) and simulated radiographic cup inclination (SRI)/ simulated radiographic cup anteversion (SRA). The simulated radiographic inclination and anteversion angles are the angles that would have been measured from a pelvic radiograph had it been taken during the operation, with the film placed perpendicular to the reference plane of the theatre table (Figure 7.4). These angles were calculated based on the definitions of operative inclination/anteversion and radiographic inclination/anteversion according to Murray referencing off the plane perpendicular to the theatre table instead of the pelvis[165].

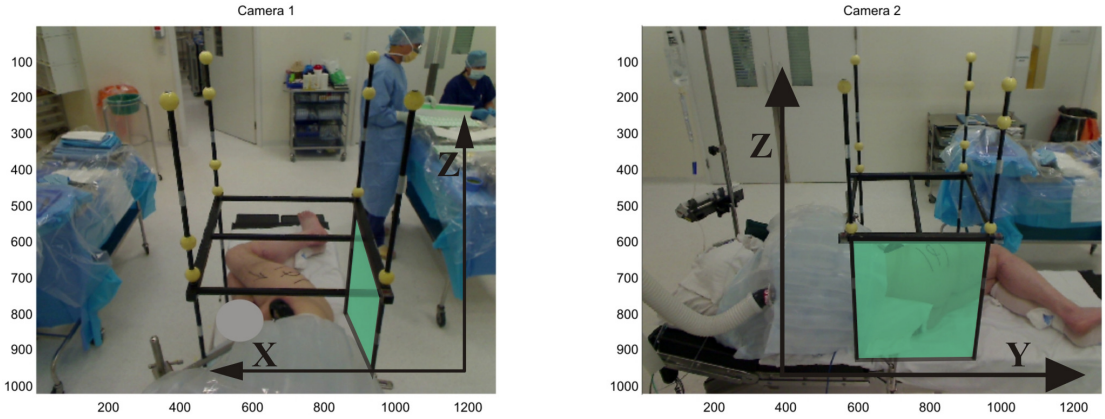


Figure 7.4: Stereo-pair images of calibration object on the operating table capturing the calibration volume prior to patient prepping. Shaded green area represents simulated radiographic cassette at right angles to the operating table. Note that it does not appear to be a rectangle on the image due to angular projections of the cameras.

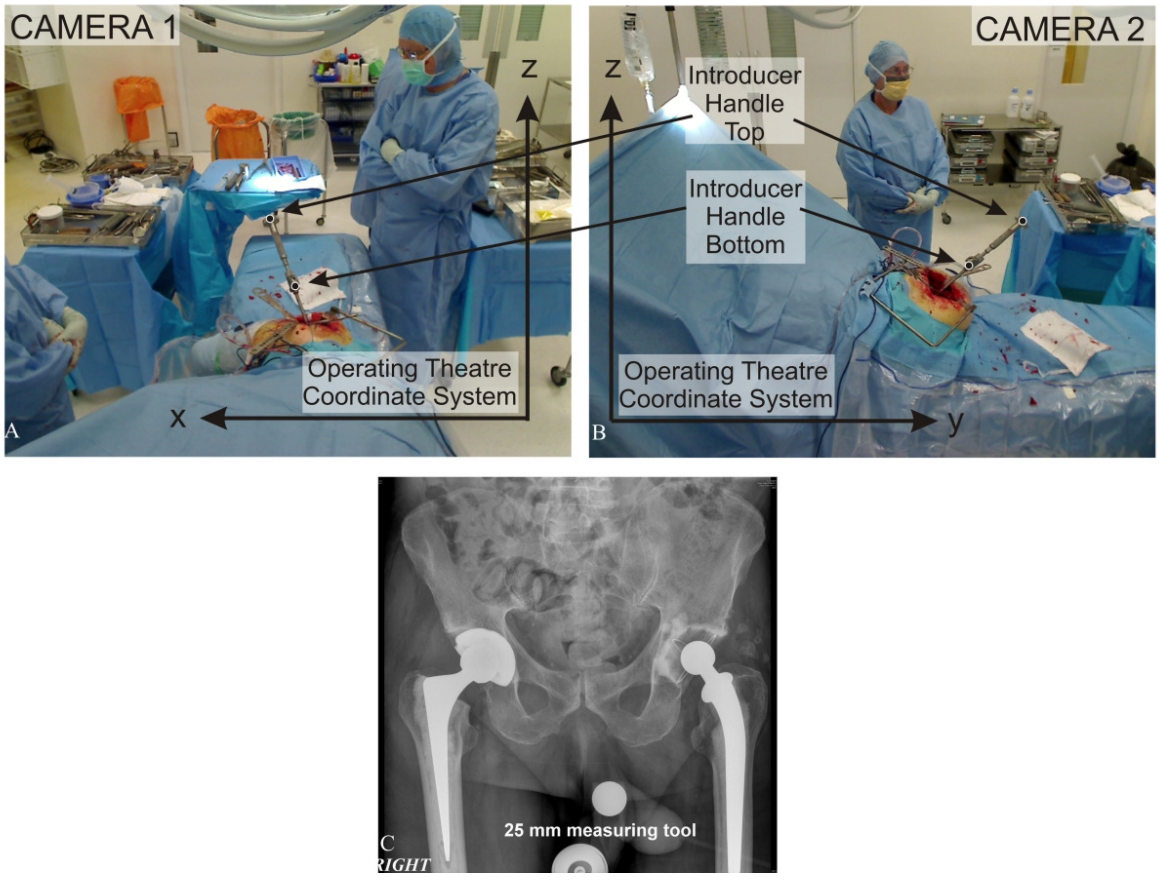


Figure 7.5: Figure illustrating intra-operative measurements made during a THA case operated via a lateral approach. Figure A is of camera 1 demonstrating theatre co-ordinates (x, z) and introducer points of interest. Figure B is of camera 2 demonstrating theatre co-ordinates (y, z) and introducer's points of interest. Figure C is the post-operative radiograph of the patient. Corresponding values of the case were: IOI: 36.4°, IOA: 22.4°, SRI: 38.5°, SRA: 17.9°, RI 38.9°, RA: 18.3°.

7.3.7 Radiographic orientation measurements

Radiographic cup orientation measurements were made from standardised post-operative, supine antero-posterior (AP) pelvic and lateral hip radiographs, which were performed as routine hospital practice. The Ein-Bild-Roentgen-Analysis (EBRA) software was used to calculate radiographic cup inclination (RI) and anteversion (RA) from AP radiographs, according to the definitions of Murray[165]. Lateral hip radiographs allowed determination of anteversion or retroversion of the acetabular component. Measurements were performed independently by two observers (GG, HP) blinded to other parameters with excellent intra- and inter-observer correlation (interclass correlation coefficients > 0.95, $p < 0.001$).

7.3.8 Data analysis

7.3.8.1 Orientation scatter

The scatter in both the intra-operative and radiographic component orientations were determined for the whole cohort. The variability in orientations was determined by the SD of the analysis and was defined as two SDs. The influence of different patient (gender, age, anthropometric factors, cup size) and surgery

related (surgeon, arthroplasty type, surgical approach, pelvic supports) factors on the variability were tested.

7.3.8.2 Differences

The differences between the post-operative radiographic cup inclination/ anteversion (RI/RA) and intra-operative cup inclination/anteversion (IOI/IOA) were defined as Δ*inclination* and Δ*anteversion* and were calculated as:

Δ*inclination* = RI – IOI,

Δ*anteversion* = RA – IOA

In order to determine if the difference between the intra-operative orientation and the post-operative radiographic orientation was a manifestation of different definitions or of pelvic movement the simulated radiographic orientation was calculated and utilised.

Difference due to definition

The differences between the intra-operative and the simulated radiographic orientation (the term ΔT was used to signify operating *T*able based coordinate systems) are a manifestation of the different definitions used and were calculated as:

$\Delta T_{inclination}$ = SRI – IOI,

$\Delta T_{anteversion}$ = SRA – IOA

Difference due to pelvic position – relative to reference plane

The difference between the simulated radiographic orientation and the post-operative radiographic orientation (ΔR used to signify *R*adiographic based coordinate systems) is a manifestation of the different position of the pelvis at the time of implantation and during the Xray and were calculated as:

$\Delta R_{inclination}$ = RI – SRI,

$\Delta R_{anteversion}$ = RA – SRA

The influence of different patient (gender, age, anthropometric factors, cup size) and surgery related (surgeon, arthroplasty type, surgical approach, pelvic supports) factors on the differences detected were tested.

7.3.9 Statistics

The strength of the linear association between the simulated-radiographic and EBRA radiographic angles (both referencing off the same planes) was established using the correlation coefficient.

Non-parametric statistical tests (Mann-Whitney *U*, Kruskal Wallis, Spearman's rho) were used. Chi-square test was used for cross-tabulated data. Statistical significance was defined as $p \leq 0.05$. Statistical analyses were performed with IBM SPSS Statistics version 19.

7.4 Results

7.4.1 Overview

At surgery, the mean IOI was 37.9° (SD: 5.5°, range: 28.1° to 49.5°) and mean IOA was 26.7° (SD: 7.9°, range: 7.8° to 44.4°). Calculating the simulated radiographic orientation from the intra-operative measurements, the mean SRI was 41.5° (SD: 5.6°, range: 30.9 to 52.6) and the mean SRA was 20.7° (SD: 6.4°, range: 6.4 to 35.4). At X-ray evaluation, the mean RI was 42.9° (SD: 6.2°, range: 27.6° to 56.2°) and the mean RA was 18.7° (SD: 7.4°, range: 3.9° to 35.1°) (Table 7.2).

Δ*inclination* was 5.0° (SD: 4.8° range: -9.8° to +15.2°) and Δ*anteversion* was -8.1° (SD: 8.1° range: -26.4° to +17.5°) ($p<0.001$). Most of the difference in the mean orientations was due to definition differences. Δ*Tinclination* was 3.5° (SD: 1.9°, range: 0.3° to 9.4°) and Δ*Tanteversion* was -6.1° (SD: 2.3°, range: -11.4° to -1.4°). However, the great variability (2SD) in the differences was mainly due to the differences in pelvic position; Δ*Rinclination* was 1.3° (SD: 5.0°, range: -13.1° to +10.5°) Δ*Ranteversion* was -2.1° (SD: 7.3°, range: -18.8 to +22.6°).

Correlations between orientations are demonstrated in Figure 7.6. SRI correlated moderately with EBRA-measured inclination (rho=0.67, $p<0.001$); whilst the correlation was weak for anteversion (rho=0.44, $p<0.001$). There was a highly significant correlation between SRI and OI (rho=0.93, $p<0.001$) and between SRA and OA (rho=0.96, $p<0.001$).

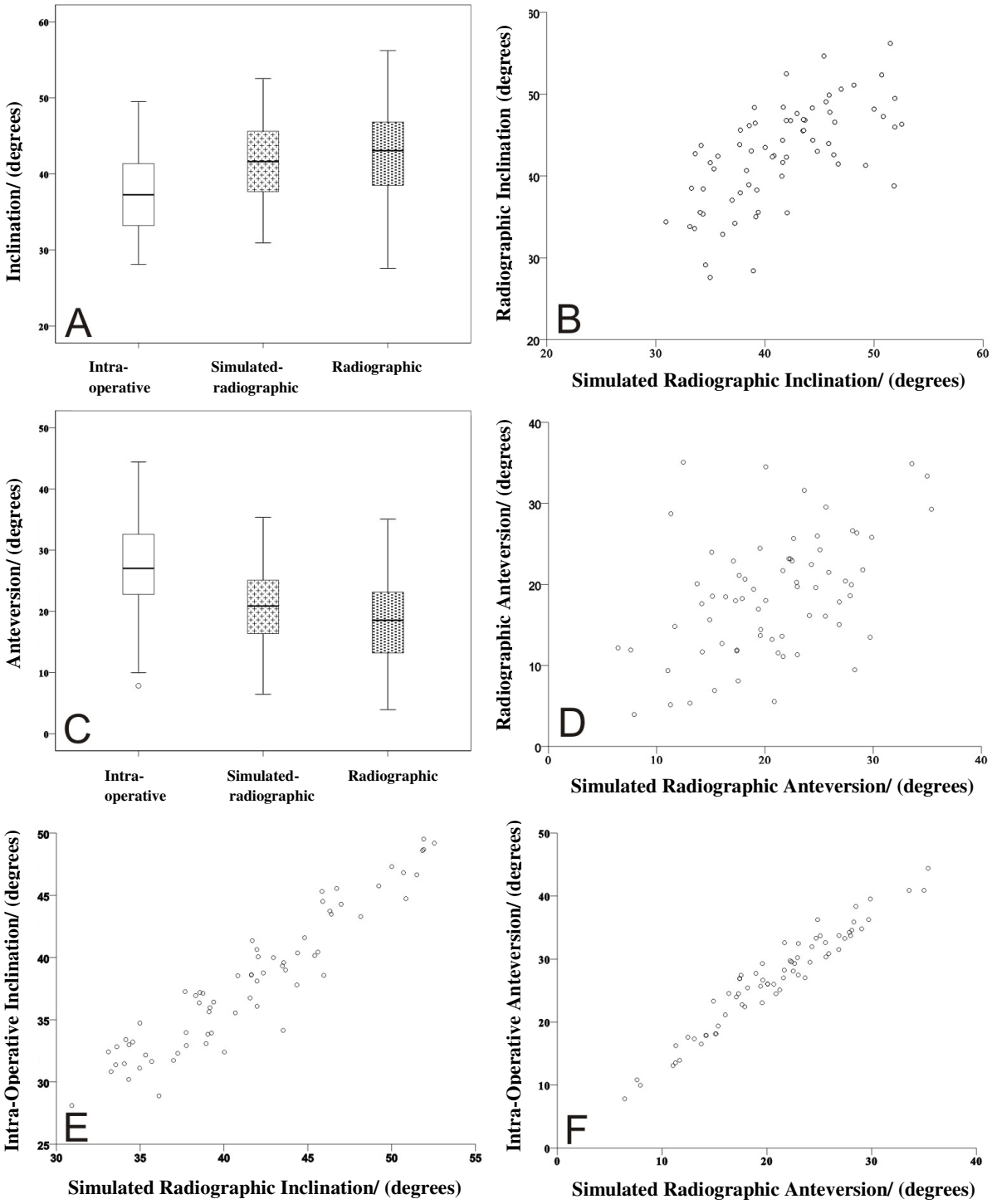


Figure 7.6: Overview of the orientations determined. A: Cup Inclination measurements obtained for the different types of inclination defined. B: Scatter plot of RI and SRI, demonstrating moderate correlation of the two. C: Cup anteversion measurements for the types of anteversion defined. D: Scatter plot of RA and SRA, demonstrating moderate correlation of the two. E: Scatter plot of IOI and SRI demonstrated highly significant correlation of the two. F: Scatter plot of IOA and SRA demonstrating highly significant correlation of the two.

	Cohort (n=71) mean/SD range
IOI/ °	37.9°/ 5.5° 28.1° to 49.5°
IOA/ °	26.9°/ 7.8° 7.8° to 44.4°
SRI/ °	41.5°/5.6° 30.9° to 52.6°
SRA/ °	20.7°/ 6.4° 6.4° to 35.4°
RI/ °	42.9°/ 6.2° 27.6° to 56.2°
RA/ °	18.7°/ 7.4° 3.9° to 35.1°
Δ*inclination*/°	5.0°/ 5.3° -9.8° to 15.2°
Δ*anteversion*/°	-8.2°/ 8.1° -26.4° to 17.5°
ΔT*inclination*/°	3.5°/ 1.9° 0.3° to 9.4°
ΔT*anteversion*/°	-6.1°/ 2.4° -1.4° to -11.4°
ΔR*inclination*/°	1.3°/ 5.0° -13.1° to 10.5°
ΔR*anteversion*/°	-2.0°/ 7.3° -18.8° to 22.6°

Table 7.2: Intra-operative, simulated radiographic, radiographic component orientations, Δ*inclination*/Δ*anteversion*, ΔT*inclination*/ΔT*anteversion*, ΔR*inclination*/ΔR*anteversion* for the whole cohort and as per surgeon.

7.4.2 Scatter of cup orientations

There was a wide scatter of cup orientations as evident from Table 7.2, and Figures 7.7 and 7.8. The variability (=2SD) of IOI was 11° and the variability of

IOA was 16°. The variability was 12° for RI and 15° for RA for the whole cohort.

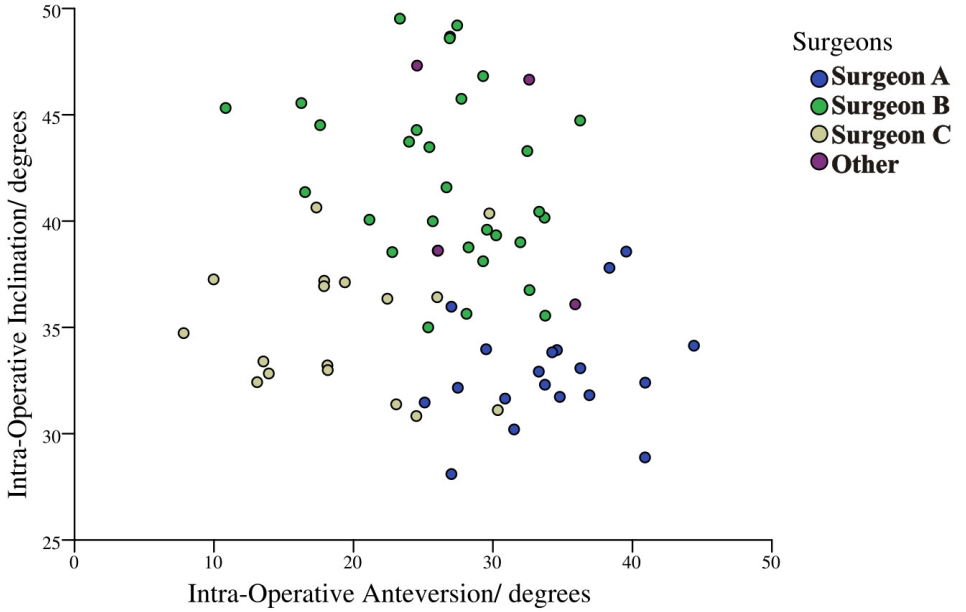


Figure 7.7: Scatter of intra-operative cup orientations for the whole cohort, colour coded per surgeon.

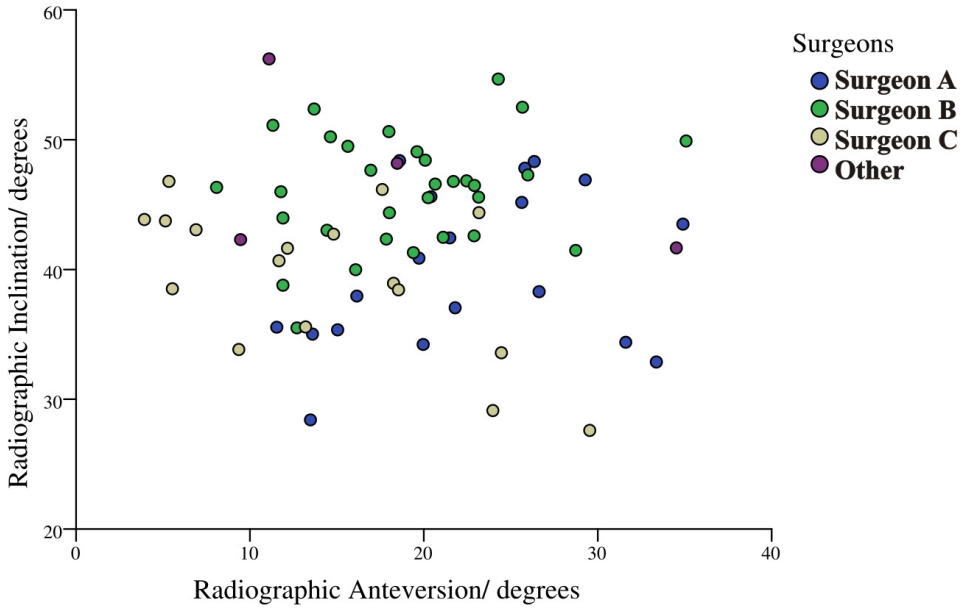


Figure 7.8: Scatter of radiographic cup orientations for the whole cohort, colour coded per surgeon.

Amongst the different patient-related factors tested (age, gender, height, weight, BMI and component size) as possibly having an effect on IOI, IOA, RI or RA

(Table 7.3 and Table 7.4), age had weak negative correlation with IOI and positive correlation with RA. No other factor tested had an effect on orientation measurements.

Factor	**Age/** Years	**Height/** m	**Weight/** Kg	**BMI/** Kg/m^2	**Cup Size/** mm
IOI/ °	rho=-0.38 p= 0.01	rho=0.23 p=0.1	rho=0.0 p=0.9	rho=-0.2 p=0.3	rho=0.14 p=0.3
IOA/ °	rho=-0.1 p= 0.7	rho=-0.0 p=0.8	rho=0.1 p=0.6	rho=0.1 p= 0.3	rho=0.14 p=0.26
RI/ °	rho=-0.2 p=0.1	rho=0.2 p=0.15	rho=0.1 p=0.6	rho=0.0 p=0.9	rho=0.0 p=0.7
RA/ °	rho=0.37 p=0.01	rho=0.0 p=1.0	rho=-0.1 p=0.7	rho=-0.1 p=0.5	rho=0.2 p=0.14

Table 7.3: The correlation of different patient factors with IOI, IOA, RI and RA.

		IOI/ ° Mean/ SD Range	p-value	IOA/ ° Mean/SD Range	p-value	RI/ ° Mean/SD Range	p-value	RA/ ° Mean/SD Range	p-value
Cohort		37.9°/ 5.5° 28.1° to 49.5°	-	26.9°/ 7.8° 7.8° to 44.4°	-	42.9°/6.2° 27.6° to 56.2°	-	18.7°/7.4° 3.9° to 35.1°	-
Gender	Male (n=25)	38.6°/5.8° 28.9° to 49.5°	0.47	27.2°/7.6° 7.8° to 40.9°	0.92	44.3°/ 5.8° 32.9° to 54.7°	0.17	18.4°/7.6° 5.5° to 34.9°	0.46
	Female (n=46)	37.5°/5.3° 28.1° to 48.6°		26.8°/8.1° 10.0° to 44.4°		42.1°/6.3° 27.6° to 56.2°		18.9°/7.4° 3.9° to 35.1°	
Appr.	Lateral (n=17)	35.0°/3.1° 30.8 to 40.6	0.02	19.0°/ 6.4° 7.8° to 30.4°	<0.001	39.3°/ 5.7° 27.6° to 46.8°	0.008	14.3°/7.9° 3.9° to 29.5°	0.01
	Posterior (n=54)	38.8°/5.8° 28.1° to 49.5°		29.4°/6.5° 10.8° to 44.4°		44.0°/5.9° 28.4° to 56.2°		20.1°/ 6.8° 8.1° to 35.1°	
Supp.	Pubis (n=31)	42.0/ 4.2 35.0 to 49.5	<0.001	26.6/ 5.7 10.8 to 36.3	0.44	46.1/ 4.3 35.5 to 54.7	<0.001	18.9/ 5.8 8.1 to 35.1	0.05
	Cylinder (n=3)	43.3/ 6.3 36.1 to 47.3		31.0/ 5.8 24.6 to 35.9		48.9/ 7.0 42.3 to 56.2		13.0/ 4.8 9.5 to 18.5	
	ASISx1 (n=25)	33.7/3.0 28.1 to 40.4		28.0/ 9.5 13.1 to 44.4		39.0/ 5.9 27.6 to 48.3		21.2/ 8.5 5.1 to 34.9	
	ASISx2 (n=12)	34.7/ 3.1 30.8 to 40.6		24.6/ 9.3 7.8 to 39.6		41.1/ 5.3 33.6 to 48.4		14.5/ 7.4 3.9 to 25.8	

Table 7.4: The effect of gender and of different surgical factors on IOI, IOA, RI and RA. Appr. = Approach used for arthroplasty, Supp.= Supports used.

Surgical factors influencing the scatter were identified, namely surgeon and procedure performed. As evident in Table 7.5, surgeons implanted the components with different IOI and IOA and hence had a resultant different RI and RA (Figures 7.9 and 7.10). The intra-surgeon variability was less and it was evident that the three surgeons had different intra-operative practice; surgeon A

provided small IOI and great IOA, surgeon B provided greater IOI and similar IOA compared to surgeon A, whilst surgeon C, provided less inclination and anteversion in comparison to the others.

	Surgeons			
	Surgeon A (n=19) mean/SD range	Surgeon B (n=31) mean/SD range	Surgeon C (n=17) mean/SD range	p-value
IOI/ °	32.9° / 2.6° 28.1° to 38.6°	42.0°/ 4.2° 35.0° to 49.5°	35.0°/ 3.0° 30.8° to 40.6°	<0.001
IOA/ °	34.0°/ 5.4° 25.1° to 44.4°	26.6°/ 5.7° 10.8° to 36.3°	19.0°/ 6.4° 7.8° to 30.4°	<0.001
SRI/ °	38.1°/ 3.8° 30.9° to 46.0°	45.6°/ 3.9° 39.1° to 52.6°	36.7°/ 3.3° 33.1° to 44.4°	<0.001
SRA/ °	27.7°/ 4.2° 21.2° to 35.4°	19.4°/ 4.6° 7.6° to 26.9°	15.4°/ 5.2° 6.4° to 25.6°	<0.001
RI/ °	39.9°/ 6.0° 28.4° to 48.4°	46.1°/ 4.3° 35.5° to 54.7°	39.3°/ 5.7° 29.1° to 46.8°	<0.001
RA/ °	22.4°/ 6.9° 11.5° to 34.9°	18.9°/ 5.8° 8.1° to 35.1°	14.3°/ 7.9° 3.9° to 29.5°	0.009
Δ*inclination*/°	7.0°/ 5.2° -4.7° to 14.6°	4.1°/ 6.0° -9.8° to 15.2°	4.3°/ 4.3° -4.1° to 14.4°	0.21
Δ*anteversion*/°	-11.6°/ 5.5° -22.8° to 4.6°	-7.6°/ 8.3° -21.2° to 17.5°	-4.7°/ 6.7° -19.0° to 5.8°	0.005
ΔT*inclination*/°	5.2°/ 1.9° 2.6° to 9.4°	3.3°/ 1.4° 0.3° to 6.1°	1.7°/ 1.1° 0.3° to 4.1°	<0.001
ΔT*anteversion*/°	-6.2°/ 1.8° -9.9 to -3.4°	-7.2°/ 2.0° -11.4 to -2.8°	-3.6°/ 1.5° -7.5 to -1.4°	<0.001
ΔR*inclination*/°	1.5°/ 4.8° -9.3° to 10.5°	0.4°/ 5.4° -13.1° to 10.5°	2.6°/ 4.9° -7.4° to 9.6°	0.37
ΔR*anteversion*/°	-5.5°/ 5.4° -16.2° to 8.0°	-0.3/ 7.2 -11.7 to 22.6	-1.1°/ 6.4° -15.3° to 8.9°	0.02

Table 7.5: Intra-operative, simulated radiographic, radiographic component orientations, Δ*inclination*/Δ*anteversion,* ΔT*inclination*/ΔT*anteversion,* ΔR*inclination*/ΔR*anteversion* per surgeon.

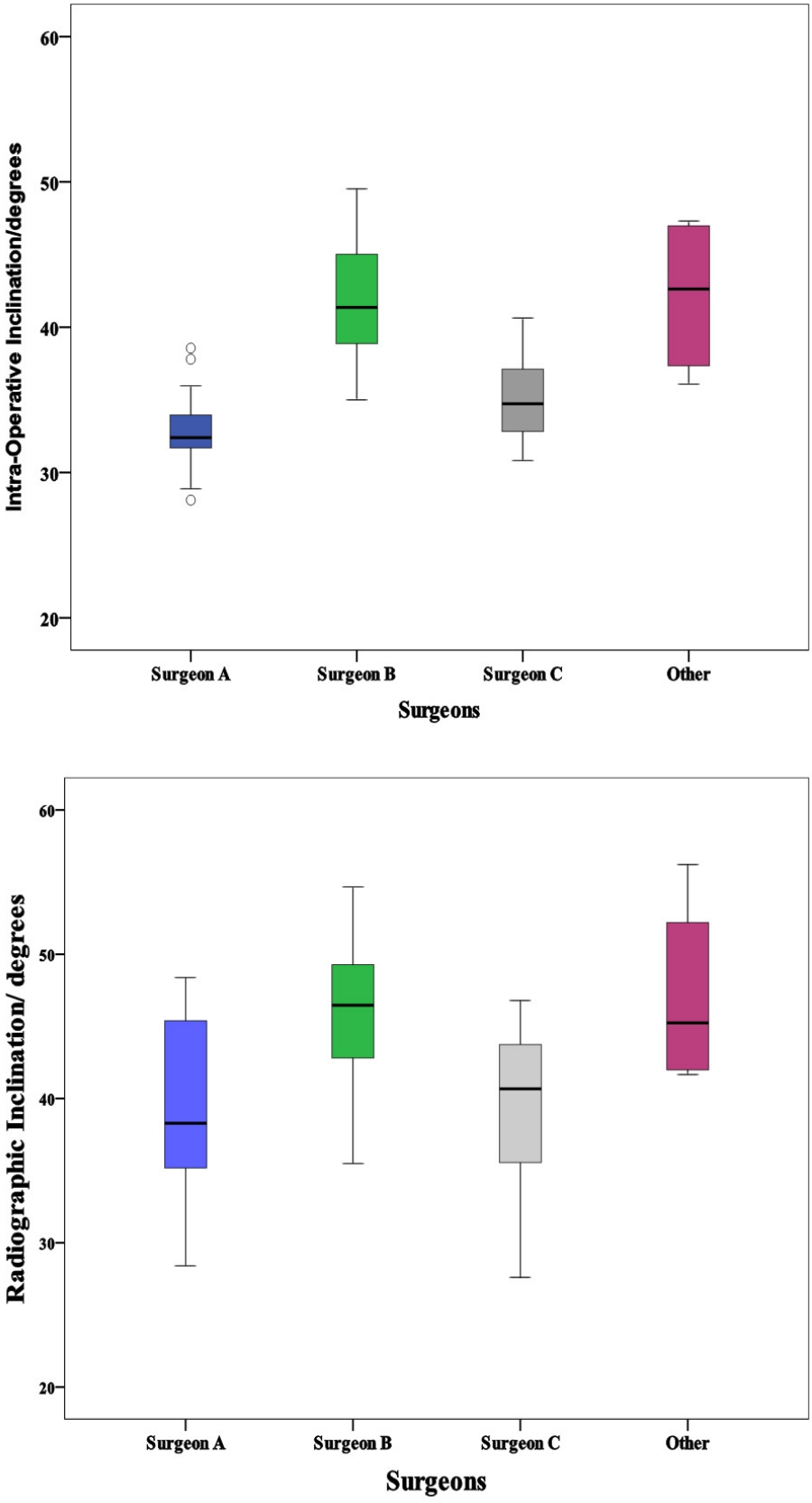


Figure 7.9: Box-plot of intra-operative and radiographic cup inclination colour-coded for the different surgeons.

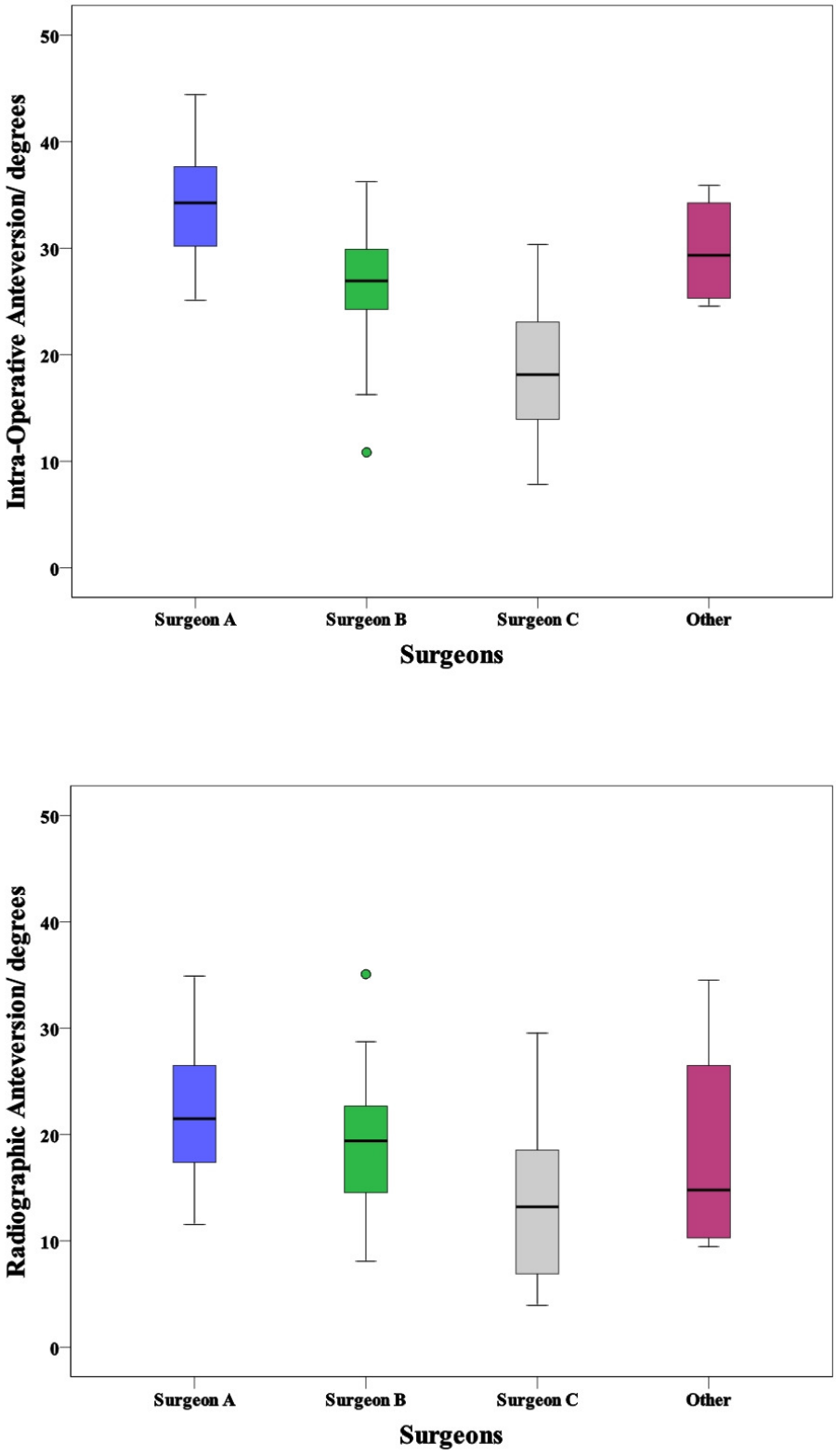


Figure 7.10: Box-plot of intra-operative and radiographic cup anteversion colour-coded for the different surgeons.

The inter-surgeon difference in intra-operative practice resulted in different achievements of orientating the cup within the various target radiographic orientations (Table 7.6).

	Cohort (%)	**Surgeons**			
		Surgeon A (%)	Surgeon B (%)	Surgeon C (%)	p-value
% with RI: 35° – 55°	87	79	100	77	0.04
% with RA: 10° – 30°	82	84	94	65	0.04
% within RI/RA 45° /20° ± 10°	73	74	94	47	0.001
% with RI: 30° – 50°	71	58	87	88	0.03
% with RA: 5° – 25°	71	95	81	82	0.5
% within RI/RA: 40° /15° ± 10°	71	53	71	81	0.1

Table 7.6: Percentages of achieving a specific radiographic orientation target for the whole cohort and as per surgeon.

Comparing the two procedures for Surgeon B (the only surgeon who performed both THA and MoMHRA), the values and scatter of IOI, IOA and RI were similar, however the values and scatter for RA were smaller in the MoMHRA in comparison to THA cases (Table 7.9).

7.4.3 Differences

No patient factors were identified to have a significant effect on the differences between the orientations as evident in Tables 7.7 and 7.8.

Factor	**Age/** Years	**Height/** m	**Weight/** Kg	**BMI/** Kg/m^2	**Cup Size/** mm
Δ*inclination*/°	rho=0.15 p=0.26	rho=-0.05 p=0.68	rho=0.94 p=0.47	rho=0.20 p=0.13	rho=-0.12 p=0.32
Δ*anteversion*/°	rho=0.29 p=0.21	rho= 0.02 p=0.89	rho=-0.08 p 0.55	rho=-0.14 p=0.29	rho=-0.04 p=0.74
ΔT*inclination*/°	rho=0.08 p=0.52	rho=0.0 p=0.9	rho=-0.1 p=0.5	rho=-0.13 p=0.3	rho=0.12 p=0.32
ΔT*anteversion*/°	rho=-0.34 p=0.005	rho=0.2 p=0.2	rho=0.1 p=0.60	rho=0.0 p=1.0	rho=0.0 p=0.8
ΔR*inclination*/°	rho=-0.16 p=0.19	rho=0.1 p=0.68	rho=-0.1 p=0.60	rho=-0.1 p=0.28	rho=0.1 p=0.7
ΔR*anteversion*/°	rho=-0.28 p=0.02	rho=-0.1 p=0.47	rho=0.1 p=0.71	rho=0.15 p=0.26	rho=0.0 p=0.8

Table 7.7: Patient factors and their correlation (Spearman's rho) with Δ*inclination*, Δ*anteversion*, ΔT*inclination*, ΔT*anteversion*, ΔR*inclination*, ΔR*anteversion*.

		Δ*inclin* Mean/SD Range	**p-value**	**Δ*antev* Mean/SD Range**	**p-value**	**ΔT*inclin* Mean/SD Range**	**p-value**	**ΔT*antev* Mean/SD Range**	**p-value**	**ΔR*inclin* Mean/SD Range**	**p-value**	**ΔR*antev* Mean/SD Range**	**p-value**
Gender	Male (n=25)	5.7°/4.3° -2.9° to 14.5°	0.33	-8.8°/ 7.7° -21.2° to 8.5°	0.66	3.5°/ 1.9° 0.3 to 7.6°	1.0	-6.4°/ 2.5° -1.4° to -9.9°	0.43	2.2°/ 4.2° -6.2° to 9.3°	0.25	-2.3°/ 6.6° -15.3°to 14.4°	0.82
	Female (n=46)	4.6°/5.9° -9.8° to 15.2°		-7.9°/ 8.4° -26.4° to 17.5°		3.4°/ 2.0° 0.4° to 9.4°		-5.9°/ 2.3° -2.1° to -11.4°		0.7°/ 5.4° -13.1° to 10.5°		-1.8°/ 7.7° -18.8°to 22.6°	
Approach	Lateral (n=17)	4.3°/4.3° -4.1° to 10.3°	0.53	-4.7°/6.7° -19.0° to 5.8°	0.01	1.7°/ 1.1° 0.3° to 4.0	<0.001	-3.6°/ 1.5° -1.4° to -7.5°	<0.001	2.6°/ 4.9° -7.4° to 9.6°	0.18	-1.1°/ 6.4° -15.3° to 8.9°	0.26
	Posterior (n=54)	5.2°/ 5.7° -9.8° to 15.2°		-9.3°/ 8.2° -26.4° to 17.5°		4.0°/ 1.8° 0.3° to 9.4°		-6.9°/ 2.0° -2.8° to -11.4°		0.8°/ 5.0° -13.1° to 10.5°		-2.4°/ 7.6° -18.8°to 22.6°	
Supports	Pubis (n=31)	4.1°/ 6.0° -9.8° to 15.2°	0.66	-7.7°/ 8.3° -21.2 to 17.5	0.22	3.3°/ 1.4° 0.3° to 6.1°	0.50	-7.2°/ 2.0° -2.8° to -11.4°	<0.001	0.4°/ 5.4° -13.1° to 10.5°	0.36	-0.3°/ 7.2° -11.7°to 22.6°	0.10
	Cylinder (n=3)	5.5°/4.4° 0.9° to 9.6		-18.0°/ 10.6° -26.4 to -6.1		4.4°/ 1.6° 2.7° to 5.9°		-8.9°/ 1.8° -7.6° to -10.9°		1.1°/ 3.3° -1.8° to 4.7°		-9.1°/ 10.5° -18.8°to 2.1°	
	ASIS x 1 (n=25)	5.3°/ 4.9° -4.7° to 13.4°		-6.9°/ 7.5° -22.8° to 8.5°		3.7°/ 2.4° 0.7° to 9.4°		-5.1°/ 2.1° -2.1° to -9.9°		1.2°/ 4.9° -10.5°to 9.6°		-1.6°/ 6.9° -16.2°to 14.4°	
	ASIS x 2 (n=12)	6.4/° 4.8° -0.9° to 14.5°		-10.1°/ 6.9° -19.0° to 4.3°		3.0°/ 2.0° 0.3° to 7.4°		-4.7°/ 2.2° -1.4° to -9.7°		3.4°/ 4.4° -4.2° to 9.3°		-5.4°/ 6.0° -15.3°to 5.7°	

Table 7.8: The effect of gender and of different surgical factors on Δ*inclination*, Δ*anteversion*, ΔT*inclination*, ΔT*anteversion*, ΔR*inclination*, ΔR*anteversion*.

On the contrary, surgical factors were identified to influence the differences between intra-operative and radiographic angles. Factors that were identified to lead to differences included: surgeon, procedure and approach.

The three surgeons had significantly different Δ*anteversion* but not Δ*inclination* (Table 7.5). This difference was due to both the definition differences (ΔT*anteversion:* p<0.001) and due to pelvic orientation difference between impaction and X-ray (ΔR*anteversion:* p=0.02) (Figure 7.11).

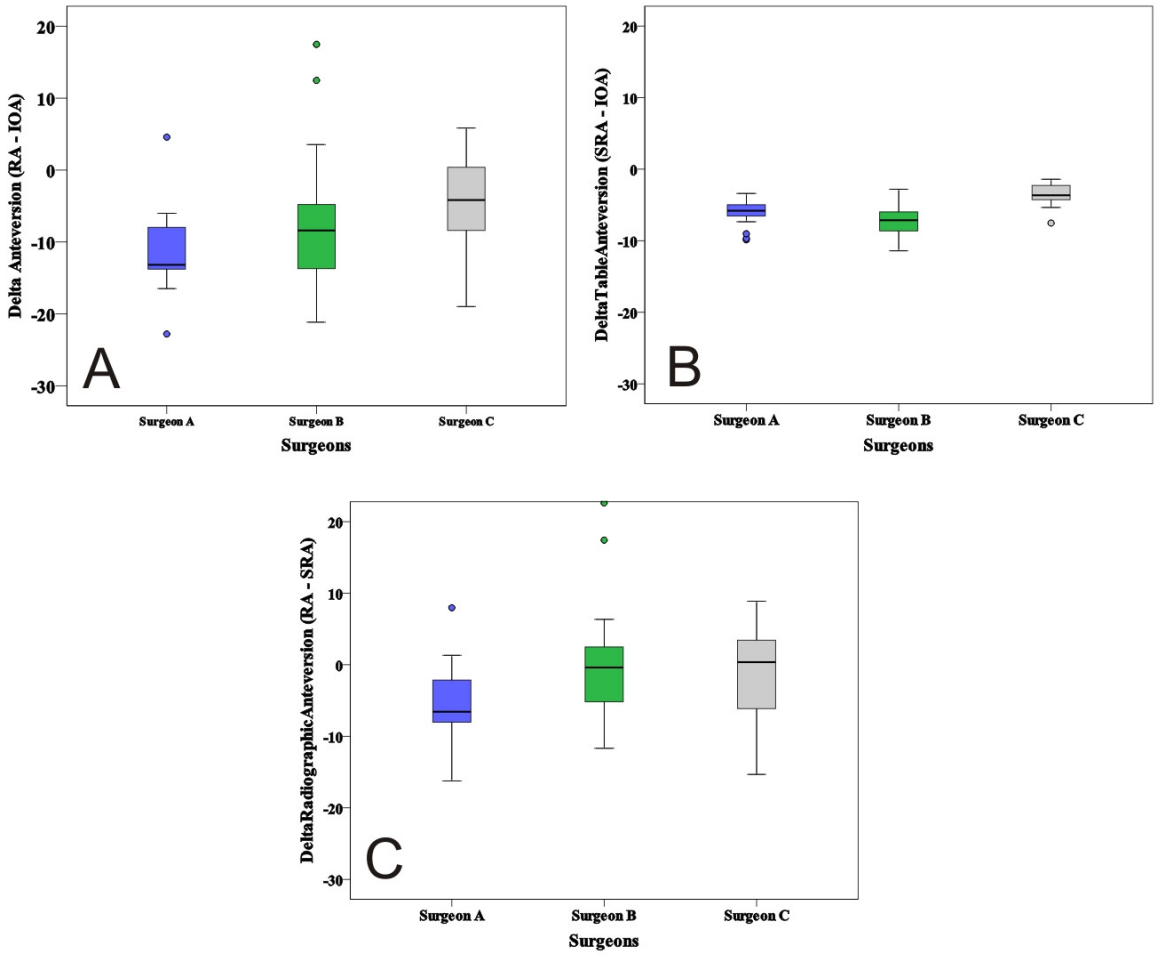


Figure 7.11: Differences in the different anteversion orientation measurements for the three surgeons. Figure A demonstrates Δanteversion, Figure B ΔTanteversion and Figure C ΔRanteversion.

In order to eliminate the variability due to the operating surgeon, the effect of procedure was examined by analysing the cases of Surgeon B, who performed 15 of the 16 MoMHRAs and 16 THAs. Type of procedure did not have an effect on Δ*inclination* (p=0.3) but did have on Δ*anteversion* (p=0.04) (Table 7.9, Figure 7.12). MoMHRAs had a Δ*anteversion* of -11° (SD: 7°), compared to -5° (SD: 8°) for the THAs. There was a significant difference in ΔR*anteversion* between the two procedures [THAs (2.6°, SD: 7.7°); HRAs (-3.3°, SD: 5.5°)] (p=0.04), but no difference in ΔT*anteversion* (p=0.08).

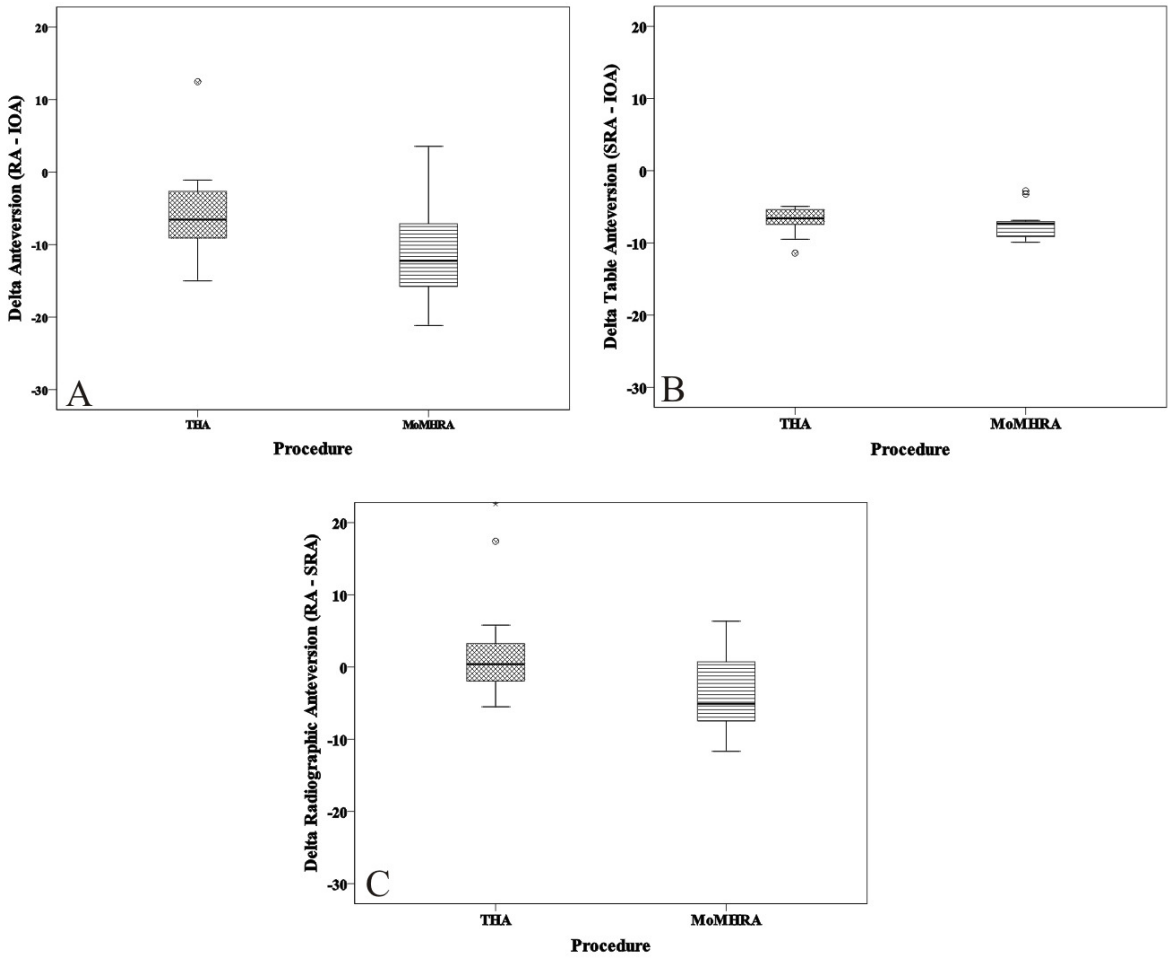


Figure 7.12: Differences in the different anteversion orientation measurements for the two procedures (THA and MoMHRA) for Surgeon B. Figure A demonstrates Δanteversion, Figure B illustrates ΔTanteversion; and Figure C illustrates ΔRanteversion.

Factor	Procedure		p-value
	THA Mean/SD Range	HRA Mean/SD Range	
IOI/ °	40.7°/3.7° 35.0° to 48.6°	43.4°/ 4.3° 35.6° to 49.5°	0.06
IOA/ °	26.4°/ 5.4° 16.3° to 36.3°	26.7°/ 6.3° 10.8° to 33.8°	0.6
RI/ °	45.8°/ 4.9° 35.5° to 54.7	46.8°/ 3.9° 40.0° to 52.4°	0.92
RA/ °	21.8°/ 6.0° 11.9° to 35.1°	15.9°/ 3.9° 8.1 to 20.7°	0.002
SRI/ °	44.3°/ 3.6° 39.1° to 51.8°	46.8°/ 3.9° 40.7° to 52.6°	0.12
SRA/ °	19.6°/ 4.3° 11.3° to 25.1°	19.2°/ 5.0° 7.6° to 26.9°	0.94
Δ*inclination*/ °	5.2°/ 7.2° -9.8° to 15.2°	3.0°/ 4.4° -4.5° to 8.6°	0.32
Δ*anteversion*/ °	-4.7°/ 8.5° -15.0° to 17.5	-10.8°/ 7.1° -21.2° to 3.5°	0.04
ΔT*inclination*/ °	3.3°/ 1.4° 1.2°to 6.1°	3.3°/1.5° 0.3°to 5.2°	0.78
ΔT*anteversion*/ °	-6.9°/ 1.8° -11.4°to -5.0°	-7.6°/ 2.1° -9.9° to -2.8°	0.08
ΔR*inclination*/ °	1.2°/ 6.4° -13.1°to 10.5°	-0.4°/ 4.1° -7.9°to 6.7°	0.29
ΔR*anteversion*/ °	2.6°/ 7.7° -5.5°to 22.6°	-3.3°/ 5.5° -11.7° to 6.3°	0.04

Table 7.9: Orientation measurements for THAs and HRAs performed by Surgeon B.

In order to eliminate the variability due to procedure performed the effect of surgical approach was examined only for the THA cases. Approach (Table 7.10) influenced Δ*anteversion* but not Δ*inclination*. Greater differences between intra-operative and radiographic orientations were detected with the posterior (Δ*anteversion*= -9°) as compared to the lateral (Δ*anteversion*= -5°) approach. This difference was mostly due to the different definitions used as evident by ΔT*inclination*/ ΔT*anteversion* ($p<0.001$) rather than the difference in position of the pelvis between implantation and X-ray ($p=0.32$).

Factor	Approach		p-value
	Lateral (n=17) Mean/SD Range	Posterior (n=38) Mean/SD Range	
OI/ °	35.0°/ 3.1° 30.8° to 40.6°	36.8°/ 5.1° 28.1° to 48.6°	0.28
OA/ °	19.0°/ 6.4° 7.8° to 30.4°	30.6°/ 6.4° 16.3° to 44.4°	<0.001
RI/ °	39.3°/ 5.7° 27.6° to 46.8°	42.9°/ 6.4° 28.4° to 56.2°	0.07
RA/ °	14.3°/ 7.9° 3.9° to 29.5°	21.8°/ 7.0° 9.5° to 35.1°	0.003
SRI/ °	36.7°/ 3.3° 33.1° to 44.4°	41.3°/ 4.9° 30.9° to 51.8°	0.001
SRA/ °	15.4°/ 5.2° 6.4° to 25.6°	24.0°/ 5.7° 11.3° to 35.4°	<0.001
Δ*inclination*/ °	4.3°/ 4.3° -4.1° to 10.3°	6.2°/ 5.9° -9.8° to 15.2°	0.20
Δ*anteversion*/ °	-4.7°/ 6.7° -19° to 5.8°	-8.8°/ 8.7° -26.4° to 17.5°	0.016
ΔT*inclination*/ °	1.7°/ 1.1° 0.3° to 4.0°	4.3°/1.8° 1.2° to 9.4°	<0.001
ΔT*anteversion*/ °	-3.6°/ 1.5° -7.5° to 1.4°	-6.6°/ 4.3° -11.4° to -3.4°	<0.001
ΔR*inclination*/ °	2.6°/ 4.9° -7.4° to 9.6°	1.4°/ 5.3° -13.1° to 10.5°	0.42
ΔR*anteversion*/ °	-1.1°/6.4° -15.3°to 8.9°	-2.1°/ 8.4° -18.8° to 22.6°	0.32

Table 7.10: Orientation measurements for different approaches in THAs only.

7.5 Discussion

On the basis of the findings of this study the null hypothesis was rejected. Cup orientation at surgery is not an accurate predictor of subsequent radiographic cup orientation. A scatter of intra-operative cup orientations was observed which was similar to the radiographic orientation scatter. Whilst radiographic cup inclination was moderately correlated to simulated radiographic cup inclination, this was not

observed for anteversion leading to the rejection of the null hypothesis. The variability in the resultant radiographic orientation is large and due to two equally contributing factors: the variability in component orientation at impaction and the variability in the difference between the pelvic orientation at the time of impaction and at X-ray.

In this study the mean acetabular inclination was 42° and the mean anteversion was 19° measured on the post-operative radiographs. These angles are ideal. However, as in all other studies reporting cup placement, there was a wide range of orientation. The inclination ranged from 28° to 57°, and the anteversion ranged from 4° to 35°. The range was therefore ±14° and ±15° respectively, or expressed in another way the variability, defined as two standard deviations, was 12° and 15° respectively. The surgeons involved in this study were all experienced and as they were aware of the nature of the study, took great care to achieve optimal orientation. Therefore, in general a much wider range of orientation will be achieved, with occasional gross outliers. Despite there being no evidence-base there is a consensus that an acceptable range is about ±10°. However, for hard-on-hard bearings it may be that the acceptable range is much narrower[129]. There is, therefore, an urgent need to improve the methods for achieving optimal orientation. Computer-navigated surgery had initially gained popularity, because the software improves ability to achieve a pre-defined target orientation[213,214]. However, certain limitations such as cost and time constraints have prevented its wide-scale use[215]. It is hence, timely and important to define the pragmatic relationship between intra-operative and radiographic cup orientation, and identify factors that influence it. This is the first study that has investigated in detail the

various factors that contribute to acetabular orientation, allowing the formulation of recommendations as to how the variability can be reduced.

There were highly significant ($p<0.001$) differences in post-operative orientation achieved by the different surgeons. For example, the mean radiographic inclinations (RI) achieved by the three main surgeons were 43°, 40° and 46° and the mean radiographic anteversions (RA) were 23°, 19° and 13°. As a result the different surgeons achieved different percentages of cups within the different potential target zones. The main reason for these differences was that the surgeons aimed to implant the components in different orientations. The mean inclinations at operation (IOI) were 33°, 42° and 35° respectively and the mean anteversions (IOA) were 34°, 26° and 18° respectively. The variability in orientation at implantation was similar for the three surgeons. The variability in inclination was about 7° and in anteversion was about 12°. The surgeons used guides to assist with implantation of sockets. However, the variability in component orientation demonstrates that surgeons tended not to align the guides with the operating table as they felt the guides did not achieve the correct position. Hassan *et al*[216] found that with the use of an intra-operative alignment guide, surgeons only achieved the pre-set radiographic target (Lewinnek Zone) in 58% of cases and concluded that pelvic orientation was the factor that led to this wide scatter. However, the findings of this study demonstrate that even with the use of alignment guides, surgeons do not impact the component with variability less than 12° for IOA. Further work is needed to determine whether this variability is due to the inability of surgeon to reliably determine and reproduce such 3-D angles with an accuracy of ±10° or whether it is due to surgical choice at the time of impaction to account for other variables such as patient's acetabular anatomy. In addition, it remains to

be tested whether adjustment of the guides such that the surgeons perceive they have achieved the correct position as intended by the design, would decrease the variability in component orientation.

By subtracting the intra-operative orientation from the post-operative radiographic orientation it was possible to identify factors that influence the component orientation other than the intra-operative orientation. The two main factors contributing to this difference relate to the definitions of orientation and the movement of the pelvis between the operative and radiographic situation. The individual effect of these can be studied by considering the simulated radiographic orientation. The different definitions resulted in little variability but a change in the mean inclination of about 4° and a change in anteversion of about 6°. On the contrary, pelvic movement resulted in large variability in the final orientation, but did not significantly affect the mean inclination (1°) or anteversion (2°). The variability in inclination resulting from pelvic movement was 10° and the variability in anteversion was 15°. This variability occurs because the relationship between the pelvis and the reference plane is different during the operation and when the post-operative radiograph was taken. Factors that contribute to this pelvic orientation difference include pelvic orientation at set-up, pelvic movement during surgery and pelvic position at X-ray. Previous studies have shown that surgeons have difficulty in reliably identifying pelvic landmarks[217] and reproducibly orientating the patients neutral on the table (anterior pelvic plane parallel to the longitudinal axis and perpendicular to the surface of the operating table)[218-220]. Similarly, studies have noted that most of the pelvic movement occurring during THA is rotational (internal rotation)[221]. To decrease the variability due to pelvic movement (orientation differences) further studies are

needed in order to improve ability in patient set-up and identify factors that reduce amount of movement during surgery.

Patient factors had no significant effect on the orientation or any of the differences. Weak correlations were detected between age, IOI and RA, but these differences reflect surgeon differences. Younger patients, had MoMHRA and were operated by Surgeon B (greater IOI), whilst older patients were operated by Surgeon A (greater RA). BMI did not influence orientation scatter and orientation differences. This is likely to be the case because none of the surgeons in this study perform minimally-invasive surgery, nor compromise operating field visibility and accessibility for length of scar.

On the contrary, surgical factors other than the surgeon had a significant effect. In particular significant orientation differences were detected with procedure type. Reviewing the practice of Surgeon B, hence controlling for the variables of patient positioning for surgery, type of support and approach, it was evident that greater difference in orientations were detected with MoMHRA in comparison to THA. Furthermore, this difference was mostly due to the difference in pelvic orientation between impaction and X-ray. It is therefore evident that this difference in orientation reflects the different amount of pelvic movement that occurs during the two procedures. This is the first study to report such differences in intra-operative pelvic movement and it is perhaps unsurprising as surgeons need to retract the intact femoral neck away from the operating field during MoMHRA acetabular preparation and cup impaction. This increased retraction gives rise to increased pelvic movement and different pelvic orientation at the time of impaction for a MoMHRA compared to a THA. The current study's findings

show that in order to achieve the desired target cup orientation in MoMHRA, the IOI should be 40° and the IOA should be 30°. Significant differences in orientation were detected with surgical approach. However, these differences were due to definitions rather than pelvic movement. Cups inserted via the lateral approach were impacted with less IOA compared to those inserted via the posterior approach due to surgeon's preference. As evident in Murray's nomograms (Appendix 6), for any given operative inclination, the less the operative anteversion, the smaller the difference between operative and radiographic anteversions. For example, with an operative inclination of 45°, the operative anteversion of 5° would translate to a radiographic anteversion of 4° (1° difference); if the operative anteversion was 20°, the radiographic anteversion would be 14° (6° difference).

There are several limitations to this study. Firstly, there were no cases of extreme cup mal-orientation as reported in other series. Such cases would have enabled the investigation of which factors contribute to the mal-orientation. Secondly, there was no record of length of incision or depth of subcutaneous fat at the incision. Although there were no minimally invasive surgeries performed and BMI was recorded, these two factors could have led to impingement of the introducer on the skin and altered the measured orientations. Thirdly, only one surgeon performed both MoMHRA and THA and whether the results of this surgeon reflect those of others needs to be confirmed. Lastly, the orientation of the pelvis at implantation could not be determined. Pelvic orientation at implantation would have enabled estimation of its contribution to the final radiographic cup orientation.

7.6 Conclusion

A wide scatter of intra-operative cup orientation was detected, with significant inter-surgeon differences in intra-operative and subsequent radiographic cup orientation. However, the findings of this study provide evidence that the variability in radiographic cup orientations detected in all series stems from two equally contributing factors; the variability of the intra-operative cup orientation at impaction and the variability in pelvic orientation at impaction compared to the time of X-ray evaluation. In order to reduce cup orientation scatter, both factors have to be addressed. The different definitions have minimal effect on variability. On average, surgeons should impact the components with an intra-operative inclination 5 degrees smaller than their desired radiographic orientation and an intra-operative anteversion 8 degrees greater than their desired radiographic orientation. For MoMHRA cases, the cup should be impacted with greater intra-operative anteversion compared to THA in order to counteract pelvic movement during surgery.

7.7 Summary

- Similarly to previous reports acceptable mean inclination and anteversion were identified; however, a wide scatter of radiographic cup orientations was observed. The variability of radiographic cup orientation was 12° for inclination and 15° for anteversion.

- The variability in radiographic component orientation is due to two equally contributing factors: variability of intra-operative cup orientation and

variability of pelvic orientation at the time of impaction. Reducing the variability in orientation by controlling these two surgical technique-dependent factors would decrease orientation scatter and hence the number of patients at risk of pseudotumour development.

- The mean difference between intra-operative and radiographic was 5° for inclination and -8° for anteversion. This is due to the different definitions by which orientation is assessed in different positions

- Surgical technique of cup orientation at the time of impaction differs significantly and this contributes to the differences in subsequent radiological cup orientation detected between surgeons.

- The difference in orientation of the pelvis between impaction and radiographic assessment is significantly larger in MoMHRAs compared to THAs. In order to account for this difference in pelvic orientation greater intra-operative cup anteversion has to provided at the time of impaction.

- To achieve an optimal orientation of a MoMHRA cup, which has been shown to 45° inclination and 20° anteversion on post-operative radiographs, the component should be impacted with an intraoperative inclination of 40° and an intra-operative anteversion of 30°.

8 CONCLUSIONS, CLINICAL RELEVANCE AND FUTURE WORK

8.1 Conclusions

A review of the literature (Chapter 2) demonstrated that despite the heightened interest in pseudotumour following MoMHRA, and the increasing number of cases reported; the information available on the clinical impact of pseudotumour was sparse. Furthermore, the review identified limited data on factors, particularly surgical, that increase risk of pseudotumour development. These findings presented the case for further studies which were described in this thesis aiming to answer the following questions:

1. What is the clinical impact of pseudotumour following MoMHRA?
2. How can the clinical impact be reduced?

The clinical impact of pseudotumour was determined in the studies described in Chapters 3 and 4. A survival study (Chapter 3) was necessary in order to define the 10-year survival (87.1%), and the 10-year incidence of implant failure due to pseudotumour (7.5%), of the most commonly used MoMHRA, the BHR. Furthermore, this study enabled the identification of certain patient factors (gender and size) that influenced survival, outcome and pseudotumour incidence. Men younger than 50 years old that had a BHR for end-stage primary OA had the highest survival (99%) and lowest pseudotumour incidence (0%), whilst women with femoral implants of diameter <46 mm had lowest survival (67%) and highest

pseudotumour incidence (29%). Pseudotumour was the most common revision cause at mid-term and pseudotumour incidence was found to increase with time.

The revision burden due to pseudotumour associated with MoMHRA was further characterised in the prevalence study (Chapter 3) amongst MoMHRA revisions performed in two specialist hip arthroplasty centres. This study identified that the incidence of MoMHRA revisions has dramatically increased over the recent years, and that pseudotumour is the most common revision indication in specialist centres (48%).

Having identified that pseudotumour is the most common mid-term failure cause, it was important to establish the outcome after revision. A case-control study was performed (Chapter 4), in order to characterise the outcome after MoMHRA revision for different failures, including pseudotumour. This study was performed on the initial cohort of MoMHRA revisions performed at the NOC. Outcome was found to be dependent on revision indication. Revisions for reasons other than pseudotumour had good outcome, which was similar to that following primary THA. However, outcome after revision due to pseudotumour, especially if revised late with associated soft-tissue and/or bony destruction was poor and inferior to the outcome of other revised MoMHRA and primary THAs. Furthermore, pseudotumour revisions were associated with an increased complication (50%) and re-revision rate (38%). In order to improve outcome, it is hence advisable that after diagnosis revision surgery is performed prior to extensive soft-tissue and/or bony destruction. Such findings have also been reported in a more recent study by DeSmet *et al*[177].

In order to minimise the clinical impact of pseudotumour, two major factors need to be addressed. Firstly, to minimise the incidence of pseudotumour development and secondly, to recognise patients at risk in order to identify its presence prior to extensive destruction. In order to minimise the incidence of pseudotumour development patient, implant and surgery related factors had to be addressed separately. The importance of implant related factors in pseudotumour development has been extensively been studied by Langton *et al*[9,27,99,101]. Chapter 3 identified patient-specific factors that significantly increase the risk of pseudotumour development as described above. The possible significance of surgical-related technique (component orientation and sizing) and native anatomy in the risk of pseudotumour development was studied in Chapter 5. Acetabular component orientation and component sizing relative to the native anatomy were identified to influence risk of pseudotumour. Acetabular component mal-orientation increases the risk of pseudotumour development and an optimal orientation zone that reduces, but does not eliminate, the risk by a factor of four was determined. Furthermore, it was evident that femoral head downsizing during the procedure was associated with an increased risk of pseudotumour development. The study identified two factors that were associated with a highly significant power in predicting pseudotumour development, particularly in females: 1. High pre-operative head-neck ratio (> 1.3) and, 2. Excessive downsizing of the femoral head during MoMHRA (> 5.3mm).

An *ex vivo* study was performed in a relatively large number of failed MoMHRAs (Chapter 6), in order to characterise pseudotumours according to various different

parameters. This study confirmed that the majority of pseudotumours are due to increased wear. Histological findings in periprosthetic tissues showed that in the majority of cases (80%) the increased wear is associated with necrosis due to the increased innate response coupled with a variable immune response. A minority of pseudotumours (20%) were associated with low prosthesis wear and had a predominant immune response resulting in necrosis. No wear or histological differences could be determined between the different pseudotumour types; however type of pseudotumour was associated with location. Furthermore, cup orientation within the previously defined optimal zone (Chapter 5) was associated with significantly reduced wear. Hence, these findings provide evidence that a significant proportion of pseudotumours (80%) can be prevented by reducing wear to within expected limits. This can be done by appropriate patient and implant selection, and optimal surgical technique ensuring appropriate component sizing and orientation.

Both studies reviewing cup orientation (Chapter 5 and 6) identified wide scatter in the MoMHRA cup orientation, highlighting the difficulty surgeons face in reproducibly achieving a target orientation. Cup orientation in hip arthroplasty was studied *in vivo* in greater detail with a photogrammetric study (Chapter 7). This provided a greater understanding of the different reference planes of cup orientation and the factors that influence orientation. Surgical factors (surgeon and procedure) were identified to have the greatest effect on the cup orientation. This was due to both surgical technique of intra-operative cup orientation and the amount of pelvic movement between impaction and radiographic assessment. These findings allowed evidence-based guidelines to be developed on how to

orientate a MoMHRA cup at impaction in order to achieve the taget radiographic orientation. A MoMHRA cup should be inserted with an intra-operative inclination of 40° and an intra-operative anteversion of 30°, in order to counteract the effects of the pelvic movement and the different reference planes between intra-operative and radiographic orientations.

Based on the findings presented in this thesis, it is therefore concluded that pseudotumour has a great clinical impact; it is the most common mid-term failure mode and is associated with inferior outcome following revision. In order to minimise the clinical impact, surgeons should consider patient and implant selection and optimise surgical technique. However, even so, a small number of pseudotumours will develop following MoMHRA that will need to be revised. Surgeons, should be aware of patients at risk (females, high HNR_{pre}, dysplasia, malpositioned component, small implant size and low coverage arc designs), appreciate the low sensitivity in detecting pseudotumours with conventional hip radiography, and have a low threshold in performing additional investigations (USS, CT, MRI, metal ions) as per local and national protocols. Such measures should lead to revision prior to extensive soft-tissue damage; thus, would improve outcome after revision[177] and reduce clinical impact further.

8.2 Clinical relevance

The work presented in this thesis has contributed to the knowledge and understanding on pseudotumours following MoMHRA. The work presented provides evidence to support the following conclusions:

- MoMHRA is an effective surgical option for younger men requiring hip arthroplasty. The ten-year survival with the BHR in young men with primary osteoarthritis is 99%. MoMHRA should continue to be used for this cohort. On the contrary, MoMHRA can not be recommended for use in females by any hip arthroplasty surgeon. High volume, highly experienced MoMHRA surgeon series have reported better survival rates compared to the findings of this thesis. Hence, MoMHRA may be a good surgical alternative in a number of females in their practice. When considering a MoMHRA in females, based on the findings of this thesis increased survival and reduced pseudotumour risk would be associated with large diameter femoral heads (> 46 mm) and hip anatomy without a high HNR_{pre}. Surgical technique should be of paramount importance with particular attention to component size selection and cup orientation.
- The ten-year incidence of pseudotumour is 7.5% and is much greater in females in comparison to males. However, the incidence of pseudotumour is increasing with time *in-situ.* This rise in incidence rise was found to occur for both genders and continued surveillance is warranted.
- The clinical impact of pseudotumour should not be underestimated. It was the most common failure in the survival study described in this thesis and was the most common mid-term failure likely to be encountered in specialist centres. As the incidence of pseudotumour increases with time, the burden of pseudotumour-related MoMHRA revisions will rise and thus, arthroplasty units should be appropriately equipped in order to meet the expected increase in demand.

- The inferior outcome encountered with pseudotumour revisions described in this thesis provides evidence that two measures are necessary in order to improve outcome: 1. Increased awareness is paramount so that diagnosis is promptly made, and revision is performed prior to extensive soft-tissue and/or bony damage; and 2. Revision surgery in cases with extensive soft-tissue and bony damage is to be performed in specialist units by orthopaedic surgeons with specific expertise (revision hip arthroplasty, pelvic reconstruction) and the availability of surgeons of other specialties (plastics and vascular) arranged as required for cases with extensive soft-tissue damage.
- Clinicians need to be aware that the presence of a normal radiographic appearance does not exclude the presence of a pseudotumour. In symptomatic patients, further radiological investigations, utilising cross-sectional soft-tissue imaging modalities is required to aid diagnosis.
- Patients reviewed in clinic with any of the following characteristics should be considered for further investigations: female gender, small size, hip dysplasia as diagnosis leading to surgery, component mal-orientation, femoral head downsize at operation evident on radiographs, positive radiographic signs.
- Surgeons should consider the following factors, that contribute to the risk of pseudotumour development, when considering patients for a MoMHRA, which can be broadly divided into patient, implant and surgery dependent factors. Patient risk factors include age, gender, underlying diagnosis and size. Implant risk factors relate to implant characteristics (Chapter 2) and the reported 10-year survival rates of the implant to be

used should be considered. Surgical factors include the pre-operative proximal femoral anatomy, especially the head-neck ratio and possibly the femoral version abnormalities as described and suggested by Daniel *et al*[172]. Lastly, routine assessment and templating of the native acetabulum in order to receive a cup within the defined optimal zone should be performed.

- In order to reduce the risk of pseudotumour, surgeons performing MoMHRA should consider the proximal anatomy, with particular attention to the HNR, which has further implication relating to size of components. As described in Chapters 4 and 5 and in the literature[222], component size is of great importance in MoMHRA. Surgeons should consider and respect the proximal femoral and acetabular anatomy, aiming to perform a bone preserving operation without altering the biomechanic characteristics (e.g. HNR alterations).
- Surgeons should aim to achieve an optimal MoMHRA cup orientation, within the defined radiographic inclination/anteversion of 45°/20° ± 10°. Such orientations are associated with reduced wear and lower risk of pseudotumour development. In order to achieve such an orientation surgeons should be aware of the relationship between the different types of cup orientations, and in particular that between operative and radiographic, as defined by Murray[165]. In addition, special attention should be paid during patient and pelvis positioning during set-up and the amount of movement during surgery, which was shown to be greater in MoMHRA compared to THA (Chapter 7). To achieve the desired target radiographic orientation, the intra-operative orientation should have an inclination of

40° and an anteversion of 30°. In order to reduce variability in radiographic cup orientation, the surgeon should address both the variability in the intra-operative orientation at cup implantation, and the amount of pelvic movement that occurs.

- Lastly, surgeons should be aware that even under optimal operating conditions for MoMHRA leading to the expected amount of bearing wear, pseudotumours can occur. Such pseudotumours are characterised by a dominant immune response and probably represent a type IV hypersensitivity reaction to the products of wear. Hence, patients undergoing MoMHRA should be appropriately informed of the risk of a possible idiosyncratic reaction occuring. To date the risk of this reaction can not be determined or quantified pre-operatively.

8.3 Recommendations for future studies

Although the present thesis examined the clinical impact of pseudotumour following MoMHRA and identified ways of minimising it, there are important questions that remain unanswered. Thus, it is hoped that this thesis will stimulate further interest and work in order for provide further insight into areas that merit further investigation.

The survival study (Study 3A) is limited by its teaching hospital setting and its time of follow-up. There is currently little data on the 10-year survival of independent series of non-specialist centres with MoMHRA. Although, 5-year survival series (96%) from such centres have been reported[223], there is currently

lack of 10-year data. Furthermore, the study performed should be repeated periodically in order to determine the longer term survivorship, outcome and pseudotumour incidence. Given the heightened concern regarding the systemic effects of CoCr particles toxicity[103], continued surveillance of pseudotumour patients for neurological, endocrinological and cardiological malfunction is warranted.

The outcome following MoMHRA revision study (Chapter 4) was a representation of the initial experience of pseudotumour revision and included patients in whom the delay in diagnosis may have lead to increased soft-tissue and bony destruction. It would be of benefit to compare the outcome after revision of the initially revised pseudotumour cohort, with a later cohort. This would test whether increased awareness of the condition leads to improved outcome as previously shown by a single surgeon series[177].

An additional question that remains unanswered is the financial burden pseudotumour poses to both patients and the health service. Patients undergoing MoMHRA are young and are normally part of the working population of a community. The primary MoMHRA is aimed at restoring their function and ability to return to their pre-disease employment status. However, a complication such as pseudotumour would probably lead to further surgery, with associated further hospitalisation and rehabilitation, and questionnable ability to return to the pre-disease work status. Thus, the associated financial burden to the patient and the social services is increased. With the increased demand on surgeons, hospitals

and local authorities to meet financial targets, such a study would provide additional information regarding the cost-effectiveness of MoMHRA.

The findings of the cup orientation study (Chapter 5), with an inability to find a risk-free zone, raise the possibility that optimum cup orientation may be patient tailored. Some surgeons believe this to be the case and hence use anatomical landmarks, such as the transverse acetabular ligament, to guide cup anteversion[224-226]. However, native acetabular anteversion can vary greatly[227] and thus lead to a significant number of component mal-orientations as judged by the optimum zone described in Chapter 5. To date no clinical or modelling studies have tested whether replicating anatomy or aiming for a given target is better in order to optimise bearing dynamics and minimise wear.

The effect of HNR alterations on impingement merit further study. Although, computer simulation models have shown the reduction in HNR to be associated with a theoretical reduction in range of movement post-operatively, this remains to be proven in clinical studies. Furthermore, modelling studies are necessary to demonstrate whether the reduction in HNR principally affects the impingement risk, the primary edge loading risk (by reducing CPR distance) or both factors equally. Similarly, further studies are required to in order to determine whether reproduction of the pre-operative HNR is possible in cases with high HNR_{art}. Modelling studies would enable clinicians to determine what degree of pre-operative HNR can be restrored without excessive acetabular bone removal. This would allow for improved pre-operative templating and screening prior to MoMHRA.

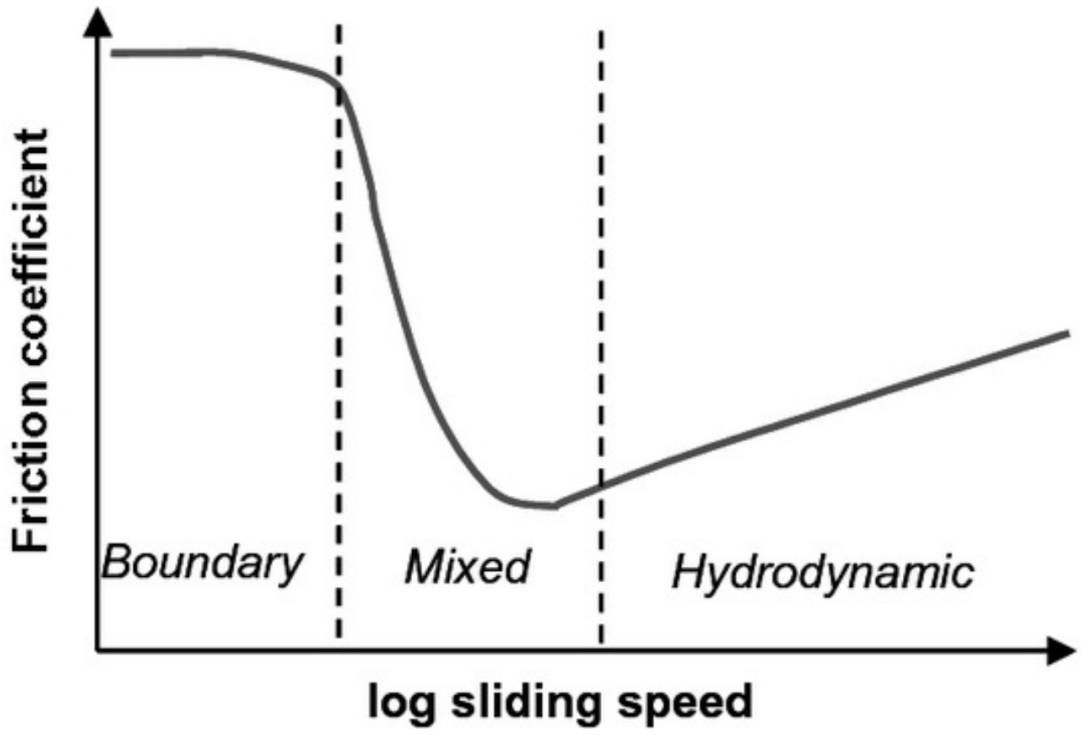
The findings of Chapter 6, pose questions for further research in order to pre-operatively identify patients that are likely to develop immunological reactions to MoM prostheses. Well-designed prospective, multi-centre, studies on MoMHRA patients looking at genetic markers, might provide further answers on how to identify patients ar risk. Similarly, in order to determine how dominant of a role either cytotocixity or hypersensitivity play, the next stage would be to perform local lymphocyte reactivity tests and cytokine assays in hip aspirates. These could be performed prospectively, both on synovial fluid at the time of operation and on pseudotumour fluid at the time of diagnosis or revision. Furthermore, since pseudotumours can develop in patients with low amount of wear, alternative bearing surfaces for hip resurfacing (e.g. ceramic on ceramic) might be an option to fully eliminate this complication which has been associated with MoMHRA.

The findings of Chapter 7, raise further questions on the ability of surgeons to judge 3-D angles with accuracy less than 10°. Further studies are required to determine whether surgeons can repeatedly orientate a cup with a given orientation and, if this is not possible what the margin of error is. In addition, further studies are required in order to determine how surgeons orientate the patient's pelvis at set-up and to quantify the amount of pelvic movement that takes place during surgery. This would aid in improving patient set-up and identifying methods of minimising movement during the procedure. These measures, would reduce the variability of pelvic position at the time of impaction and, therefore, variability of radiographic orientation post-operatively. Lastly, further research on instrumentation that aids surgeon during surgery in order to achieve a given cup

orientation, without the limitation of computer navigation surgery, is warranted. One such example is the Hip Sextant[228], which has recently received clearance by the FDA and the British Standards Institution, but needs further validation by independent centres prior to recommendation for use.

Appendix 1: The Stribeck Curve

The Stribeck Curve



The Stribeck Curve[1] can be used to describe the friction properties between two surfaces. It is a plot of friction as it relates to viscosity, speed and load. On the vertical axis of the graph is the friction coefficient. The horizontal axis is of a parameter that combines the other variables (mN/P) [m=fluid viscosity, N=relative speed, P= load on the interface per unit bearing width].

Boundary lubrication is characterised by little fluid in the interface and large surface contact, resulting in high friction. As speed or viscosity increase or the load decreases, the surfaces begin to separate and a fluid film begins to form.The film is thin, but can support part of the load. This leads to mixed lubrication. The surfaces can continue to separate as the speed or viscosity increase until there is full fluid film lubrication and no surface contact. The friction coefficient will reach its minimum and there is a transition to hydrodynamic lubrication. No friction or wear occurs during hydrodynamic lubrication since there is full-fluid film and no contact between the surfaces.

The friction can increase in the hydrodynamic region; this can be explained by fluid drag (friction produced by the fluid); higher speed may result in thicker fluid but it also increases the fluid drag on the moving surfaces.

Mixed lubrication occurs betweeen boundary and hydrodynamic lubrication. The fluid film thickness is slightly greater than the surface roughness, but the surfaces are still close enough to together to affect each other.

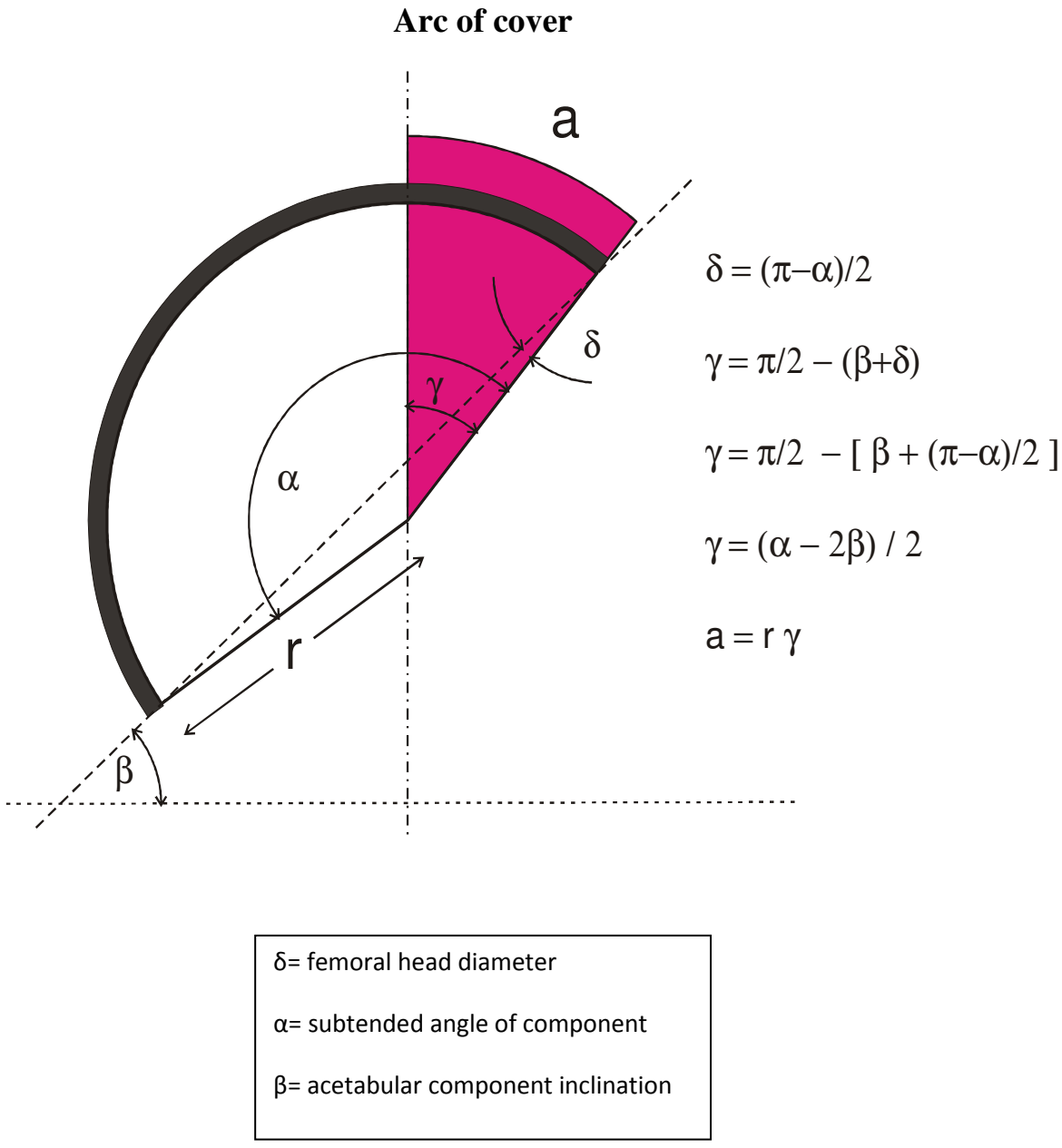
Appendix 2: Table of Elements MoMHRA

Elements of the CoCr alloy used in the manufacturing of MoMHRA[25]

	Composition, % (mass/mass)	
Element	**Min**	**Max**
Chromium	27.0	30.0
Molybdenum	5.0	7.0
Nickel	0.0	0.5
Iron	0.0	0.75
Carbon	0.0	0.35
Silicon	0.0	1.0
Manganese	0.0	1.0
Tungsten	0.0	0.2
Phosphorus	0.0	0.02
Sulfur	0.0	0.01
Nitrogen	0.0	0.25
Aluminium	0.0	0.1
Titanium	0.0	0.1
Boron	0.0	0.010
Cobalt	Balance*	Balance*

*Balance: Equal to the difference of 100% and the sum percentage of the other specified elements.

Appendix 3: Arc of Cover



δ= femoral head diameter

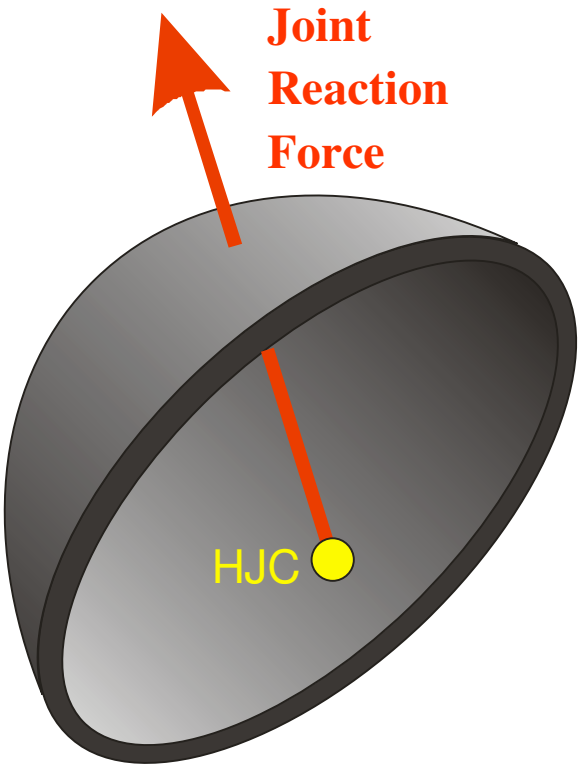
α= subtended angle of component

β= acetabular component inclination

A3.1: Calculations performed in order to calculate coverage arc as per each MoMHRA cup[100].

Appendix 4: Contact – Patch to Rim Distance

Contact – Patch to Rim Distance (CPR)



Distance from the acetabular component centre to the rim (C2R) is:

C2R = Subtended articular angle/360* π*r

As per Bergmann's data[2] the Hip Joint Reaction Force is directed 14° inferolaterally in the coronal plane and 16° anteriorly in the sagittal plane.

Assuming that the centre of the contact pathc is the same as the centre of the hip joint reaction force vector, the contact patch from the centre of the acetabular component in the coronal plane is:

[(Cup inclination angle – 14)/360]*2*π*r

The contact patch distance from the centre of the acetabular component in the sagittal plane is:

[(Cup anteversion angle + 16)/360]*2*π*r

Resulting contact patch distance from the centre of the acetular component (CPC) is:

CPC = √(contact patch distance in coronal plane^2 + contact patch distance in sagittal plane^2)

CPR distance = C2R – CPC

Appendix 5: MRI

Magnetic Resonance Imaging (MRI)

MRI is a medical imaging technique used to visualise internal structures. It makes use of the property of nuclear magnetic resonance to image protons of the body. An MRI scanner works by applying a strong magnetic field to the body, which aligns all the protons along a single axis. A radio frequency (RF) pulse is then emitted, which knocks the protons off this axis. Once the RF pulse is turned off, the magnetic field causes them to return to alignment (relaxation phase), and in the process they emit RF waves which are then detected to form the image. There are two types of relaxation; longitudinal and transverse. T1 imaging uses longitudinal relaxation signals to form its image, and T2 uses transverse relaxation signals.

T1-weighted MRI images

A 90° RF pulse is used to displace the protons and the protons rotate in the X-Y plane, in phase with each other. After the RF is switched off, the protons come out of phase. The decaying signal sent as the protons come onto resting in the Z-plane is the T1 image. The decaying signal is measured over a time labelled as TR. The shorter the TR the stronger the T1 contrast. On T1, fat-containing tissues are bright and water- and fluid- containing tissues are dark.

T2- weighted MRI images

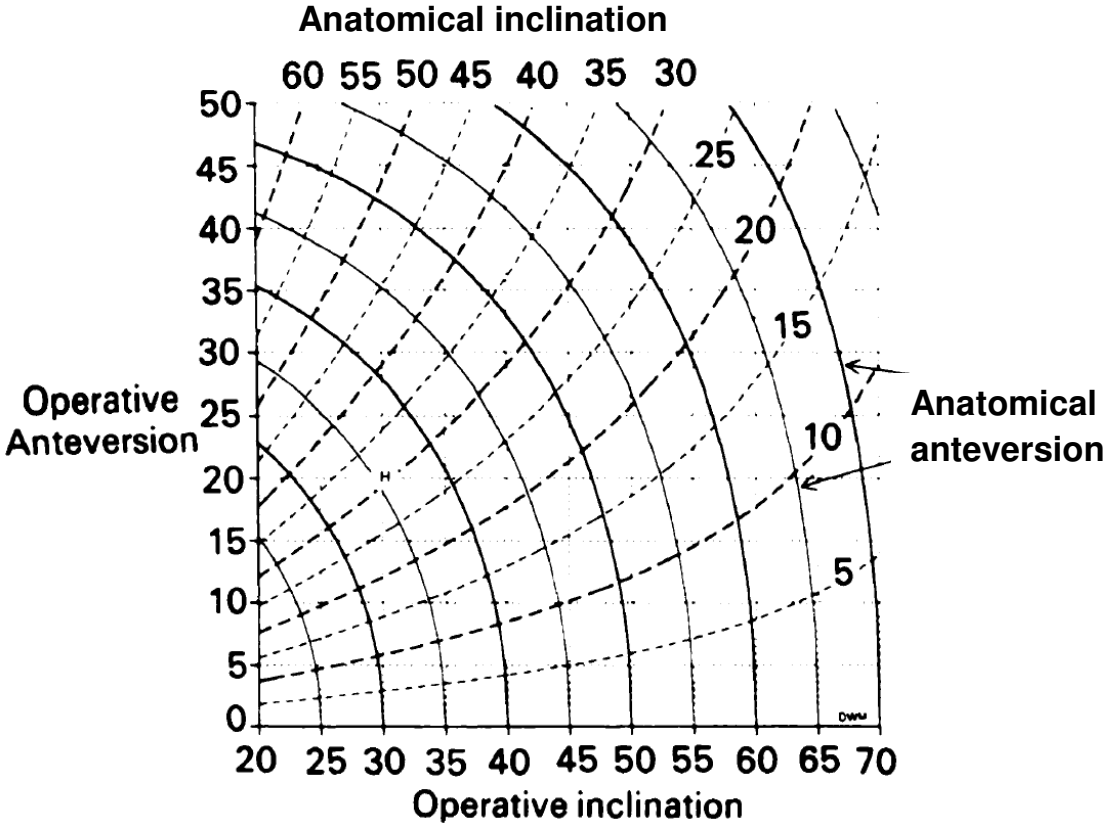
A90° RF pulse is used similarly to T1. However, as the protons are in the dephasing state a 180° RF impulse is applied, which puts them back in phase. After this second pulse, the protons dephase again. T2 images are aimed at emphasising tissues that remain in phase for longer time and hence maintain a stronger signal. This is achieved by delaying the sampling timed (known as TE). To maximise T2 contrast a long TE should be used. On T2, water- and fluid-containing tissues are bright and fat-containing tissues are dark. Therefore, T2 is particularly suited to image oedema of tissues.

Short inversion Time Inversion Recovery (STIR) MRI images

STIR is a sequence with specific timing so as to suppress the signal from fat. An inversion recovery pulse sequence is a pulse sequence preceded by a 180° RF pulse. STIR is based on the difference in T1 relaxation times between water and fat.

Appendix 6: Murray's Nomograms & Equations

Murray's Nomograms & Equations for acetabular component orientation[165] – Reproduced with the kind permission of Professor David Murray.



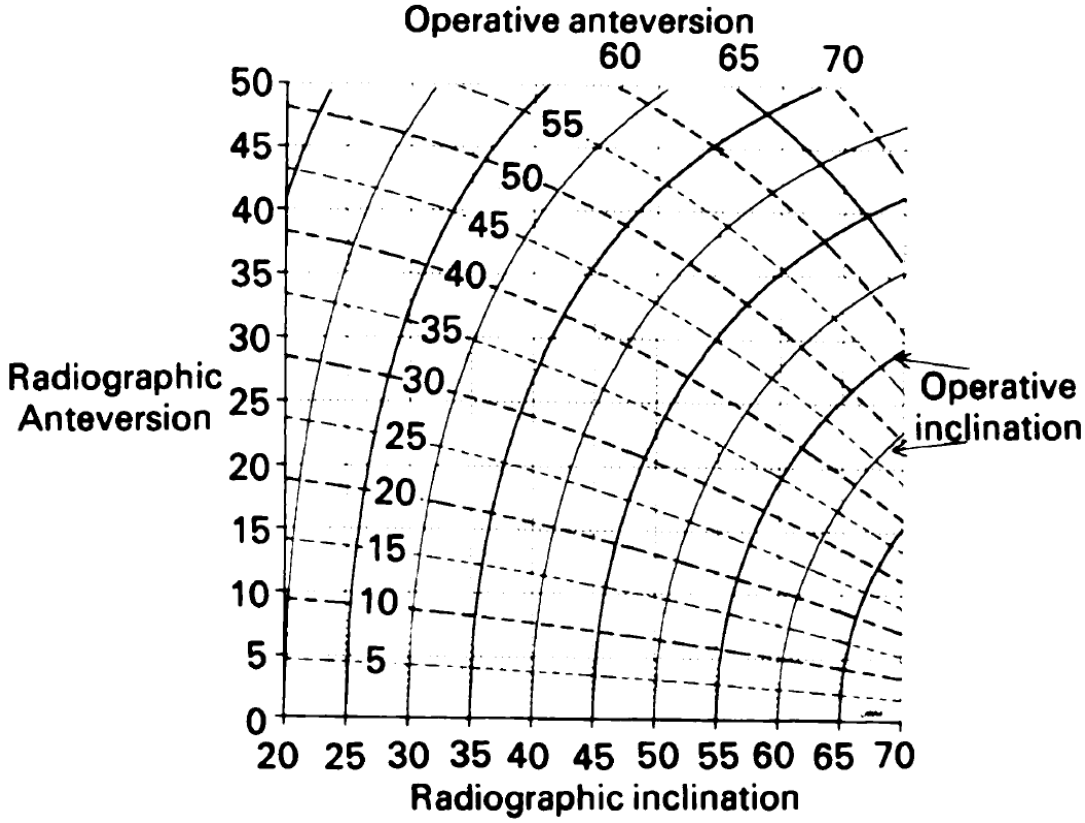
Tan (AA) = Sin (OA) / Tan (OI)

Cos (AI) = Cos (OI) x Cos (OA)

Tan (OA) = Sin (AA) x Tan (AI)

Sin (OI) = Sin (AI) x Cos (AA)

A6.1: Nomogram to convert anatomical to operative cup orientations and vice versa as per Murray.



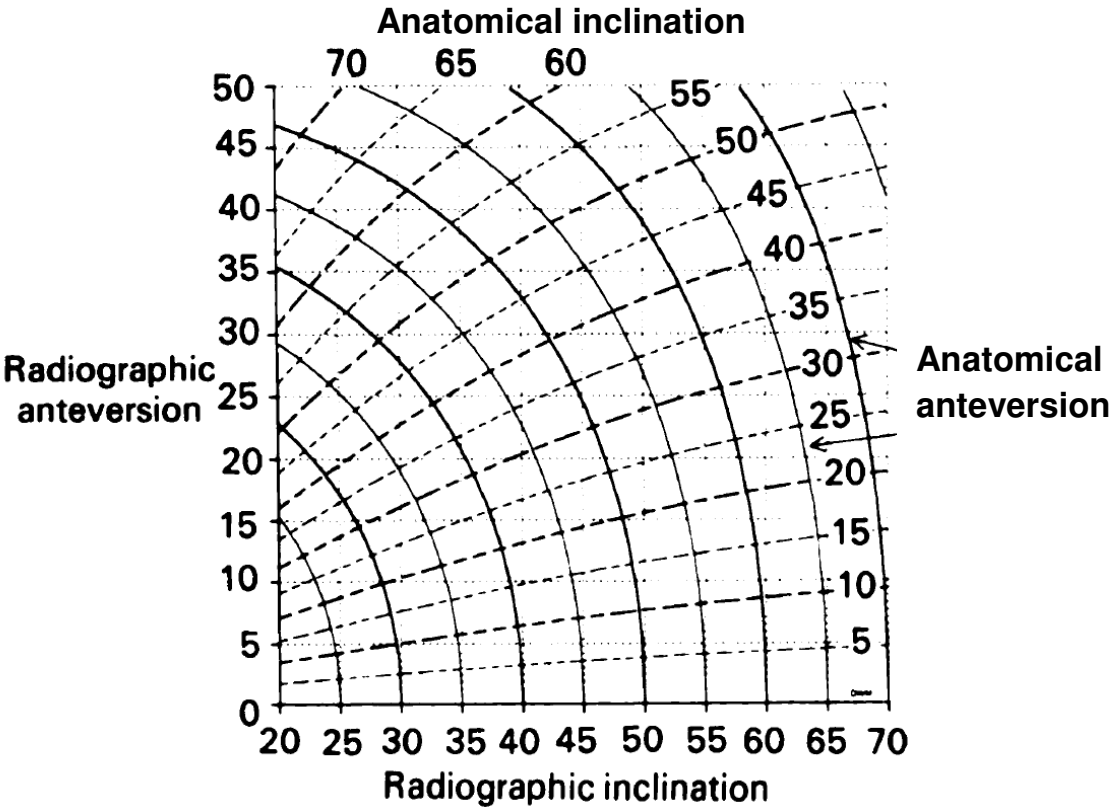
Tan (OA) = Tan RA / Cos (RI)

Sin (OI) = Sin (RI) x Cos (RA)

Sin (RA) = Sin (OA) x Cos (OI)

Tan (RI) = tan (OI) / Cos (OA)

A6.2: Nomogram to convert operative to radiographic cup orientations and vice versa as per Murray.



Tan AA = Tan (RA) / Sin (RI)

Cos (AI) = Cos (RI) x Cos (RA)

Sin (RA) = Sin (AA) x Sin (AI)

Tan (RI) = Tan (AI) x Cos (AA)

A6. 3: Nomogram to convert anatomical to radiographic cup orientations and vice versa as per Murray.

Appendix 7: Hip Questionnaire

Hip Questionnaire

PATIENT OUTCOME ASSESSMENT
METAL-ON-METAL RESURFACING HIP REPLACEMENT

	Date of birth: **Hospital number:** **Date of operation:** **Side:**

1. Have you had any operations on your **«side»** hip since your **«side»** hip resurfacing operation on**«operation_date»**? (Please tick box)

Yes ❑ **No** ❑ **→If 'no' go to question 2 below**

If yes: Which operation(s) have you had on the **«side»** hip?

(Please tick boxes)

a. Treatment of dislocation (hip came out of joint) ❑
b. Treatment of fracture (broken bone) ❑
c. Redo (Revision) of «side» hip resurfacing ❑
d. Another («side») hip operation ❑

At which hospital(s) did you have this operation(s)?

NAME OF HOSPITAL(S)/TOWN	WHEN? (YEAR)	**«side» hip** TYPE OF OPERATION

2. Do you have any other problems - apart from your **«side»** hip - which make everyday activities (eg. walking, washing, dressing) difficult?

No ❑ **Yes** ❑ - If 'Yes', Please specify: .....

3. Overall, how pleased have you been with your **«side»** resurfacing hip replacement?

Very pleased	Fairly pleased	Not very pleased	Very disappointed
❑	❑	❑	❑

Date completed: _____/_____/

Appendix 8: Oxford Hip Score

Oxford Hip Score (OHS)

OXFORD HIP QUESTIONNAIRE

Date: ☐☐/☐☐/☐☐

Op date: : ☐☐/☐☐/☐☐

✓tick one box for every question.

PROBLEMS WITH YOUR LEFT/RIGHT HIP

1. ***During the past 4 weeks*****.....**

How would you describe the pain you usually had from your hip?

None	Very mild	Mild	Moderate	Severe
❑	❑	❑	❑	❑

2. ***During the past 4 weeks*****.....**

Have you had any trouble with washing and drying yourself (all over) because of your hip?

No trouble at all	Very little trouble	Moderate trouble	Extreme difficulty	Impossible to do
❑	❑	❑	❑	❑

3. ***During the past 4 weeks*** **.....**

Have you had any trouble getting in and out of a car or using public transport because of your hip? *(whichever you tend to use)*

No trouble at all	Very little trouble	Moderate trouble	Extreme difficulty	Impossible to do
❑	❑	❑	❑	❑

4. ***During the past 4 weeks*****.....**

Have you been able to put on a pair of socks, stockings or tights?

Yes, Easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, Impossible
❑	❑	❑	❑	❑

5. ***During the past 4 weeks*****.....**

Could you do the household shopping on your own?

Yes, Easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, Impossible
❑	❑	❑	❑	❑

6. ***During the past 4 weeks*****.....**

For how long have you been able to walk before pain from your hip becomes severe? (*with or without a stick)*

No pain/ More than 30 minutes	16 to 30 minutes	5 to 15 minutes	Around the house only	Not at all -pain severe on walking
❑	❑	❑	❑	❑

LEFT / RIGHT HIP

✓tick one box for every question

7 ***During the past 4 weeks*****.....**

Have you been able to climb a flight of stairs?

Yes, Easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, Impossible
❑	❑	❑	❑	❑

8 ***During the past 4 weeks*****.....**

After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your hip?

Not at all painful	Slightly painful	Moderately painful	Very painful	Unbearable
❑	❑	❑	❑	❑

9 ***During the past 4 weeks*****.....**

Have you been limping when walking, because of your hip?

Rarely/ never	Sometimes, or just at first	Often, not just at first	Most of the time	All of the time
❑	❑	❑	❑	❑

10 ***During the past 4 weeks*****.....**

Have you had any sudden, severe pain - 'shooting', 'stabbing' or 'spasms' - from the affected hip?

No days	Only 1 or 2 days	Some days	Most days	Every day
❑	❑	❑	❑	❑

11 ***During the past 4 weeks*****.....**

How much has pain from your hip interfered with your usual work *(including housework)*?

Not at all	A little bit	Moderately	Greatly	Totally
❑	❑	❑	❑	❑

12 ***During the past 4 weeks*****.....**

Have you been troubled by pain from your hip in bed at night?

No nights	Only 1 or 2 nights	Some nights	Most nights	Every night
❑	❑	❑	❑	❑

Appendix 9: UCLA Activity Score

UCLA Activity-Level Rating[1]

Level	Activity	Please indicate
10	Regularly participate in *impact sports* such as jogging, tennis, skiing, acrobatics, ballet, heavy labour or backpacking	❑
9	Sometimes participate in *impact sports*	❑
8	Regularly participate in *very active* events, such as bowling or golf	❑
7	Regularly participate in *active* events, such as bicycling	❑
6	Regularly participate in *moderate activities*, such as swimming and unlimited housework or shopping	❑
5	Sometimes participate in *moderate activities*	❑
4	Regularly participate in *mild activities*	❑
3	Sometimes participate in *mild activities*	❑
2	Mostly *inactive*: restricted to minimal activities of daily living	❑
1	Wholly *inactive*: dependent on others; cannot leave residence	❑

[1] **Zahiri CA, Schmalzried TP, Szuszczewicz ES, Amstutz HC.** Assessing activity in joint replacement patients. J Arthroplasty. 1998 Dec;13(8):890-5.

Appendix 10: Ethics committee approval

NHS
National Research Ethics Service

Berkshire Research Ethics Committee
Building L27
University of Reading
London Road
Reading
RG1 5AQ

Telephone: 0118 918 0550/1
Facsimile: 0118 918 0559

05 August 2010

Prof. David. W. Murray
Professor of Orthopaedic Surgery
National Health Service
Botnar research centre
Nuffield Orthopaedic Centre
Windmill Road
Oxford, OX3 7LD

Dear Prof. Murray

Study Title: **Identifying the Relationship between operative and radiographic acetabular component orientation.**

REC reference number: **10/H0505/45**

Thank you for your letter of 07 July 2010, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to

the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk

Where the only involvement of the NHS organisation is as a Participant Identification Centre (PIC), management permission for research is not required but the R&D office should be notified of the study and agree to the organisation's involvement. Guidance on procedures for PICs is available in IRAS. Further advice should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Investigator CV		08 April 2010
Protocol	2.1	15 April 2010
CV for George Grammatopoulos		
REC application	2.5	09 April 2010
Covering Letter		08 April 2010
Letter from Sponsor		15 April 2010
GP/Consultant Information Sheets	1.1	08 April 2010
Participant Information Sheet: track changes	2.1	08 July 2010
Participant Consent Form: clean copy	2.1	08 July 2010
Response to Request for Further Information		07 July 2010
Participant Information Sheet: clean copy	2.1	08 July 2010
Participant Consent Form: track changes	2.1	08 July 2010
Letter from Statistician	Andrew Judge	15 April 2010

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk

10/H0505/45	**Please quote this number on all correspondence**

Yours sincerely

pp

Professor Nigel Wellman
Chair

Email: scsha.berksrec@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: Sponsor contact - Mrs Fiona Parker, Nuffield Orthopaedic Centre
Student – Mr George Grammatopoulos

Appendix 11 – ASA grades[229]

ASA grade	Characteristics
I	A normal healthy patient.
II	A patient with mild systemic disease.
III	A patient with severe systemic disease.
IV	A patient with severe systemic disease that is a constant threat to life.
V	A moribund patient who is not expected to survive without the operation.
VI	A declared brain-dead patient whose organs are being removed for donor purposes.

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