Title Page

Title: What is the natural history of asymptomatic pseudotumours in metal-on-metal hip resurfacing patients?

Short title: Asymptomatic pseudotumours in metal-on-metal hip resurfacing patients

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Abstract

Purpose

We assessed the natural history of asymptomatic pseudotumours associated with metal-on-metal hip resurfacings (MoMHRs), and factors associated with future revision.

Methods

In 2007-2008 we identified 25 MoMHRs (21 patients; mean age 59.9 years; 76% female) with asymptomatic pseudotumours. All patients underwent identical initial assessment (ultrasound, blood metal ions, radiographs, Oxford Hip Score (OHS)) **and were considered asymptomatic because they denied experiencing hip symptoms, were satisfied with their MoMHR surgery, and had good or excellent OHSs (≥ 34).** In 2012-2013, repeat assessments were performed in all non-revised patients.

Results

Revision for pseudotumour was performed/recommended in 15 MoMHRs (60%) at a mean 2.7 years (range 0.4-6.4 years) from initial assessment, with 14 developing symptoms before revision. Non-revised MoMHRs (**n=10**) underwent repeat ultrasound at a mean 5.1 years (range 4.0-6.5 years) later, with no changes in pseudotumour volume ($p=0.956$) or OHS ($p=0.065$) between assessments. High blood cobalt ($p=0.0048$) and chromium ($p=0.0162$), large pseudotumours ($p=0.0458$), low OHS ($p=0.0183$), and bilateral MoMHRs ($p=0.049$) predicted future revision. Patients with blood metal ions above established unilateral/bilateral

thresholds and/or initial pseudotumours $>30\text{cm}^3$ had an 86.7% sensitivity, 70.0% specificity, 81.2% positive predictive value, and 77.8% negative predictive value for future revision.

Conclusions

MoMHR patients with initially asymptomatic pseudotumours often become symptomatic and require revision. Patients with high blood metal ions and/or pseudotumours $>30\text{cm}^3$ should remain under annual surveillance or be considered for revision (especially in patients **also having** lower initial OHSs, bilateral MoMHRs, **and/or** those becoming symptomatic). Less regular surveillance of patients outside these parameters appears acceptable.

Key words

asymptomatic; follow-up; hip resurfacing; pseudotumour; revision

Introduction

High short-term revision rates due to pseudotumours have been reported with metal-on-metal (MoM) hip arthroplasties [1,2]. As pseudotumours can be destructive to periprosthetic bone and soft-tissues, revision is often challenging with poor outcomes following revision reported [3,4]. To identify pseudotumours early, regular MoM patient follow-up is currently recommended [5-7]. This surveillance has detected a significant number of asymptomatic pseudotumours on cross-sectional imaging, with a wide range in prevalence reported (4%-61%) [8-11].

Patients with asymptomatic pseudotumours currently pose a management dilemma to surgeons, especially if there is no associated bone or soft-tissue damage, with no robust thresholds for revision surgery provided [12]. This is because the natural history of asymptomatic pseudotumours remains unclear, therefore it is not known whether all such lesions will progress, and if so how quickly progression occurs.

Although recent studies have assessed MoM hips using serial imaging [13-17], few specifically looked at patients with asymptomatic pseudotumours [15-17] with only 1 study focusing on the natural history of these lesions in MoM hip resurfacing (MoMHR) patients [16]. Minimal changes **were reported** in 14 MoMHRs with asymptomatic pseudotumours when MRI was repeated within 1-year [16]. However 2 other studies with short-term follow-up observed lesion progression was common on serial imaging [15,17]. To manage patients with asymptomatic pseudotumours appropriately, further information about the natural history of these lesions is required at extended follow-up. Factors associated with the need for future revision must also be identified.

We assessed: (1) the natural history of asymptomatic pseudotumours in MoMHRs, and (2) factors from the initial assessment associated with future revision surgery in asymptomatic pseudotumour patients.

Patients and Methods

Between 2007-2008 a prospective cohort study was performed of 201 asymptomatic MoMHRs in 158 patients (mean age 56.0 years; 61% male) [8]. **Patients were considered asymptomatic when assessed because they all: (1) denied experiencing any hip related symptoms, (2) were satisfied with the surgical results, and (3) had good (34-41) or excellent (42-48) initial OHSs [18].** These patients were initially assessed at a mean 3.9 (range 3.0-7.4) years from MoMHR (111 (55%) Birmingham Hip Resurfacing (Smith & Nephew, Warwick, UK), 82 (41%) Conserve Plus (Wright Medical, Memphis, Tennessee), and 8 (4%) Recap (Biomet, Bridgend, UK)). **25 MoMHRs had asymptomatic pseudotumours at initial assessment and were included in the present study.**

In 2007/8 all 25 MoMHRs underwent identical initial assessment: hip radiographs and ultrasound, blood metal ions, completion of the Oxford Hip Score (OHS) and the University of California, Los Angeles (UCLA) activity score questionnaire. When these asymptomatic pseudotumours were initially identified, the possible management options were discussed with patients. This included explaining the **unknown** natural history of these lesions, and that early outcomes following revision for symptomatic pseudotumours **were** poor [3,19]. As patients were asymptomatic, no individual wished to undergo revision following initial pseudotumour detection.

In light of subsequent concerns about asymptomatic pseudotumours associated with MoM hips and their unknown natural history [9-11,15], all non-revised MoMHRs (n=10) **underwent** repeat assessment (hip ultrasound, radiographs, OHS and UCLA score questionnaires) in 2012/13. The OHS was scored from 0 (worst outcome) to

48 points (best outcome) [20,21], and the UCLA activity scores from 1 (wholly inactive) to 10 (regular participation in impact sports) [22].

Details about blood metal ion sampling, radiographic analysis (Image J; US National Institutes of Health, Maryland, USA), and ultrasound examination have been described [8,23]. All ultrasound scans were performed by one experienced musculoskeletal radiologist (performed over 500 ultrasounds for MoMHR), which is recommended for achieving results comparable to MRI [24]. The radiologist was blinded to all clinical information. A pseudotumour was defined as a cystic, solid, or mixed mass with evidence of communication with, but extending beyond the confines of, the anatomic hip joint. In all cases pseudotumour volume (product of the maximum recorded dimension in each of **3** orthogonal planes in centimetres), consistency (solid, cystic, or mixed) and location were recorded.

Statistical analysis

Analyses were performed using Stata Version 13.1 (Lakeway Drive, Texas, USA). Either the median and interquartile range (IQR) or the mean and range were used depending on data distribution. For patients undergoing repeat investigation, change in pseudotumour volume and change in UCLA score were assessed using paired t-tests, and change in OHS was assessed using a Wilcoxon signed-rank test.

To assess factors from the initial assessment associated with future revision of asymptomatic pseudotumours, statistical tests were chosen to reflect the exposure variable and data distribution. These included unpaired t-tests (age, acetabular inclination and anteversion, time from MoMHR to first scan, UCLA score), the

Wilcoxon rank-sum test (femoral component diameter, blood cobalt and chromium concentrations, OHS, initial pseudotumour volume), and Fisher's exact test (gender, MoMHR design, bilateral MoMHRs, initial pseudotumour consistency and location). The level of significance was $p < 0.05$.

Using factors **predicting** future revision, diagnostic test characteristics (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)) with 95% confidence intervals were calculated for various clinical scenarios based on the results of the initial assessment. Previously proposed blood metal ion thresholds were used: $5\mu\text{g/l}$ [25], $7\mu\text{g/l}$ [5], and those accounting for unilateral (cobalt $>4.0\mu\text{g/l}$ and/or chromium $>4.6\mu\text{g/l}$) and bilateral (cobalt $>5.0\mu\text{g/l}$ and/or chromium $>7.4\mu\text{g/l}$) MoMHRs [26]. The maximum value of either ion was used in each patient [25], apart from when using the unilateral/bilateral thresholds. Pseudotumours above 30cm^3 have previously been considered significant lesions [15]. This threshold was used to calculate diagnostic test characteristics for various clinical scenarios along with **2** others based on our data distribution ($>20\text{cm}^3$ and $>50\text{cm}^3$).

Results

In 2007/8, 25 asymptomatic pseudotumours (21 patients) were identified. Mean age at initial assessment was 59.9 years (39.2-73.1 years) and 76% (n=19) **of MoMHRs were implanted in females**. Revision surgery was performed or recommended in 15 MoMHRs (60%; revised group) with the remaining 10 MoMHRs undergoing repeat assessment (40%; surveillance group).

Revised group (n=15)

Revision was performed (n=14) or recommended (n=1) at a mean 2.7 years (range 0.4-6.4 years) from initial assessment. **Revision surgery was performed in 14 MoMHRs that were initially asymptomatic because all hips eventually developed symptoms (hip/groin pain, swelling, noises), and in most cases also had increasing blood metal ion concentrations or progression of cross-sectional imaging abnormalities (Table I). In all cases** pseudotumours **were** confirmed both intra-operatively and histopathologically, **with the articulation exchanged to** a non-MoM bearing. The median pre-revision OHS decreased from 37 (IQR 34-45) to 32 (IQR 21-39) at a mean of 2.0 years post-revision (0.8-4.5 years), which was not significant (p=0.230).

Revision was recommended in a 55 year-old male patient (Conserve MoMHR; blood cobalt 3.6µg/l and chromium 2.0µg/l) following repeat ultrasound performed 4.0 years **later**. Initial ultrasound demonstrated a 60cm³ mixed anterior and lateral pseudotumour. This enlarged significantly to 346cm³ by repeat ultrasound with progression of the lateral component to a solid consistency, **and** development of a new cystic component posteriorly. Revision surgery was recommended but the

patient refused given he remained completely asymptomatic with no functional restriction (OHS=48). This patient remains under regular surveillance.

Surveillance group (n=10)

10 non-revised MoMHRs (9 patients) underwent repeat ultrasound at a mean of 5.1 years (range 4.0-6.5 years) from initial assessment, and a mean of 8.2 years (range 5.1-13.3 years) from primary MoMHR. No pseudotumour underwent aspiration and/or biopsy prior to repeat imaging. Median OHS at initial assessment was 47 (IQR 44-48) compared to 46 (IQR 38-48) at repeat assessment ($p=0.065$). Mean UCLA at initial assessment was 6.9 (range 3-9) compared to 6.4 (range 4-8) ($p=0.102$). No patient had evidence of radiological failure (loosening, osteolysis, femoral neck narrowing) on initial or repeat radiographs.

Repeat ultrasound of 10 asymptomatic pseudotumours (Table II) demonstrated **8** remained stable ($n=4$), or decreased in volume ($n=4$), and **2** pseudotumours increased in volume (from 9cm^3 - 61cm^3 and 17cm^3 - 36cm^3). No significant change in pseudotumour volume occurred between repeat ultrasound ($p=0.956$). No pseudotumour completely disappeared after repeat ultrasound, however **1** patient (Table II: patient 1) with an initially anterior and posterior cystic pseudotumour had regression of the anterior component.

Factors associated with future revision surgery

5 factors from the initial assessment predicted future revision in asymptomatic pseudotumour patients (Table III): high blood cobalt ($p=0.0048$) and chromium

concentration ($p=0.0162$), increased pseudotumour volume on initial ultrasound ($p=0.0458$), low initial OHS ($p=0.0183$) and bilateral MoMHRs ($p=0.049$).

Clinical scenarios were formulated based on blood metal ion concentrations and/or pseudotumour volumes from the initial assessment. Diagnostic test characteristics for identifying MoMHRs requiring pseudotumour revision were assessed for each scenario (Table IV). When using blood metal ions alone, optimal diagnostic test characteristics for identifying MoMHRs requiring revision were obtained when patients were above unilateral and bilateral specific thresholds [26] (sensitivity=67.7%, specificity=80.0%, PPV=83.3%, NPV=61.5%). When using initial pseudotumour volume alone, test characteristics were optimal for identifying revised MoMHRs when pseudotumour volume was above 30cm³ (sensitivity=60.0%, specificity=90.0%, PPV=90.0%, NPV=60.0%). When combining investigations, the optimal diagnostic test characteristics for identifying MoMHRs requiring revision were obtained when patients were above the respective unilateral or bilateral blood metal ion thresholds and/or had a pseudotumour volume above 30cm³ at initial assessment (sensitivity=86.7%, specificity=70.0%, PPV=81.2%, NPV=77.8%).

Discussion

Little is known about the natural history of asymptomatic pseudotumours associated with MoM hips at over 2-years follow-up [15-17], with no robust guidance provided on managing patients [5-7,12]. We assessed the natural history of asymptomatic pseudotumours in MoMHRs at extended follow-up and factors associated with future revision.

MoMHR patients with initially asymptomatic pseudotumours often become symptomatic and require revision. Patients with high blood metal ions (above unilateral/bilateral thresholds [26]) at initial assessment and/or pseudotumours above 30cm³ often required revision. These patients should either be kept under annual surveillance or considered for revision. We **consider revision preferable to annual surveillance if patients with high blood metal ions and/or pseudotumours above 30cm³ also have** suboptimal OHS's (<42), bilateral MoMHRs, **and/or develop** symptoms during longitudinal follow-up. Less regular surveillance of asymptomatic pseudotumours outside these parameters appears acceptable given minimal changes occurred in this subgroup during follow-up. Our recommendations may be used until more robust evidence is available regarding the natural history of asymptomatic pseudotumours.

3 studies have documented the natural history of asymptomatic pseudotumours in 10-24 MoM hips at a mean of 0.7-2.1 years [15-17]. Variable rates of pseudotumours progressing (0%-60%), remaining stable (0%-93%), and decreasing (7%-40%) on ultrasound or MRI were reported [15-17]. Our study observed most asymptomatic pseudotumours undergoing repeat ultrasound do not progress, with no significant

change in pseudotumour volume or OHS between scans. However, if we include revised cases in the progression group, the rate of initially asymptomatic pseudotumours progressing was much higher at 68% (17/25). Importantly our interval between repeat imaging (range 4.0-6.5 years) is more than twice that of previous studies [15-17]. Therefore our study provides important information regarding the natural history of asymptomatic pseudotumours at extended follow-up.

Similar to other studies [16,17] we did not observe complete resolution of any pseudotumours, though the anterior pseudotumour component in **1** patient resolved. Using repeat ultrasound Almousa *et al.* reported complete disappearance of **3** asymptomatic pseudotumours associated with large-diameter total hip replacements [15]. We suspect differences in patient populations and implants used could explain these differences regarding the potential for complete resolution.

Recently the clinical relevance of asymptomatic pseudotumours associated with MoMHRs has been questioned [16]. Our findings suggest initially asymptomatic pseudotumours frequently become symptomatic 0.4-6.4 years **later** and require revision. Furthermore, others have highlighted concerns that no robust thresholds for performing revision in pseudotumour patients exist [12,15,17]. Authorities advise considering revision in patients with imaging abnormalities or those with progressive lesions and/or those with raised blood metal ions [5-7]. However such guidance is difficult to implement without knowledge of what specific imaging abnormalities and changes are clinically significant. Our study is the first proposing thresholds for considering closer follow-up and/or surgery in MoMHRs with asymptomatic pseudotumours.

We identified **5** factors (high blood cobalt and chromium concentration, increased pseudotumour volume, low OHS, bilateral MoMHRs) from the initial assessment associated with future revision. Furthermore, all but **1** of the revised group developed symptoms before revision. Asymptomatic pseudotumours were more likely to require revision in patients with blood metal ions above established unilateral/bilateral thresholds [26], and/or pseudotumour volumes above 30cm³. This threshold provided good and balanced diagnostic test characteristics. We therefore recommend this threshold for considering more regular follow-up and/or revision. Our threshold supports previous observations that lesions below 30cm³ are suitable for surveillance [15]. As low OHS (<42, given no patient in the non-revision group had an OHS below 42) and bilateral MoMHRs were also independent predictors of revision, we suggest considering revision in patients meeting our thresholds who also have these factors. Bilateral patients may be at increased risk of future revision due to the increased metal ion release from two bearings [26], as well as the potential delayed hypersensitivity reaction causing arthroplasty failure after implantation of the second MoMHR [27]. Patients meeting our proposed thresholds who develop new symptoms over longitudinal follow-up should also be considered for revision.

Significantly inferior OHSs in asymptomatic pseudotumour patients compared to those without pseudotumours were observed in our earlier report [8]. Despite using a clear definition for being “asymptomatic”, we observed significantly inferior initial OHSs in asymptomatic pseudotumours eventually requiring revision compared to those asymptomatic pseudotumours under surveillance. Therefore both the patients

with pseudotumours and the subgroup eventually revised were not truly “asymptomatic”, with evidence of functional impairment at initial assessment. It is important to carefully question patients about MoMHR related problems, with our data suggesting the OHS represents a useful screening tool to detect subtle differences in function.

It is recognised no threshold proposed for revision will be perfect. However, the high sensitivity and PPV suggests our threshold is effective for identifying patients eventually needing revision. This is important given short-term outcomes following pseudotumour revision are poor [3,4], so timely surgery is preferable before the onset of irreversible bone and soft-tissue destruction which itself relies on appropriate identification of at-risk patients. Surgeons should therefore have detailed discussions with asymptomatic pseudotumour patients meeting our proposed thresholds. Our experience is that patients are reluctant to undergo further surgery when pain free. However, we now provide clinicians with data on future revision risk based on initial assessment parameters, which can be used to counsel patients. Suboptimal outcomes currently reported following pseudotumour revisions must be highlighted [3,4], though evidence suggests increasing experience **and having a lower threshold for performing revision surgery** can improve **subsequent outcomes** [28].

We recommend that patients meeting our proposed threshold remain under annual surveillance if surgeons are reluctant to intervene whilst asymptomatic, or if patients decline revision. However, we advise caution for surgeons adopting a conservative approach towards asymptomatic pseudotumours meeting our proposed thresholds.

Although the decrease in OHS following revision of 14 pseudotumours was not statistically significant (likely due to small numbers), we consider this decline clinically significant given patients can detect a **5**-point change in OHS [29]. Therefore our patients were functionally worse off following revision. This provides some support for considering early revision of asymptomatic pseudotumours in patients meeting our thresholds.

Our observations suggest not all asymptomatic pseudotumours need revision within 4.0-6.5 years of detection. We suspect **2** types of asymptomatic pseudotumours exist: (1) progressive lesions potentially causing bone and soft-tissue damage which often become symptomatic and require revision [3,4], and (2) benign periprosthetic fluid collections similar to those reported with non-MoM hip bearings which may represent a normal “physiological” response to arthroplasty [9,30]. These latter lesions may have been incorrectly termed “pseudotumours” by ourselves and other authors [8-10,15-17,24,30], and when blood metal ions are normal may represent patients outside our proposed thresholds with little risk of progression who are suitable for surveillance. We suggest such patients are reviewed within **4**-years of initial assessment using repeat imaging and blood metal ions, with individuals instructed to return earlier if symptoms develop.

It is recognised our proposed thresholds have exceptions. We consider solid pseudotumours and patients with bone and/or soft-tissue damage are indications for revision given these factors are associated with adverse outcomes [3,31,32]. Therefore our thresholds only apply to asymptomatic cystic or mixed pseudotumours.

This study has limitations. Our findings may not apply to other MoM designs. Although we had a similar cohort size and much longer interval between repeat imaging than previous studies [15-17], it is recognised our recommendations are based on relatively small numbers with some subgroup analyses likely to be underpowered. This must be considered when interpreting our findings. However, our study adds important information regarding the natural history of asymptomatic pseudotumours at extended follow-up, with our recommendations useful until more evidence becomes available. Furthermore, it is unlikely other studies will have larger numbers with longer follow-up in the near future given we first described pseudotumours in both symptomatic and asymptomatic MoMHRs [8,18]. Although revision represents a definite end-point, individual surgeons may have different thresholds for performing revision which is a limitation. Our findings only apply to asymptomatic pseudotumours imaged up to 6.5 years from initial assessment. A strict definition for pseudotumour was used which included intra-articular communication, though others have used broader definitions and/or classified extra-articular lesions as pseudotumours [10,33]. **Intra-observer reliability of ultrasound measurements was not assessed, whilst inter-observer reliability could not be assessed as one radiologist performed all examinations. We are unaware of any studies assessing intra-observer and inter-observer reliability of pseudotumour measurements using ultrasound, and therefore cannot quantify the magnitude of acceptable measurement variation. However, studies demonstrate that ultrasounds performed by experienced musculoskeletal radiologists can produce results comparable to MRI, with ultrasound measurements also likely to have acceptable intra-observer agreement [24,34].**

Conclusions

MoMHR patients with initially asymptomatic pseudotumours often become symptomatic and require revision. Patients most likely to require future revision had high blood metal ions at initial assessment and/or initial pseudotumours above 30cm³. We propose these parameters as a threshold for considering either closer follow-up or revision surgery (especially in patients **also having** lower initial OHSs, bilateral MoMHRs, **and/or** those developing symptoms during longitudinal follow-up). Less regular surveillance of asymptomatic pseudotumour patients outside these parameters appears acceptable given little significant changes occur during extended follow-up. Our management recommendations may be used in the interim until more robust information is available regarding the natural history of asymptomatic pseudotumours.

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References

1. Smith AJ, Dieppe P, Vernon K, Porter M, Blom AW. Failure rates of stemmed metal-on-metal hip replacements: analysis of data from the National Joint Registry of England and Wales. *Lancet* 2012; **379**: 1199–1204.
2. Smith AJ, Dieppe P, Howard PW, Blom AW; National Joint Registry for England and Wales. Failure rates of metal-on-metal hip resurfacings: analysis of data from the National Joint Registry for England and Wales. *Lancet* 2012; **380**: 1759-1766.
3. Grammatopoulos G, Pandit H, Kwon YM, Gundle R, McLardy-Smith P, Beard DJ, *et al.* Hip resurfacings revised for inflammatory pseudotumour have a poor outcome. *J Bone Joint Surg [Br]* 2009; **91-B**: 1019-1024.
4. Matharu GS, Pynsent PB, Dunlop DJ. Revision of metal-on-metal hip replacements and resurfacings for adverse reaction to metal debris: a systematic review of outcomes. *Hip Int* 2014; **24**: 311-320.
5. Medical and Healthcare products Regulatory Agency (MHRA) (2012). Medical Device Alert: all metal-on-metal (MoM) hip replacements. MDA/2012/036. <http://www.mhra.gov.uk/>. (last accessed 24 February 2016).
6. European Federation of National Associations of Orthopaedics and Traumatology (2012). Consensus statement “Current Evidence on the Management of Metal-on-Metal Bearings.” http://www.efort.org/communications/pdf/2012_05_10_MoM_Consensus_statement.pdf (last accessed 24 February 2016).
7. U.S. Food and Drug Administration (2013). Medical Devices. Metal-on-Metal Hip Implants. Information for Orthopaedic Surgeons. <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/Implantsa>

ndProsthetics/MetalonMetalHipImplants/ucm241667.htm (last accessed 24 February 2016).

8. Kwon YM, Ostlere SJ, McLardy-Smith P, Athanasou NA, Gill HS, Murray DW. “Asymptomatic” pseudotumors after metal-on-metal hip resurfacing arthroplasty: prevalence and metal ion study. *J Arthroplasty* 2011; **26**: 511–518.
9. Williams DH, Greidanus NV, Masri BA, Duncan CP, Garbuz DS. Prevalence of pseudotumor in asymptomatic patients after metal-on-metal hip arthroplasty. *J Bone Joint Surg [Am]* 2011; **93-A**: 2164-2171.
10. Hart AJ, Satchithananda K, Liddle AD, Sabah SA, McRobbie D, Henckel J, et al. Pseudotumors in association with well-functioning metal-on-metal hip prostheses: a case-control study using three-dimensional computed tomography and magnetic resonance imaging. *J Bone Joint Surg [Am]* 2012; **94-A**: 317–325.
11. Fehring TK, Odum S, Sproul R, Weathersbee J. High frequency of adverse local tissue reactions in asymptomatic patients with metal-on-metal THA. *Clin Orthop Relat Res* 2014; **472**: 517-522.
12. Matharu GS, Mellon SJ, Murray DW, Pandit HG. Follow-up of metal-on-metal hip arthroplasty patients is currently not evidence based or cost effective. *J Arthroplasty* 2015; **30**: 1317-1323.
13. Ebreo D, Bell PJ, Arshad H, Donell ST, Toms A, Nolan JF. Serial magnetic resonance imaging of metal-on-metal total hip replacements. Follow-up of a cohort of 28 mm Ultima TPS THRs. *Bone Joint J* 2013; **95-B**: 1035-1039.

14. Reito A, Elo P, Puolakka T, Pajamäki J, Nieminen J, Eskelinen A. Repeated magnetic resonance imaging in 154 hips with large-diameter metal-on-metal hip replacement. *Acta Orthop* 2014; **85**: 570-576.
15. Almousa SA, Greidanus NV, Masri BA, Duncan CP, Garbuz DS. The natural history of inflammatory pseudotumors in asymptomatic patients after metal-on-metal hip arthroplasty. *Clin Orthop Relat Res* 2013; **471**: 3814-3821.
16. van der Weegen W, Brakel K, Horn RJ, Hoekstra HJ, Sijbesma T, Pilot P, *et al.* Asymptomatic pseudotumours after metal-on-metal hip resurfacing show little change within one year. *Bone Joint J* 2013; **95-B**: 1626-1631.
17. Hasegawa M, Miyamoto N, Miyazaki S, Wakabayashi H, Sudo A. Longitudinal Magnetic Resonance Imaging of Pseudotumors Following Metal-on-Metal Total Hip Arthroplasty. *J Arthroplasty* 2014; **29**: 2236-2238.
18. Kalairajah Y, Azurza K, Hulme C, Molloy S, Drabu KJ. Health outcome measures in the evaluation of total hip arthroplasties: a comparison between the Harris hip score and the Oxford hip score. *J Arthroplasty* 2005; **20**: 1037-1041.
19. Pandit H, Glyn-Jones S, McLardy-Smith P, Gundle R, Whitwell D, Gibbons CL, *et al.* Pseudotumors associated with metal-on-metal hip resurfacings. *J Bone Joint Surg [Br]* 2008; **90-B**: 847-851.
20. Dawson J, Fitzpatrick R, Carr A, Murray D. Questionnaire on the perceptions of patients about total hip replacement. *J Bone Joint Surg [Br]* 1996; **78-B**: 185-190.
21. Murray DW, Fitzpatrick R, Rogers K, Pandit H, Beard DJ, Carr AJ, *et al.* The use of the Oxford hip and knee scores. *J Bone Joint Surg [Br]* 2007; **89-B**: 1010-1014.

22. Amstutz HC, Thomas BJ, Jinnah R, Kim W, Grogan T, Yale C. Treatment of primary osteoarthritis of the hip: a comparison of total joint and surface replacement arthroplasty. *J Bone Joint Surg [Am]* 1984; **66-A**: 228–41.
23. Matharu GS, Mansour R, Dada O, Ostlere S, Pandit HG, Murray DW. Which imaging modality is most effective for identifying pseudotumours in metal-on-metal hip resurfacings requiring revision: ultrasound or MARS-MRI or both? *Bone Joint J* 2016; **98-B**: 40-48.
24. Garbuz DS, Hargreaves BA, Duncan CP, Masri BA, Wilson DR, Forster BB. The John Charnley Award: Diagnostic accuracy of MRI versus ultrasound for detecting pseudotumors in asymptomatic metal-on-metal THA. *Clin Orthop Relat Res* 2014; **472**: 417-423.
25. Hart AJ, Sabah SA, Bandi AS, Maggiore P, Tarassoli P, Sampson B, *et al.* Sensitivity and specificity of blood cobalt and chromium metal ions for predicting failure of metal-on-metal hip replacement. *J Bone Joint Surg [Br]* 2011; **93-B**: 1308-1313.
26. Van Der Straeten C, Grammatopoulos G, Gill HS, Calistri A, Campbell P, De Smet KA. The 2012 Otto Aufranc Award: The interpretation of metal ion levels in unilateral and bilateral hip resurfacing. *Clin Orthop Relat Res* 2013; **471**: 377–385.
27. Pandit H, Vlychou M, Whitwell D, Crook D, Luqmani R, Ostlere S, *et al.* Necrotic granulomatous pseudotumours in bilateral resurfacing hip arthroplasties: evidence for a type IV immune response. *Virchows Arch* 2008; **453**: 529-534.

28. De Smet KA, Van Der Straeten C, Van Orsouw M, Doubi R, Backers K, Grammatopoulos G. Revisions of metal-on-metal hip resurfacing: lessons learned and improved outcome. *Orthop Clin North Am* 2011; **42**: 259-269.
29. Beard DJ, Harris K, Dawson J, Doll H, Murray DW, Carr AJ, *et al.* Meaningful changes for the Oxford hip and knee scores after joint replacement surgery. *J Clin Epidemiol* 2015; **68**: 73-79.
30. Bisseling P, de Wit BW, Hol AM, van Gorp MJ, van Kampen A, van Susante JL. Similar incidence of periprosthetic fluid collections after ceramic-on-polyethylene total hip arthroplasties and metal-on-metal resurfacing arthroplasties: results of a screening metal artefact reduction sequence-MRI study. *Bone Joint J* 2015; **97-B**: 1175-1182.
31. Liddle AD, Satchithananda K, Henckel J, Sabah SA, Vipulendran KV, Lewis A, *et al.* Revision of metal-on-metal hip arthroplasty in a tertiary center: a prospective study of 39 hips with between 1 and 4 years of follow-up. *Acta Orthop* 2013; **84**: 237-245.
32. Munro JT, Masri BA, Duncan CP, Garbuz DS. High complication rate after revision of large-head metal-on-metal total hip arthroplasty. *Clin Orthop Relat Res* 2013; **472**: 523-528.
33. Lainiala O, Elo P, Reito A, Pajamäki J, Puolakka T, Eskelinen A. Comparison of extracapsular pseudotumors seen in magnetic resonance imaging and in revision surgery of 167 failed metal-on-metal hip replacements. *Acta Orthop* 2014; **85**: 474-479.
34. Matharu GS, Janardhan S, Brash L, Pynsent PB, Dunlop DJ, James S. The utility of repeat ultrasound imaging in the follow-up of metal-on-metal hip arthroplasty patients. *Ann R Coll Surg Engl* 2016; **98**: 143-149.

Table I Details of asymptomatic pseudotumours in metal-on-metal hip resurfacing patients requiring revision surgery (n=14)

Patient age at initial scan (years) / gender	Primary HR / time to revision from first ultra-sound (years)	Initial ultra-sound findings	Factors contributing to decision to perform revision surgery			
			Symptoms	Raised metal ions (blood / synovial)	Cross-sectional imaging findings progressing	Details
65.6 M	Conserve / 2.2	7 cm ³ Cystic Anterior	Yes	No	Yes	- Developed hip pain/discomfort - MRI: volume increase to 10.2 cm ³
39.2 F	Conserve / 0.8	37 cm ³ Cystic Posterior	Yes	Yes	No	- Developed hip pain/discomfort with clicking - Blood Co=12.3 µg/l and Cr=22.8 µg/l (below 7 µg/l initially) - Ultrasound: volume stable
51.3 F	Conserve / 1.8	18 cm ³ Cystic Anterior	Yes	No	Yes	- Developed hip pain/discomfort - MRI: volume increase to 40 cm ³
66.7 F	BHR / 2.2	135 cm ³ Cystic Posterior + Lateral	Yes	No	No	- Developed hip pain/discomfort - Hip eventually felt weaker/unstable - MRI: volume stable
73.1 M	BHR / 3.6	48 cm ³ Mixed Posterior + Lateral	Yes	No	No	- Developed hip pain/discomfort - Emergency presentation with dislocation secondary to pseudotumour
55.0 F *	BHR / 3.8	120 cm ³ Solid Anterior	Yes	No	No	- Developed hip pain/discomfort - MRI: volume stable
55.0 F *	BHR / 3.8	22 cm ³ Cystic Posterior	Yes	No	Yes	- Developed hip pain/discomfort/swelling - MRI: volume increase to 364 cm ³
55.1 F *	Recap / 2.9	40 cm ³ Cystic Posterior + Lateral	Yes	Yes	No	- Developed hip pain/discomfort with clicking - Blood Co=14.3 µg/l and Cr=29.2 µg/l (below 7 µg/l initially) - Ultrasound: volume stable
55.1 F *	Recap / 3.4	35 cm ³ Mixed Posterior	Yes	Yes	No	- Developed hip pain/discomfort - Blood Co=14.3 µg/l

		+ Lateral				and Cr=29.2 µg/l (below 7 µg/l initially) - Ultrasound: volume stable
70.5 F	BHR / 0.4	36 cm ³ Solid Anterior	Yes	Yes	No	- Developed hip pain/discomfort - Blood Co=22.5 µg/l and Cr=12.7 µg/l (below 7 µg/l initially) - MRI: volume stable
65.5 F	BHR / 1.4	27 cm ³ Mixed Posterior + Lateral	Yes	Yes	No	- Developed hip pain/discomfort - Synovial Co=89.2 µg/l and Cr=3293 µg/l - MRI: volume stable
55.3 F *	BHR / 2.3	15 cm ³ Mixed Anterior	Yes	No	Yes	- Developed hip pain/discomfort - MRI: volume increase to 90 cm ³
55.3 F *	BHR / 0.5	90 cm ³ Mixed Anterior	Yes	No	No	- Developed hip pain/discomfort with clicking - MRI: volume stable
53.3 F	Conserve / 6.4	26 cm ³ Mixed Anterior + Posterior	Yes	No	Yes	- Developed hip pain/discomfort - MRI: volume increase to 53 cm ³

BHR = Birmingham Hip Resurfacing; Cr = chromium; Co = cobalt; F = female; HR = hip resurfacing; M = male; MRI = magnetic resonance imaging

*Patients with bilateral hip resurfacings which both required revision surgery for pseudotumour.

Table II Natural history of asymptomatic pseudotumours in metal-on-metal hip resurfacing patients (n=10) assessed using repeat ultrasound examination

Patient age at initial scan (years) / gender	Primary HR / time in-situ (years)	Time between repeat imaging (years)	Blood metal ions (µg/l)	Cup inclination / anteversion (degrees)	Initial ultrasound findings	Repeat ultrasound findings	Clinical outcome
70.6 M	Conserve / 2.8	4.0	Co 1.2 Cr 0.4	40.8 / 8.2	23 cm ³ Cystic Anterior + Posterior	8 cm ³ Cystic Posterior	No revision as regressed. Remains under review.
54.9 F	Conserve / 2.3	4.2	Co 2.7 Cr 4.7	46.9 / 15.8	20 cm ³ Cystic Anterior + Posterior	4 cm ³ Cystic Anterior + Posterior	No revision as regressed. Remains under review.
65.6 F	Conserve / 1.8	4.3	Co 4.3 Cr 3.9 *	53.7 / 22.3	14 cm ³ Mixed Lateral	14 cm ³ Mixed Lateral	No revision as stable. Remains under review.
63.7 F	Conserve / 3.0	4.3	Co 1.2 Cr 1.0	26.0 / 25.0	9 cm ³ Cystic Posterior	61 cm ³ Cystic Posterior	No revision as has no symptoms. Remains under review.
60.2 M	Conserve / 2.7	5.2	Co 2.4 Cr 1.3	56.5 / 12.7	27 cm ³ Cystic Posterior	5 cm ³ Cystic Posterior	No revision as regressed. Remains under review.
61.1 F	Conserve / 1.9	5.2	Co 15.2 Cr 13.8	61.7 / 15.4	17 cm ³ Mixed Anterior	17 cm ³ Mixed Anterior	No revision as stable. Remains under review.
65.1 F #	BHR / 2.7	5.6	Co 4.8 Cr 7.2 *	40.0 / 32.0	17 cm ³ Cystic Posterior	36 cm ³ Cystic Posterior	No revision as has no symptoms. Remains under review.
65.1 F #	BHR / 6.5	5.6	Co 4.8 Cr 7.2 *	42.0 / 12.0	17 cm ³ Cystic Posterior	18 cm ³ Cystic Posterior	No revision as stable. Remains under review.
52.9 M	Conserve / 2.6	5.6	Co 4.0 Cr 1.6	54.2 / 18.4	30 cm ³ Cystic Posterior	13 cm ³ Cystic Posterior	No revision as regressed. Remains under review.
71.4 F	BHR / 6.8	6.5	Co 0.8 Cr 1.0	50.1 / 25.0	100 cm ³ Cystic Posterior	100 cm ³ Cystic Posterior	No revision as stable. Remains under review.

BHR = Birmingham Hip Resurfacing; Cr = chromium; Co = cobalt; F = female; HR = hip resurfacing; M = male

* Patient has bilateral metal-on-metal hip resurfacing at the time of blood sampling.

Patient has bilateral asymptomatic pseudotumours.

Table III Factors from the initial assessment associated with the need for subsequent revision surgery in patients with asymptomatic pseudotumours

Factor	Hips under surveillance (10 hips in 9 patients)	Hips revised or recommended for revision (15 hips in 12 patients)	P-value
Gender	7 (70%) Female 3 (30%) Male	12 (80%) Female 3 (20%) Male	0.653
Age at first ultrasound	Mean 63.1 years (range 52.9-71.4 years)	Mean 57.8 years (range 39.2-73.1 years)	0.090
Unilateral or bilateral metal-on- metal hips	3 (30%) Bilateral 7 (70%) Unilateral	11 (73%) Bilateral 4 (27%) Unilateral	0.049*
Hip resurfacing design	BHR 3 (30%) Conserve 7 (70%) Recap 0 (0%)	BHR 9 (60%) Conserve 4 (27%) Recap 2 (13%)	0.082
Time between hip resurfacing and first ultrasound	Mean 3.3 years (range 1.8–6.8 years)	Mean 3.9 years (range 1.0–5.8 years)	0.401
Femoral component diameter	Median 46 mm (IQR 44-48 mm)	Median 46 mm (IQR 44-50 mm)	0.567
Acetabular inclination	Mean 47.2° (range 26.0°-61.7°)	Mean 49.0° (range 41.0°-62.6°)	0.627
Acetabular anteversion	Mean 18.7° (range 8.2°-32.0°)	Mean 16.3° (range 5.1°-34.3°)	0.555
Blood cobalt concentration	Median 3.4 µg/l (IQR 1.2 µg/l – 4.8 µg/l)	Median 7.9 µg/l (IQR 4.8 µg/l – 14.3 µg/l)	0.0048*
Blood chromium concentration	Median 2.8 µg/l (IQR 1.0 µg/l – 7.2 µg/l)	Median 9.4 µg/l (IQR 3.8 µg/l – 22.8 µg/l)	0.0162*
Initial OHS (0-48 scale)	Median 47 (IQR 44-48)	Median 38 (IQR 34-46)	0.0183*
Initial UCLA score (1-10 scale)	Mean 6.9 (range 3-9)	Mean 5.7 (range 3-8)	0.104
Initial pseudotumour volume	Median 18.7 cm ³ (IQR 16.9 cm ³ -27.0 cm ³)	Median 36.0 cm ³ (IQR 22.4 cm ³ -60.0 cm ³)	0.0458*
Initial pseudotumour consistency	Cystic 7 (70%) Mixed 3 (30%) Solid 0 (0%)	Cystic 6 (40%) Mixed 7 (47%) Solid 2 (13%)	0.389
Initial pseudotumour	Anterior+/-Lateral 1 (10%)	Anterior+/-Lateral 7 (47%) Posterior+/-Lateral 7 (47%)	0.092

location **	Posterior+/-Lateral 6 (60%) Other 3 (30%)	Other 1 (6%)	
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IQR = inter-quartile range; OHS = Oxford hip score

* Statistically significant ($p < 0.05$)

** Pseudotumour location was grouped into 3 for analysis purposes ("Other" includes anterior and posterior lesions, and isolated lateral lesions).

Table IV Diagnostic test characteristics using results from the initial assessment to identify asymptomatic pseudotumour patients subsequently requiring revision surgery

	Hips (%)	Sensitivity	Specificity	PPV	NPV
Blood metal ions > 5 µg/l	13 (52)	66.7 (38.4-88.2)	70.0 (34.8-93.3)	76.9 (46.2-95.0)	58.3 (27.7-84.8)
Blood metal ions > 7 µg/l	13 (52)	66.7 (38.4-88.2)	70.0 (34.8-93.3)	76.9 (46.2-95.0)	58.3 (27.7-84.8)
Blood metal ions > published levels *	12 (48)	66.7 (38.4-88.2)	80.0 (44.4-97.5)	83.3 (51.6-97.9)	61.5 (31.6-86.1)
Initial volume > 50 cm³	5 (20)	26.7 (7.8-55.1)	90.0 (55.5-99.7)	80.0 (28.4-99.5)	45.0 (23.1-68.5)
Initial volume > 30 cm³	10 (40)	60.0 (32.3-83.7)	90.0 (55.5-99.7)	90.0 (55.5-99.7)	60.0 (32.3-83.7)
Initial volume > 20 cm³	16 (64)	80.0 (51.9-95.7)	60.0 (26.2-87.8)	75.0 (47.6-92.7)	66.7 (29.9-92.5)
Blood metal ions > published levels * and/or initial volume > 30 cm³ **	16 (64)	86.7 (59.5-98.3)	70.0 (34.8-93.3)	81.2 (54.4-96.0)	77.8 (40.0-97.2)

PPV = positive predictive value; NPV = negative predictive value

All diagnostic test characteristic values are provided as percentages with 95% confidence intervals provided in brackets. The prevalence of asymptomatic pseudotumours subsequently requiring revision surgery for all clinical scenarios was 60%.

*Published blood metal ion thresholds were used which were devised from a large cohort of hip resurfacing patients, and which take into account whether patients had unilateral (cobalt > 4.0 µg/l and/or chromium > 4.6 µg/l) or bilateral (cobalt > 5.0 µg/l and/or chromium > 7.4 µg/l) metal-on-metal hip bearings [26].

** All possible combinations of blood metal ion and initial pseudotumour volume thresholds were analysed, but for simplicity only the combination producing the optimal diagnostic test characteristics have been presented.