Heavy reading in heavy metal
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Chapter 8

General discussion
The Orthopaedic Department of Isala hospital, Zwolle, the Netherlands implanted many large head metal-on-metal (MoM) prostheses from January 2005 till 2010. This resulted in 2012 in a publication in which we reported a high incidence of pseudotumour formation after large diameter MoM total hip replacement in our prospective cohort study.\(^1\) This publication added knowledge regarding classification and presentation of pseudotumour formation and showed that magnetic resonance imaging (MRI) was not favourable over computed tomography (CT) in detecting clinical significant capsular reactions.

The usability of CT and the observations regarding morphological reactive capsular changes laid the foundation for this thesis in which we described the role of CT in total hip arthroplasty (THA) in general and in the detection, stratification and incidence of pseudotumours, investigated the bone mineral density of the acetabular roof and quantified the positive effect of orthopedic metal artefact reduction post-processing protocol (O-MAR) on metal artefacts.

## THE ROLE OF CT IN THE DETECTION OF PSEUDOTUMOURS

Hitherto, surveillance of MoM THA and MoM hip resurfacing arthroplasties (HRA) patients is not evidence based.\(^2\) Factors that make it difficult to make guidelines concern different prosthetic devices, symptomatic versus non-symptomatic cases and above all there is a variety of imaging tools used. The imaging tools ultrasound (US), MRI, and CT all have been used to diagnose wear-related corrosion problems after hip arthroplasty. The relative advantages and disadvantages of these modalities remain a source of controversy.

### CT

The use of CT in Isala hospital, Zwolle, The Netherlands and Martini hospital, Groningen, the Netherlands to detect pseudotumours proved to be efficient and sufficient. Our results contributed to the debate on what screening modality could be used for detecting capsular pathological reactions (chapters 3 and 4).\(^1,3-5\) CT is a reliable method for the pre-operative evaluation of femoral head and neck deformities, for the diagnosis of femoro-acetabular impingement (FAI) either pre-operatively or post-resurfacing, and for diagnosing post-operative soft tissue reactions (chapter 2).\(^6\) When the ipsilateral knee is included, adequate measurement of femoral anteverision relative to the retro-condylar axis of the knee can be performed.\(^7\) CT can also be used for evaluation of the distinctive components and their underlying geometrical relations after the performed surgical procedure (chapters 2 and 3).\(^1,4,6,8-13\)
A disadvantage of a CT scan that is caused by the design of the scanner, is the finding that, in case of a CT scan made in supine position, measurements of the inclination and version of the acetabular component do not take into account the natural pelvic tilt. These measurements cannot be simply extrapolated to the standing position or compared to measurements on standing radiographs. Cone beam CT in standing weight-bearing position is available but only for foot, ankle and knees. The limited field of view in cone beam CT will obstruct the availability of cone beam CT for imaging of the hips.\textsuperscript{14-18}

In this thesis, we presented a CT classification of the hip capsule in capsular reactions detected after MoM THA which shows good intra- and interobserver reliability and is independently associated with revision surgery. In a multiple logistic regression prediction model including revision and several other unilateral significant MoM-related variables of interest, the simplified A-C classification showed to be the independent predictor for revision that is most likely not attributed to chance (chapter 3).\textsuperscript{4} Our CT classification can improve communication between the radiologist and the orthopedic surgeon in screening or follow-up populations and shows the importance of cross sectional imaging in detecting pathological capsular reactions that are possibly in need for revision.

**CT versus US and MARS-MRI**

CT provides several potential advantages over US. CT is less operator-dependent and it also provides information regarding component positioning.\textsuperscript{19} However, CT scans are limited in their ability to provide enhanced soft tissue contrast, they require ionizing radiation, and they have not yet been proven to predict the severity of tissue destruction intra-operatively as is the case for the use of MR.

Nam et al. stated in their review on the advantages and disadvantages of the different imaging modalities to diagnose MoM hip arthroplasty (HA) wear-related corrosion problems, that studies assessing the use of CT in the detection of adverse tissue reactions have been limited to cohort studies on consecutive patients, and that its sensitivity and specificity have not been directly compared with other imaging modalities.\textsuperscript{19} However, in 2012 Bosker et al. investigated the additional value of CT. In an initial screening of all patients with pseudotumours identified on CT and all patients with high serum ion levels, many complaints and no positive findings on CT underwent an additional MRI. No additional pseudotumours were identified with MRI. Therefore screening by means of MRI showed in this study no advantage over CT with regard to identification of those patients that were a candidate for revision.\textsuperscript{1}

In 2014 Robinson et al. investigated 50 MoM HA patients (30 female) with unexplained painful prostheses and these patients underwent metal artefact reduction sequences (MARS) MRI and CT imaging. CT was found to be superior to MRI for detection of
Discussion

Osteolysis adjacent to MoM HA, and should be incorporated into diagnostic algorithms. However, CT was unable to classify and failed to detect many pseudotumours, and it was unreliable for assessment of muscle atrophy. They concluded that where MARS MRI is contraindicated or unavailable, CT would be an unsuitable substitute and other modalities such as US should be considered. However, in this study old CT techniques were used without hybrid iterative reconstruction techniques and without dedicated CT metal artefact reduction (MAR) protocols making it in our opinion hard to properly compare these two modalities. Over the last five years we have invested in improving CT image quality using younger generation 256-multislice detector CT scanners, hybrid iterative techniques and MAR software. This has strengthened us in our idea that CT is an excellent, more cost effective alternative for MARS-MRI.

US, CT and MR

In summary, all three imaging modalities may have a role in the assessment of adverse local tissue reactions after THA. US may serve as a screening technique for the detection of larger periprosthetic collections and follow-up by US seems reliable enough in experienced hands. Only MRI has been shown to predict the severity of tissue destruction found at revision and correlate to the degree of tissue necrosis at histologic evaluation. CT has gained territory over the last two years due to improved imaging techniques, MAR protocols and our finding that the CT grading system showed highest correlation with revision surgery over other clinical parameters in one of the largest investigated homogeneous cohorts (chapter 3).

DISTINCTIVE MOM BEARINGS AND INCIDENCE OF PSEUDOTUMOURS

There are several distinctive MoM bearings available for the treatment of patients with osteoarthritis. Depending on the MoM implant used, more or less pseudotumour formation can be expected. In this thesis we investigated the Birmingham hip resurfacing (BHR) MoM HRA. We compared our findings with the Biomet M2a-Magnum/ReCap MoM because both cohorts were screened by means of CT and read with the use of the same CT classification. Pseudotumours were detected on CT scans of 28 % of the patients that underwent BHR (chapter 4). Most pseudotumours (72.5 %) in THA BHR were asymptomatic. Failure of the BHR implant occurred in 5.6 % of the patients due to a symptomatic pseudotumour after an average follow-up of forty-one months. This was substantially lower than the incidence of pseudotumour formation (39 %) and subsequent revision (12 %) found with the Biomet M2a-Magnum/ReCap MoM. In 2016 Matharu et al reported a higher incidence of 11.2 % failure and subsequent revision due to pseudotumour formation in MoM HRA than Bisschop et al.
MC et al. recently published the result of 160 MoM THAs implanted in their clinic from 2006-2010. In total, 13 (8.1 %) of the THAs were eligible for revision after the recall. In most patients the reason for revision was pseudotumour formation. A total of 14 (8.75 %) pseudotumours were diagnosed at the first recall. The revision percentage is in line with our findings. The detection of capsular abnormalities however is higher in our cohort. This seems to indicate the strong capacity of CT in detecting capsular abnormalities. Overall, these results show that a comprehensive follow-up strategy is essential for MoM THAs to promptly identify and manage early complications.

A full comparison between the different types of MoM bearings is beyond the scope of this thesis but it is clear that design is an important factor.

Interestingly, it was recently shown in a randomised controlled trial (RCT) that pseudotumour formation is not solely confined to MoM bearings. Van der Veen et al. found that when the established vigorous CT pseudotumour protocols designed for MoM THA are applied to patients with a metal-on-polyethylene (MoP) articulation, 20 % are likely to be diagnosed with a pseudotumour.

Several risk factors for developing a pseudotumour such as component positioning, gender, elevated serum ion levels, clinical complaints were identified and investigated in numerous studies. We found, however, that in the decision process for revision, imaging seems to be the most important predictor of all different THA related parameters investigated (chapter 3). Serum ion levels such as cobalt and chromium are poor unique predictors for pseudotumour presence. Importantly, pain seems to be an important predictor besides imaging results and hence further investigations in these patients is warranted. Even in the presence of normal ion levels, radiological imaging is considered mandatory as strong capsular reactions can be present without complaints. This was recently confirmed by Hjorth et al. They found no association between pseudotumour formation and serum metal-ion levels, metal patch test reactivity, and atopic dermatitis in 5-7 years follow-up. In addition, Liow et al. recently found that there was no significant correlation between aseptic lymphocytic vasculitis-associated lesions (ALVAL) scores and prerevision surgery, metal ion levels or intraoperative tissue damage, suggesting that the biological mechanism of histologic morphology cannot be solely attributed to elevated metal ion levels and is likely multifactorial, reflecting a complex interplay between implant and patient factors. Nevertheless, we have shown that there seems to be a high concordance between a morphological detectable reactive capsule and serum ion levels in a large screening cohort (chapter 3). The perceived importance of elevated ion levels in these patients by clinicians and patients
was confirmed in a systematic review on metal ion concentrations in body fluids after implantation of hip replacements with MoM bearing. In this review it was concluded that after hip replacement with contemporary MoM bearings the release of metal ions is highest in stemmed implants with large heads followed by resurfacing devices and also - but on a lower level - small heads. The authors of this review concluded that deposition of metal products may not only lead to local but possibly also systemic adverse health outcomes.

**REVISION AND BONE MINERAL DENSITY**

Revisions are being undertaken mainly when complaints, capsular reactions and high serum ion levels are present. The main reason for this reticence is the high impact on the patient.

In addition to the consequences of revision, the revision itself is also a challenge. Due to the increasing number of THAs, the amount of hip revision procedures continues to rise. Careful patient selection and bone loss evaluation is crucial for a correct management of femoral revision procedures. The key point in femoral revision is to obtain a reliable primary stability of the stem, with the least invasive implant as possible, to preserve and if possible to restore the bone stock. In the various MoM THA populations assessing bone stock is of interest to the orthopaedic surgeon when planning the surgical revision procedure in which it is necessary to restore the acetabulum with plates and screws and in some cases transplantation of autologous bone after excision of the cup.

Because of the MoM THA screening program we had access to numerous CT scans with a unilateral MoM THA. This gave us the opportunity to investigate whether bone mineral density (BMD) can be quantified using conventional CT. We showed that there is no need to use an external phantom to quantify CT BMD measurements of body tissue (chapter 5). Furthermore, a statistically significant bone density difference was found by means of CT analysis when the MoM THA implanted hip was compared with the contralateral side. Pseudotumour formation did not correlate with bone density differences. Only the in situ time of the MoM THA showed a significant correlation with the bone density difference (chapter 6). Another way to use CT for bone integrity assessment was introduced by Pitto et al. They used quantitative CT-assisted osteodensitometry to predict bone remodeling and the quality of implant fixation using prostheses with different design and / or biomaterials. Quantitative CT-assisted osteodensitometry provides three-dimensional (3D) volumetric analysis with a standard CT scanner protocol. Additional software measures the relative density of the bone in Hounsfield units (HU) of each CT slice. A calibration phantom with a cylindrical section...
with a known content of hydroxyl-apatite is needed and scanned together with the patient. This allows conversion of radiological density measurements to true volumetric mineral density measurements (mg CaHA/ml). In the future, this tool could be used for pre-clinical validation of new implants before their introduction on the market.\textsuperscript{32}

Conversion of radiological density measurements into true volumetric mineral density measurements might also be the case for conventional non-iodine CT scans because in CT the contrast to noise ratio (CNR) and overall image quality seems to improve with each CT scanner generation including newly implemented iterative reconstruction protocols. We have shown that no phantom is needed with the phantomless bone mineral density (PLBMD) method (chapter 5).\textsuperscript{30}

We believe that in the future a conventional non-iodine CT scan will provide the orthopaedic surgeon with information whether there is a need for harvesting bone in order to reconstruct the acetabulum. Nevertheless, a reference standard needs to be developed for age, gender and body mass index (BMI) if we want to measure BMD in the pelvis without the use of an external phantom (chapter 5 and 6).\textsuperscript{30,31}

**Follow-up**

After the first screening round there was a substantial percentage of patients without capsular reactions and a smaller percentage of patients with pathological capsular reactions that did not meet the criteria for revision or who did not want to be revised. Therefore, we do not know the natural history in extenso of the capsular reactions from available large screening prospective cohort studies yet. There is also no international consensus on follow-up schemes yet. All data presented in this thesis are from a first line screening protocol. In a time course analysis based on CT results in a cohort of 706 hips it was estimated that the majority of Isala patients implanted with a MoM THA is likely to develop a pseudotumour in the near future.\textsuperscript{24} Future follow-up studies will show whether the estimation in this study population is indeed correct. A 10 year follow-up study of the Isala population will soon add knowledge on the progression of capsular pathology over time in a population that was initially screened by CT.

Kwon et al. recently found that the natural history of type I cystic pseudotumours continues to be nonprogressive in most “asymptomatic” MoM HA patients at minimum 4 years, indicating the importance of patient symptoms and MRI characteristic features in the clinical decision-making process. Routine follow-up MARS-MRI evaluation of “asymptomatic” patients with low-grade cystic pseudotumours in the absence of interval clinical changes may therefore not be indicated.\textsuperscript{33} Low et al. used US for follow-up and found ultrasonic progression in 19 % of cases.\textsuperscript{2} Briant-Evans et al. used MRI for follow-up and found 10 % of cases to be progressive.\textsuperscript{34} In asymptomatic cases van der Weegen et al. found little change within one year after MoM hip resurfacing with the use of MARS-MRI.\textsuperscript{35} Based on the expected small chance on progression after a
short interval we decided to follow-up our patients using CT at 1 year for identifying immediate positive cases and 5 and 10 years for patients that did not receive a revision after one year.

The question on mechanism of failure in MoM HA defined as a need for revision has been extensively investigated over the last years. This question is recently eloquently addressed by Langton et al. in 2016 in BMJ open. It appears to depend in summary on four factors: device-related factors regarding design, device related factors regarding manufacturing, surgical factors and host factors.25

**O-MAR**

Metal artefacts cause a large disturbance in the image which make it often impossible for the radiologist to assess the surrounding soft tissues and also the surrounding bone. Up to 2010 the communis opinion amongst radiologists regarding the pelvis with pelvic implants was that these CT scans were almost unable to be read due to the metal artefacts. The improvement in CT hardware and subsequent evolution of reconstruction methods such as hybrid iterative reconstruction techniques and full model-based iterative reconstruction (MBIR) techniques have increased CNR and seem to decrease metal artefacts. Newly introduced MAR techniques immediately show their subjective advantage since black areas in the CT scan without any information become suddenly visible.

Quantification of the strength of the MAR technique was nevertheless not yet established. We found that a significant reduction of metal artefacts that were caused by MoM THA, was dependent on the amount of disturbance in attenuation caused by the metal artefacts and relatively improved between 32 and 68 % using O-MAR. O-MAR showed a significant improvement in CNR as well. The improvement in CNR was also dependent on attenuation disturbance by the metal artefact and varied between 52 and 72 % *(chapter 7)*.36

Whether spectral CT imaging alone without dedicated MAR protocols is superior to conventional CT imaging that can make use of established dedicated metal protocols, needs to be investigated in the future.

**FUTURE PERSPECTIVE OF MOM THA IMAGING**

It would have been interesting to combine our CT scans with PET imaging by means of photon emission tomography (PET) CT instead of CT alone to study the inflammatory activity of the hip capsule, as well as bone single photon emission computed tomog-
raphy (SPECT) CT to study local bone activity around the implant.\(^{37-39}\) In this way we would have gained insight in the inflammatory nature of the morphological changes of the hip capsule, which in turn potentially discriminates active lesions from steady state lesions.

Due to increased computing power by the latest Teraflop processor chips that were introduced recently, even a full iterative reconstruction technique, Iterative Model based Reconstruction (IMR), became available. In 2011 IMR showed already the potential of clinically acceptable reconstruction times with an image quality better than achieved before.\(^{40}\) Nowadays there are several publications on the effect of IMR on image quality and its capacity to reduce dose.\(^{61-66}\) The combined improvement in hardware and software has improved the quality of CT scans dramatically. The combination of O-MAR and IMR has the potential to further improve visualisation of surrounding tissue in CT scans containing metal implants.

A recent study of Boudabbous et al. (2015) showed that MBIR reduces the size of metal artefacts on CT images and allows a better analysis of the soft tissue surrounding the metal implant when compared with Filtered Back Projection (FBP).\(^{47}\) This is the only study investigating metal artefacts using MBIR, however without the use of MAR software and without investigating dose reduction capabilities. Boudabbous et al. (2015) found that boundaries between water and the pellets and between the prosthesis and the surrounding water seem to be sharper.\(^{47}\) Dedicated metal artefact post processing protocols improve CNR and decrease metal artefacts even more.\(^{48-58}\) Therefore, overall CT quality will improve, and reading MoM related disease in CT will be less challenging for the general radiologist.

Thus the use of up-to-date model-based iterative reconstruction techniques allows significant dose reduction while maintaining and even increasing image quality resembling state of the art imaging of the pelvis with large metal implants.\(^{21,44}\) In combination with dedicated MAR post processing software IMR has the potential to improve readability of the pelvis with metal hip implants dramatically.\(^{44}\) Unfortunately, this is not widely implemented yet because it is more expensive than current CT imaging and it needs extra investments from health institutions and their subsequent imaging departments who already need to reduce costs for each scan due to relative budget cuts in a demographically aging population. Nevertheless, in general over time multiple detector computed tomography (MDCT) systems have become more widely available and reconstruction techniques necessary to create images from rough physical photon-extinction data evolved from FBP to iDose\(^{4}\) (hybrid iterative reconstruction technique).

Various dual energy CT techniques that are already available have decreased metal artefacts in comparison to conventional CT imaging. Overall image contrast may be reduced when optimizing MAR using dual energy techniques. These techniques only do not handle photon starvation.\(^{48,50,52,54,59-67}\)
The next step in combining spectral monochromatic CT imaging techniques with dedicated MAR protocols has been taken by GE and Siemens. This is not commercially available yet for the dual detector CT technique of Philips. Now that we have used different photon energies to reconstruct images from distinctive extinction data, the next step could be to actually count the amount of photons that reach the detector from a certain energy level and use this information in addition to reconstruct images. This photon counting technique in CT is a recent, highly experimental CT technique. Nevertheless, theoretically it is very promising because photon counting will give the preferred input to reconstruction techniques to only use information from those photons one wants to use for reconstructing images in the total spectrum of photons generated.

Overall, we can be confident that in the future better images will be available with further radiation dose reduction: We will just see more with less dose. Heavy reading in metal implants will be something we can leave behind us in the future because of the recent CT developments.

O-MAR holds an unique place amongst the newly developed CT techniques as it handles photon starvation. Being more able to actually read the CT scans of the pelvis in large metal implants will pave the way for future readers to truly quantify their observations in CT and thus unravel current mysteries of changes of body tissue after THA in general.
REFERENCES


