Fixation and Migration in Total Hip Arthroplasty

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UNIVERSITY OF GOTHENBURG

Gothenburg 2025

Cover illustration: ‘’Mathematics of Motion’’ by Vasileios Angelomenos

Illustrations: Vasileios Angelomenos

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ISBN 978-91-8115-495-5 (PRINT)
ISBN 978-91-8115-496-2 (PDF)

Printed in Borås, Sweden 2025
Printed by Stema Specialtryck AB

We are what we repeatedly do. Excellence, then, is not an act, but a habit.

– Aristotle

The same sun that melts the wax, hardens the clay.

– Nigerian saying

All models are wrong…but some are useful

– George P. Box

I would like to dedicate this PhD thesis to my wife Daryna and my daughter Eva Lydia for their support and love throughout this voyage of research.

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ABSTRACT

Early implant migration in cemented total hip arthroplasty (THA) is a strong surrogate for later aseptic loosening; thus, precise, repeatable micromotion measurements are central to safe, stepwise evaluation of new cements and emerging imaging methods. This thesis addresses two linked needs: (i) clinical and experimental validation of low-dose CT–based radiostereometric analysis (CT-RSA) compared to marker-based RSA (MBRSA), and (ii) RSA-based, randomized comparison of a reformulated gentamicin-loaded cement (Refobacin Bone Cement R, 2016) versus the widely used Palacos R+G.

Study I was a prospective sub-study that showed that CT-RSA matched MBRSA for assessing acetabular cup migration, with precision and method agreement within clinically relevant bounds at 1 year.

Study II was a single-centre randomized comparison of Refobacin Bone cement R and Palacos R+G, also examining two vacuum mixing systems. 2-year femoral stem subsidence, cement mantle quality, stem alignment, and patient-reported outcomes (PROM) were similar across groups, no revisions occurred, and mixing system choice had no measurable effect.

Study III was a second prospective sub-study that found CT-RSA comparable to MBRSA for measuring femoral stem subsidence at 1 year, meeting a predefined minimal important difference. Moreover, CT-RSA demonstrated excellent intra- and inter-observer reliability.

Study IV was an experimental phantom study with controlled known translations that confirmed sub-tenth-millimetre precision and accuracy for CT-RSA and excellent observer reliability; performance was maintained even after coordinate-system transformation.

In conclusion, across clinical and experimental settings, CT-RSA provided cup and stem migration measurements comparable to MBRSA, with good clinically relevant precision and excellent intra-/interobserver reliability, while enabling a marker-free workflow. The reformulated Refobacin Bone Cement R performed equivalently to Palacos R+G at 2 years with a force-closed stem and cement and mixing system choice did not influence migration or PROM. Taken together, these studies support CT-RSA as a validated alternative for early migration surveillance in cemented THA and reaffirm the value of RSA-based, stepwise introduction when assessing new cements and measurement methods.

Keywords: Total hip Arthroplasty, Migration, Radiostereometric Analysis, CT-based, RSA, CT-RSA, Cement, Precision, Accuracy, Reliability, Agreement.

ISBN 978-91-8115-495-5 (PRINT)
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1 SAMMANFATTNING PÅ SVENSKA

Artros i höften behandlas ofta med total höftartroplastik (THA). För cementerade implantat är tidig mikrorörelse en etablerad prediktor för framtida lossning, vilket gör exakta migrationsmätmetoder avgörande. Guldstandard är markörbaserad radiostereometri (MBRSA), men lågdos-CT-baserad RSA (CT-RSA) kan erbjuda en markörfri och mer tillgänglig metod om den valideras kliniskt. Avhandlingen bygger på fyra studier. Studier I–III ingick i en prospektiv, randomiserad "Cementstudie" vid Sahlgrenska Universitetssjukhus. Patienterna fick cementerad THA och randomiserades till operation med Palacos R+G eller Refobacin Bone Cement R och följdes upp i 2 år. En fördefinierad subgrupp genomgick även CT-RSA i Studie I och III. Studie IV var en kontrollerad in-vitro studie.

Studie I jämförde CT-RSA och MBRSA för cementerade acetabulära cuppar. CT-RSA uppvisade precision i nivå med MBRSA och likvärdiga mätningar av proximal/distal migration vid 1 år.

Studie II jämförde migration av stammen när det omformulerade Refobacin cement används gentemot Palacos R+G. Vid 2 år sågs inga signifikanta skillnader i stammens migration mellan de olika cementgrupperna, patientrapporterade utfall (PROM) förbättrades likartat och inga revisioner rapporterades.

Studie III jämförde MBRSA och CT-RSA avseende stammens migration och bedömde CT-RSAs observatörsreliabilitet. Metoderna överensstämde väl vid 1 år och CT-RSA hade utmärkt intra-/interobservatörsreliabilitet.

Studie IV fastställde CT-RSAs mätprestanda avseende precision, noggrannhet och reliabilitet under kontrollerade förflyttningar.

Sammanfattningsvis CT-RSA mäter cup- och stammigration jämförbart med MBRSA och med mycket hög reliabilitet, samtidigt som arbetsflödet förenklas genom markörfrihet. Refobacin visade fixationsprestanda motsvarande Palacos R+G och val av cement påverkade varken migration eller PROM. Samlat stöder arbetet CT-RSA som ett validerat alternativ för tidig migrationsövervakning i THA och belyser värdet av en stegvis, RSA-baserad introduktion av nya cement och mätmetoder.

2 LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Angelomenos V, Mohaddes M, Itayem R, Shareghi B. Precision of low-dose CT-based micromotion analysis technique for the assessment of early acetabular cup migration compared with gold standard RSA: a prospective study of 30 patients up to 1 year. *Acta Orthopaedica.* 2022 Apr 22;93:459-465.

II. Angelomenos V, Mohaddes M, Kärrholm J, Malchau H, Shareghi B, Itayem R. A prospective randomized study of Refobacin Bone Cement R versus Palacos R + G. *The Bone & Joint Journal*. 2024;106-B(5):435-441.

III. Angelomenos V, Shareghi B, Itayem R, Mohaddes M. Comparison of the CT-based micromotion analysis method versus marker-based RSA in measuring femoral head translation and evaluation of its intra- and interobserver reliability: a prospective agreement diagnostic study on 27 patients up to 1 year. *Acta Orthopaedica*. 2025 Jan 9;96:38-44.

IV. Angelomenos V, Shareghi B, Mohaddes M, Malchau H, Kärrholm J, Itayem R. Evaluating precision, accuracy, and observer reliability of CT-RSA in measuring implant migration in total hip arthroplasty: an in vitro study. *Submitted.*

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4 ABBREVIATIONS

THA	Total Hip Arthroplasty
RSA	Radiostereometric Analysis
CT	Computed Tomography
CT-RSA	Computed Tomography Radiostereometric Analysis
CTMA	Computed Tomography Micromotion Analysis
MBRSA	Marker-Based Radiostereometric Analysis
HU	Hounsfield Units
MAR	Metal Artefact Reduction
CN	Condition Number
ME	Mean Error of rigid body fitting
COM	Centre of Mass
MPR	Multi-planar Reconstruction
SD	Standard Deviation
LoA	Limits of Agreement
HHS	Harris Hip Score
OHS	Oxford Hip Score
FJS	Forgotten Joint Score
UCLA	University of California, Los Angeles Activity Scale
IQR	Interquartile Range
ICC	Intraclass Correlation Coefficient
PROM	Patient Reported Outcome Measures

ASA	American Society of Anaesthesiologists
ANOVA	Analysis of Variance
ISO	International Organisation for Standardization
ED	Effective Dose
PMMA	Polymethyl Methacrylate
AI	Artificial Intelligence
CI	Confidence Intervals
GRAAS	Guidelines for Reporting Reliability and Agreement Studies
SPSS	Statistical Package for the Social Sciences
RMSE	Root Mean Square Error
CCD	Caput–Collum–Diaphyseal angle of the femur
FEA	Finite Element Analysis

5 DEFINITIONS IN SHORT

Aseptic loosening	Aseptic loosening refers specifically to the mechanical failure of the interface between the implant and the bone in the absence of infection.
Mean error (ME) of rigid body fitting	A metric used in RSA to describe the stability of the marker beads within a rigid body. In general, an upper limit of ME of 0.35 is recommended [1,2].
Condition number	A metric used in RSA that describes the scattering of the marker beads in the bone. A low CN denotes good scattering. In general practice CN below 150 or even lower are recommended. CNs of 100-120 are considered reliable for the detection of implant migration [1,2].
Subsidence	Distal migration of a femoral implant; in the context of this thesis, it corresponds to negative translation on the Y-axis.
Force-closed stem	Polished, tapered cemented stem concept where controlled distal migration within the cement mantle is expected over time, where the stem wedges into the cement, creating a balance of forces for fixation.
Shape-closed stem	Stem concept designed to mechanically interlock with cement, theoretically limiting subsidence compared with force-closed designs.
Centralizer	Distal implant component that centres the stem in the canal and integrates with the cement mantle during polymerization.

Barrack grades (A–D)	Radiographic grading of cement mantle quality from complete fill (A) to deficient mantle/100% radiolucency (D) [3].
Bland–Altman plot	Statistical method to assess agreement between two measurement techniques by plotting differences vs. means and deriving LoA.
Intraclass correlation coefficient	Reliability index for intra-/interobserver agreement.
Minimal important difference	Pre-specified threshold regarded as clinically/analytically meaningful.
Hounsfield Unit	CT density scale.
Metal artefact reduction	CT acquisition/reconstruction techniques that reduce metal-induced artefacts, enabling lower dose and better segmentation.
DICOM coordinate system	Standard imaging coordinate system used by CT.
Uniplanar calibration cage	Radiographic frame used in marker-based RSA to establish a calibrated 3D coordinate system for precise migration measurements.
Point-motion analysis	RSA measurement variant where a single anatomical point (here the femoral head centre) is tracked relative to bone markers.

6 INTRODUCTION

Total hip arthroplasty (THA) is one of the most successful interventions in modern orthopaedic surgery, significantly improving patients' quality of life through the restoration of joint function and relief from debilitating pain [4] with a 10-year survival rate exceeding 95% for the usual THA candidate [5]. Despite these facts and widespread implementation, challenges related to implant stability, migration, and long-term survivorship continue to persist. These challenges often entail revision surgeries, which carry increased risks and socioeconomic burdens for both patients and healthcare systems. Thus, a deeper understanding of implant stability and early migration patterns is imperative for improving outcomes and reducing revision rates.

The evaluation of early implant migration has been identified as a critical predictor of implant longevity. Studies have consistently demonstrated a strong correlation between early implant migration within the first two postoperative years and subsequent loosening and failure [6,7]. Therefore, accurate and early detection of implant migration could improve clinical outcomes by enabling timely intervention strategies and implant selection, potentially extending implant longevity and improving patient prognosis.

6.1 CURRENT DIAGNOSTIC APPROACHES AND LIMITATIONS

Radiostereometric analysis (RSA) remains to this day the gold standard for measuring implant micromotion due to its high accuracy and precision. Marker-based Radiostereometric Analysis (MBRSA) requires the insertion of tantalum markers into the bone and implant and requires an RSA laboratory, trained personnel, and specialized RSA software [8]. Despite its high precision, MBRSA's clinical application may be limited by logistical and practical implications, such as the invasive placement of markers and the availability of specialized RSA laboratories. In addition, the marker placement can occasionally affect measurement accuracy due to poor visibility or inadequate distribution of the tantalum markers. This issue became, though, less relevant with the introduction of Model-based RSA [9].

In contrast, Computed Tomography Radiostereometric Analysis (CT-RSA) has emerged as a promising, less invasive alternative, offering comparable results to MBRSA without requiring tantalum markers [8,10–14]. CT-RSA uses standard clinical CT equipment, and low-dose scan protocols, facilitating

wider adoption and possibly less complicated implementation. CT-RSA has, thus been proposed as an alternative to conventional MBRSA.

Despite these facts, comprehensive clinical validation remains necessary to establish the equivalence of CT-RSA to RSA across various joints, fixation methods and implants. Such validation is essential to justify broader research clinical adoption and establish new diagnostic standards that could influence future clinical guidelines and practices.

6.2 IMPLANT MIGRATION AND RISK OF ASEPTIC LOOSENING

Implant migration, defined as the displacement of an implant relative to the host bone after implantation, is a critical predictor of the long-term success and stability of orthopaedic implants. Early migration in the context of total hip arthroplasty, particularly during the initial two postoperative years, has consistently been identified as a predictive factor for aseptic loosening [6,7,15], one of the most common reasons for implant failure. Numerous clinical studies have demonstrated that implants with minimal early migration exhibit significantly lower risks of long-term aseptic loosening compared to those exhibiting pronounced early migration, particularly distal migration for femoral stems and proximal and rotational instability for acetabular cups [6,7,15].

This type of loosening arises from a complex interaction of biomechanical factors such as inadequate initial fixation, continuous micromotion, and biological responses including bone remodelling and inflammatory reactions to wear debris and particulate materials. The initiation of aseptic loosening frequently begins with subtle, often clinically undetectable, micromotions at the implant-bone interface in uncemented THA or implant-cement-bone interface in cemented THA.

In detail, aseptic loosening of a cemented femoral component begins with intraoperative cement interdigitation and a continuous cement mantle that provide primary mechanical fixation [16]. During early cyclic loading, small micromotions develop at the stem- or cup–cement interface and/or cement–bone interfaces (polished tapered stems may allow controlled stem–cement micromotions [17,18], whereas mantle defects or poor interdigitation shift harmful shear to cement–bone [19]). Repeated motion pumps fluid along small interface gaps [20], transports wear debris and mechanically irritates tissues causing inflammation. Cement microcracking and fretting start to

generate PMMA/metal/polyethylene particles [19,21] that sustain the inflammatory process [22]. Persistent micromotion allows the formation of a low-stiffness fibrovascular membrane between the interfaces [23], which further decreases interface interlock. Progressive debonding at either interface amplifies subsidence, while cyclic stresses and stress risers produce cement fatigue and cement fractures. At the same time, particle-stimulated macrophage/osteoclast activity leads to periprosthetic osteolysis [23], reducing structural support and escalating micromotions (Figure 1). Loss of structural support in the bone further yields progressive migration/subsidence, varus tilt, and/or retroversion rather than benign early settling, with radiographs showing widening radiolucent lines, calcar resorption, and further cement mantle fractures. Clinically, pain under load and continued migration on radiography [6,7,24] signal failure of stable fixation in the absence of infection, i.e., aseptic loosening.

In summary, persistent implant migration beyond the initial stage of fixation inhibits the establishment of robust and stable biological fixation, ultimately resulting in progressive loosening and potential implant failure. Consequently, the early detection of implant migration serves as an important prognostic indicator, enabling identification of high-risk implants early in the postoperative course, thereby allowing timely interventions.

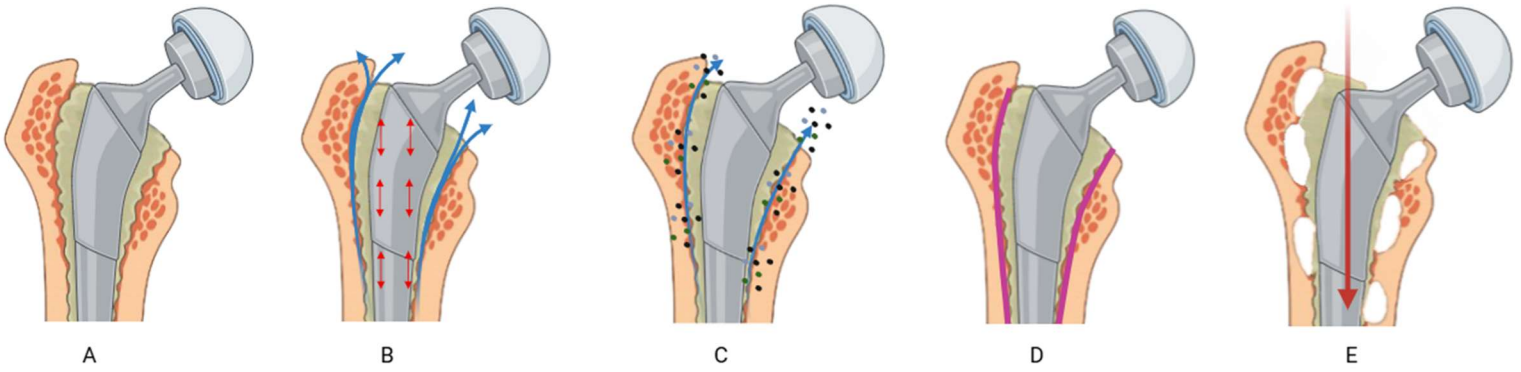

Figure 1. (A) Pressurized cement interdigitation and an intact cement mantle provide primary mechanical fixation. (B) Early cyclic loading induces small interface micromotions (red arrows) that 'pump' fluid (blue arrows) along interface gaps. (C) Cement microcracking and fretting release particles (wear debris) that are dispersed by fluid flow. (D) Persistent motion forms a low-stiffness fibrovascular membrane (purple curved line) and accelerates cement fatigue and interfacial debonding. (E) Particle-driven osteolysis reduces structural support, leading to progressive subsidence/tilt and aseptic loosening.

6.3 THE ROLE OF BONE CEMENT IN IMPLANT MIGRATION

Bone cement—most commonly polymethyl-methacrylate (PMMA)—is a key component in fixating implants during cemented total hip arthroplasty (THA). Rather than acting as an adhesive, its main role is to create a mechanical interlock between the implant surface and the surrounding bone. This interlock provides the initial stability needed for successful fixation and helps distribute physiological loads efficiently from the implant to the bone.

Although commonly called "bone cement," polymethyl-methacrylate does not actually bond to bone. Instead, once injected it flows into the trabecular bone network and around the implant, hardening into a grout-like mantle that locks the stem mechanically to the surrounding cancellous network. A dense, well-interdigitated micro-interlock is crucial as it spreads physiological loads more uniformly from prosthesis to bone, dampens repetitive stress peaks, and thereby limits formation of a fibrous layer at the bone-cement interface (as described previously); changes that predispose to

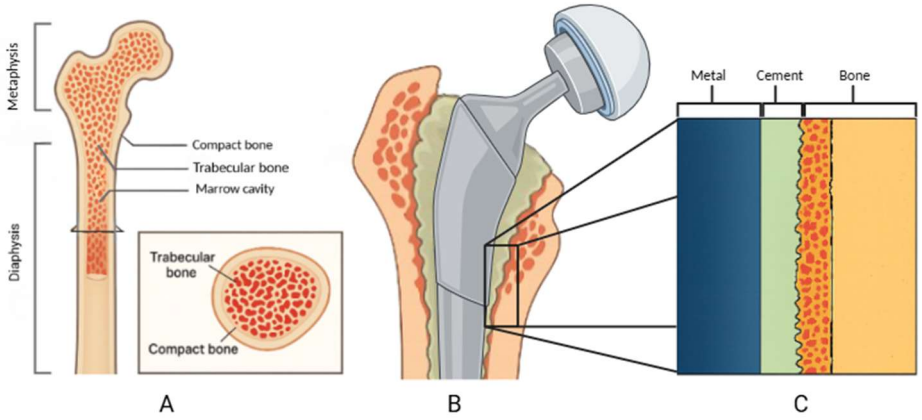

Figure 2 (A) Cross-sectional anatomy of the proximal femur with cortical shell and trabecular network. (B) Cemented femoral stem seated within a PMMA mantle. (C) Enlarged section of the metal–cement–bone interfaces showing PMMA interdigitating into cancellous bone, forming a mechanical micro-interlock that stabilises the stem and distributes load.

cemented-stem loosening [25,26]. Moreover, the exothermic polymerization of PMMA can present risks. During curing, temperatures can exceed 70°C, potentially causing thermal necrosis of the surrounding bone tissue. This

thermal damage can weaken the bone-cement interface, increasing the risk of micromotion and subsequent implant loosening [27].

Advancements in bone cement formulations aim to address these challenges. Incorporating additives such as phase-change materials and nanoparticles has shown promising results in reducing the exothermic peak during polymerization, thereby mitigating thermal damage. Additionally, techniques like vacuum mixing and pre-cooling of cement components have been used to enhance the mechanical properties of the cement and reduce porosity, further improving implant fixation [27].

In theory, minor modifications to cement composition may, though, influence polymerization, mechanical strength, antibiotic elution, and, consequently, the clinical performance of the implant [28,29]. Modifications to bone cement, such as the addition of antibiotics or alterations in formulation (e.g., viscosity [30], monomer ratio [31], radiopacifier content [32]), have been extensively studied and generally show no detrimental effect on implant stability, early micromotion, long-term migration and subsequently implant survival in cemented arthroplasty, provided that appropriate cementing techniques are applied [33]. While excessive antibiotic loading can compromise mechanical properties, commercially premixed antibiotic cements at standard doses maintain structural integrity and meet ISO strength requirements [34,35].

Summarizing the above, bone cement plays a critical role in implant stability in THA by minimizing micromotion and enabling effective load transfer. Modifications to its components—such as changes in monomer ratio, filler content, or additives—can influence setting characteristics, thermal behaviour, and mechanical properties. Continued research into these compositional adjustments is key to improving the safety, handling, and long-term performance of cemented fixation in orthopaedic surgery.

6.3.1 REFOBACIN BONE CEMENT R

Refobacin Bone Cement R is a high-viscosity, gentamicin-loaded PMMA cement developed for use in fixation of cemented implants. It was introduced in 2005 in order to replace the original cement Refobacin Palacos R and further modified in 2016 with a minor alteration of the powder component. As the successor to the widely used Refobacin Palacos R, this new formula was introduced to comply with contemporary regulatory requirements and changes in manufacturing processes affecting

both monomer and polymer components. Despite modifications in the formula [29], the cement was assumed to have similar biomechanical properties to those of its predecessor, although previous in-vitro studies suggested that this may not be the case [29].

Research on new bone cement formulations remains of vital importance. Although established antibiotic-loaded PMMA cements like the previous Refobacin Palacos R and the newer Palacos R + G have demonstrated long-term clinical success, changes in raw materials or production methods - as seen in the development of Refobacin Bone Cement R - necessitate careful clinical evaluation. Regulatory shifts and supply chain modifications have made the reformulation of previously established cements increasingly common. With that said, even subtle alterations to cement composition can affect polymerization behaviour, mechanical integrity, antibiotic release kinetics, and ultimately clinical performance [28,34,36].

Given the strong association between early implant migration and the long-term risk of aseptic loosening, it is essential that new or modified cements undergo rigorous preclinical and clinical assessment. Total hip arthroplasty requires long-term implant stability to be successful, and the bone-cement interface is crucial for the success of cemented fixation. Thus, every change in cement chemistry and composition must be scrutinized through high-precision tools such as radiostereometric analysis (RSA) to ensure it does not negatively impact the stability of implant fixation.

Investigating new cements such as Refobacin Bone Cement R, is therefore not only justified but essential. As highlighted in Study II later on, the introduction of new cement formulations should always be accompanied by clinical trials evaluating their influence on implant migration, handling characteristics, and other performance-related outcomes. This ensures that any new product meets the same standards of safety and efficacy as its predecessors, thereby maintaining the reliability of cemented fixation in joint replacement surgery.

6.4 MARKER-BASED RSA

Since its introduction by Selvik in the 1970s, MBRSA has become the orthopaedic gold standard for quantifying three-dimensional micromotion of joint implants in vivo. By implanting tantalum beads in bone, cement and/or prosthesis and analysing paired stereoradiographs, the method

achieves high precision and accuracy, repeatedly confirmed in older and contemporary studies [37].

Over the past five decades MBRSA has provided a unique early-warning system for aseptic loosening. Meta-analyses and registry studies demonstrate that excessive migration within the first 6–24 months—commonly distal, respectively proximal translations of 0.2–1 mm for hip stems or cups—predicts later revision with high sensitivity [1,6,38–41]. These predictive capabilities underpin the ISO 16087:2013 [2] standard and the stepwise "safe introduction" framework now required for novel implants in Scandinavia and beyond.

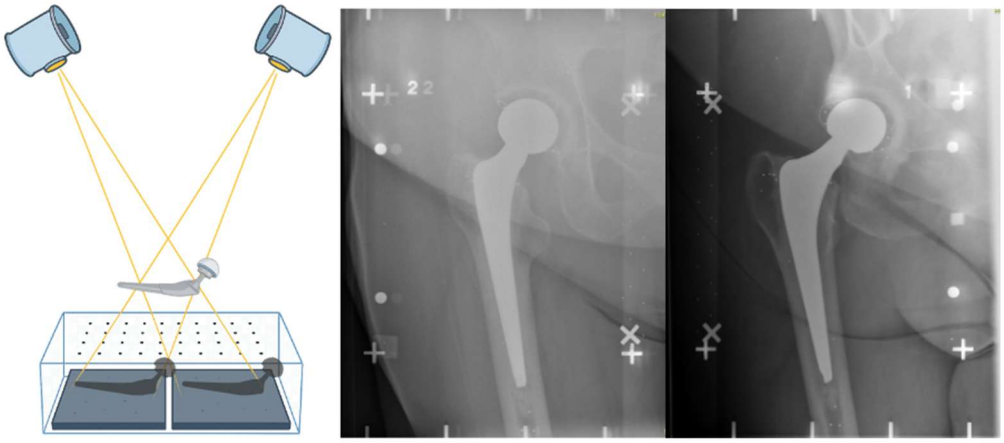

Figure 3 (A) Schematic representation of the usual RSA setup: two synchronised X-ray tubes are positioned obliquely at 45° to each other and centred on the implant. The limb is placed inside a rigid calibration cage containing fiducial markers that define the global 3D coordinate system and solve tube geometry. Simultaneous biplanar exposures produce paired images from which the software reconstructs the 3D positions of tantalum markers (marker-based) or the implant model (model-based) and computes migration between follow-ups (B) Example stereoradiographs showing the femoral stem with cage markers visible, used to reconstruct 3D geometry and quantify implant migration.

Technological refinements—digital detectors, uniplanar cages, automated bead localisation—have preserved sub-millimetre accuracy while reducing

radiation doses. Consequently, RSA has evolved from an experimental tool into a regulatory surrogate endpoint: small, well-powered RSA cohorts can forecast long-term survival of implants years before conventional registry signals emerge [42]. This body of evidence has played a key role in shaping implant design—such as the use of polished force-closed stems, cross-linked polyethylene liners, and porous surface coatings—and continues to serve as a benchmark for evaluating implant migration using newer imaging techniques.

In summary, five decades of high-precision data confirm that MBRSA remains indispensable for the early detection of mechanically at-risk implants, and the acceleration of evidence-based innovation in arthroplasty [37].

6.4.1 LIMITATIONS OF MARKER-BASED RSA

Despite its high precision and accuracy, MBRSA carries a set of methodological and practical shortcomings that have increasingly motivated the search for alternative migration-monitoring tools.

Invasiveness and implant restrictions: The technique requires intra-operative insertion of 0.8–1 mm tantalum beads into both host bone and cement and, in many protocols, the implant itself [1,42,43]. This prolongs the operating time, is not feasible for all implant geometries [44], and precludes retrospective analyses of already-implanted devices [8,45]. Furthermore, if a stem is not pre-marked, rotations around the three orthogonal axes cannot be captured; a problem that can partially be solved using Model-based RSA[46].

Marker-related image loss and data attrition: Beads may be obscured by the implant or by each other (over-projection), or display sub-optimal spatial scatter, elevating the condition number (CN > 125) or the mean rigid-body error (ME > 0.35 mm). Such situations force researchers to exclude some examinations or even entire image series and patients, a problem that can account for 3.5-22% marker-related dropouts in recent studies [47,48].

Specialised infrastructure and cost: MBRSA requires a purpose-built RSA laboratory, a rigid calibration cage, and dedicated analysis software. These requirements can limit the use of the method to a handful of well-equipped centres and limit scalability; by contrast, CT-RSA can be run on

standard CT scanners “in smaller institutes” without an RSA laboratory [8]. Though, a CT-RSA dedicated analysis software is required.

Cumulative radiation exposure: Although a single RSA examination delivers only ~0.05-0.2 mSv of radiation [8,11,49–51], typical migration protocols entail sometimes multiple takes to ensure image quality and at least 5–7 follow-ups within two years. The cumulative dose therefore approaches or exceeds 1 mSv [8,50]. However, these doses are still below the proposed limits of the European guidelines on exposure in medical and biomedical research [52].

Analytical fragility and operator dependency: Rigid-body assumptions mean that any early bead migration relative to bone introduces systematic error [42]; precision therefore depends on meticulous bead placement and stringent quality control. Manual identification of markers and evaluation of condition number and mean error still rely on experienced analysts, prolonging post-processing and could introduce interobserver variability.

Collectively, these limitations explain both the development of model-based RSA and the current momentum towards the CT-RSA method that seek to preserve micrometre-scale precision and accuracy while decreasing the considerations about invasiveness, laboratory dependence and dropout risk that continue to limit the capabilities of conventional MBRSA.

6.5 A FEW WORDS ON MODEL-BASED RSA

Model-based Radiostereometric Analysis (model-based RSA) is a successor to MBRSA also used to measure micromotions of orthopaedic implants in vivo with high accuracy but without the need for implanted markers. By contrast, model-based RSA uses 3D surface models of the implants to track their position and migration over time. Below are the basic principles of model-based RSA presented.

6.5.1 PRINCIPLES OF MODEL-BASED RSA

Digital Implant Model (CAD Surface Model): Initially, a high-resolution three-dimensional representation of the implant’s surface geometry is constructed, typically derived either from computer-aided design (CAD) data provided by the implant manufacturer or by direct scanning of the implant itself [44]. This digital implant model is of great importance, as it

serves as the reference template to match against the implant silhouette captured on radiographic images.

Markerless Implant Tracking: Unlike MBRSA, the model-based method does not require placement of tantalum markers[6]. This simplifies surgery, reduces intraoperative complexity, and makes retrospective RSA analyses possible.

Radiographic Imaging (Stereoradiographs): Model-based RSA involves simultaneous acquisition of two radiographs such as in marker-based RSA in an angle using either a uniplanar or a biplanar configuration. This setup usually incorporates a calibration cage containing markers, providing a spatial reference framework essential for precise geometric analysis of implant motion within the bone [42].

Pose Estimation Algorithm: Dedicated model-based RSA software processes the stereoradiographic images to calculate the position and orientation (pose) of the implant[44]. The procedure utilizes an optimization algorithm to align the contours of the implant's digital CAD model with the corresponding silhouettes projected on the radiographic images. This iterative matching process determines the three-dimensional spatial configuration of the implant, defined by its translations and rotations relative to the bone.

Comparison of Implant Position over time: The positional data collected immediately postoperatively provide a baseline reference. Sequential measurements taken at predefined intervals (e.g., 3 months, 1 year, and longer) are compared against this initial reference to quantify the precise translations (expressed in millimetres) and rotations (expressed in degrees) occurring along and about the orthogonal axes (X, Y, and Z).

Measurements in Six Degrees of Freedom (6-DOF): Model-based RSA quantifies motion across three translational axes (medial-lateral, proximal-distal, and anterior-posterior) and three rotational axes allowing a comprehensive assessment of implant stability.

Low Radiation Exposure: Typically, model-based RSA examinations are associated with a relatively low radiation dose, approximately 0.2 mSv per measurement session, aligning well with safety guidelines for repeated radiographic follow-up studies [52].

Limitations of model-based RSA

The precision of model-based RSA is influenced by several factors, including the quality of the implant's digital surface model and patient positioning during radiographic imaging [53,54]. Additionally, the absence of markers in model-based RSA can create challenges in cases involving low-contrast or geometrically complex implants [55] .

Comparative Analyses and Future Directions

Comparative studies show that model-based RSA yields migration estimates closely matching marker-based RSA, with differences largely confined to systematic errors rather than mean outcomes, and accuracy is comparable, and precision is generally clinically acceptable [47,55]. Recent work also demonstrates good agreement between model-based RSA and AI-based CT-RSA [51].

In conclusion, model-based RSA is a less invasive, efficient way to assess implant migration, but its accuracy depends on high-quality implant models and imaging protocols. Further research and technical improvements are needed to address these limitations and fully realize its value in implant migration evaluation.

6.6 CT-RSA

Over the last two decades low-dose computed tomography has been harnessed to replicate the micromotion tracking that traditional MBRSA established in the 1970s. CT-RSA registers successive CT volumes of bone and implant surfaces, allowing six-degree-of-freedom migration to be calculated without tantalum beads or a purpose-built laboratory. Initial phantom and pilot studies showed that CT-RSA could measure implant movement with sub-millimetre accuracy [10]. More recent clinical studies have confirmed that CT-RSA meets the same early migration thresholds (0.2–1 mm) that have established RSA as a reliable predictor of future aseptic loosening [8,12,13,45,56].

6.6.1 PRINCIPLES OF CT-RSA

Developed as a less-invasive alternative to MBRSA, CT-RSA employs a series of low-dose CT scans to track implant position over time without the

need for implanted tantalum markers [8,45]. The foundational principle of CT-RSA involves performing repeated low-dose CT scans at specific postoperative intervals and calculating micromotion over time, exactly as MBRSA and model-based RSA.

1) Initially, a baseline CT scan is obtained postoperatively, typically within the first few days following surgery. Subsequent scans at predetermined intervals enable the detection of implant micromotion, both translational and rotational, relative to the baseline position.

2) During the analysis, the dedicated software segments and registers the implant and surrounding bone based on predefined Hounsfield unit thresholds (Figure 4A, 4B, 4D and 4E). Typically, thresholds of approximately 250-300 HU for bone and around 1900-2200 HU for implants are used, though these thresholds may be adjusted depending on the specific implant materials and clinical scenario. The segmentation process defines the surface outline of the implant and surrounding bone, allowing them to be aligned for spatial analysis.

3) The next step involves the registration process where the segmented reference and moving bodies from different scans are closely aligned. This alignment process generates a visual overlap aided by a chromatic scale, providing visual feedback on the quality of the alignment (Figure 4C and 4F). This facilitates precise matching, ensuring tracking of the relative positions of the implant and bone between scans.

4) Quantification of the implant migration is achieved through three-dimensional spatial analysis, calculating translations and rotations along the predefined three orthogonal axes (X, Y, and Z).

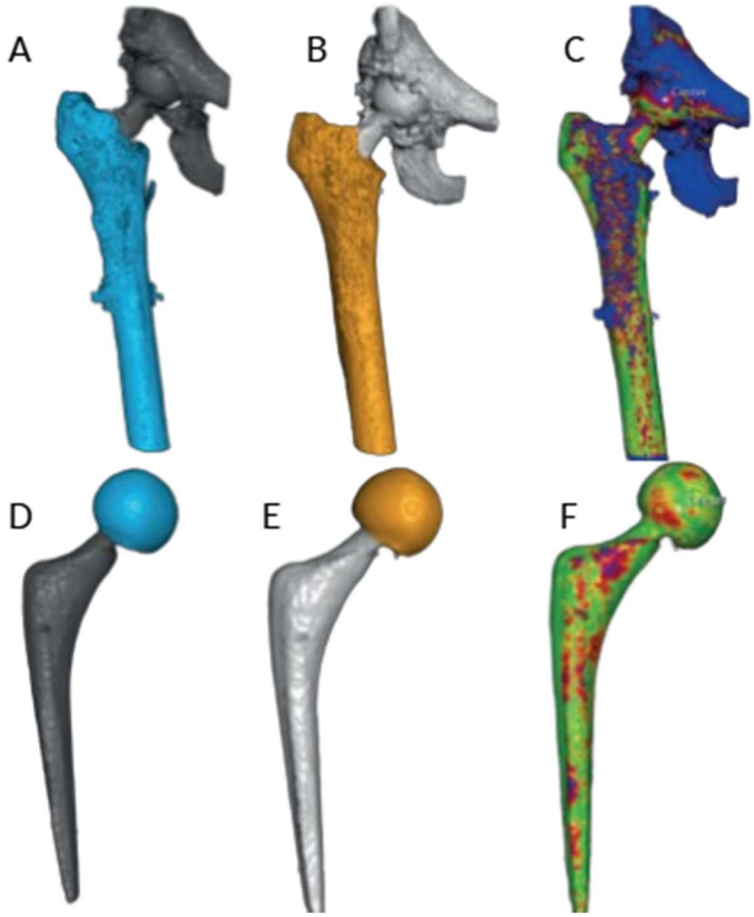

Figure 4 (A) Baseline low-dose CT with segmented femur (light blue). (B) Follow-up CT with segmented femur (orange). (C) Alignment of the reference body, in this case the femur, on both the baseline and follow-up CT-dataset with a colour-coded overlay (green = good overlap; red/blue = mismatch) used for visual quality control. (D) Baseline CT with segmented implant surface (light blue). (E) Follow-up CT with segmented implant surface (orange). (F) Alignment of the moving body, in this case the implant, on both the baseline and follow-up CT-dataset with a colour-coded overlay prior to migration computation.

6.6.2 ADVANTAGES OF THE CT-RSA METHOD

CT-RSA has been proposed to provide a simpler workflow, broader accessibility, and potentially higher imaging value, thus, making it logically a practical alternative to RSA [8,12,13,45,51].

Marker-free workflow eliminates the need for marker insertion, over-projection, and dropout due to poor scatter, enabling retrospective recruitment and multicenter scalability.

Accessible hardware, as standard CT scanners and off-the-shelf software replace bespoke RSA suites, broadening availability to smaller institutions.

Robust image quality, as high-resolution scanners and metal-artefact reduction protocols facilitate segmentation even around radiodense alloys, while low-dose protocols are possible to approach RSA exposure levels.

Increased clinical value of each scan, as the volumetric data provided allows simultaneous evaluation of osteolysis, bone quality, and implant orientation.

6.6.3 LIMITATIONS OF THE CT-RSA METHOD

Limitations exist with CT-RSA as with any other modality studying implant migration. CT-RSA has higher radiation exposure, lacks numerical quality metrics, and can be affected by image artefacts or resolution issues. Moreover, it requires coordinate realignment for analysis. Despite that, it seems to retain RSA's predictive value but needs further validation.

Radiation burden: Even optimized protocols expose patients to roughly four-fold higher dose than a single RSA pair (0.8 mSv vs 0.2 mSv); cumulative exposure remains a design consideration for long term follow-ups [8,45,56].

Lack of intrinsic quality metrics: CT-RSA cannot yet compute the rigid-body condition number (CN) or mean error (ME) or provide a similar numerical value as a measure of image or measurement quality [8,42,45]. Validity rests, thus, on colour-overlay and assessor judgement, although repeatability is reported to be excellent after brief training [45,57].

Image-related exclusions: Motion artefact or low-resolution scans still lead to lost cases (e.g. ≈10 % in Study I and III), mandating protocol optimisation and, where feasible, pilot scouting [8,45].

Coordinate-system adjustment: The DICOM axes of the CT-scans must be realigned to the RSA anatomical frame before direct comparison, adding a preprocessing step that could potentially add a source of measurement variability [8,42,45].

In summary, CT-RSA retains RSA's predictive value for early detection of at-risk implants while eliminating its surgical and logistical barriers. Still, concerns about radiation exposure and quality control highlight the need for further validation.

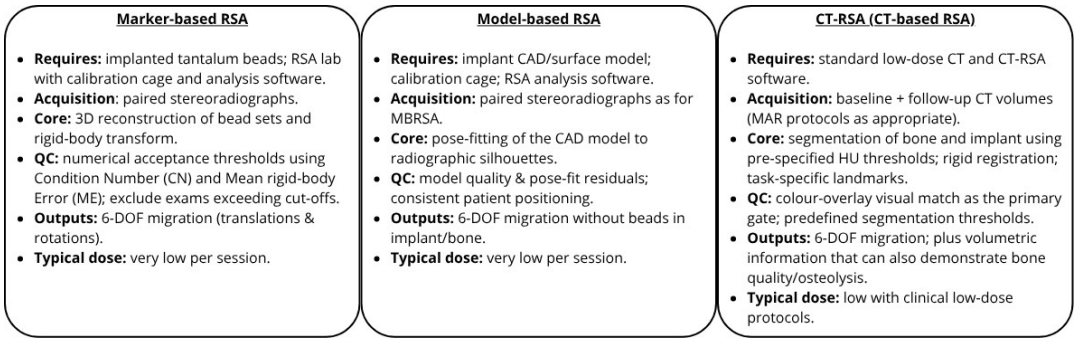

Figure 5 Overview of three migration-measurement approaches. All quantify six-degree-of-freedom migration (6-DOF) but differ in prerequisites, acquisition, and quality control (QC).

6.7 THE IMPORTANCE OF VALIDATION AND STEPWISE INTRODUCTION OF NEW METHODS IN RESEARCH AND CLINICAL PRACTICE

6.7.1 INTRODUCTION

In orthopaedic research and practice—particularly in (THA)—new measurement tools, imaging modalities, and implant techniques must undergo rigorous validation before widespread adoption. A stepwise, evidence-based introduction of innovations is crucial to ensure patient safety and reliable outcomes. RSA has emerged as a gold-standard tool for measuring implant migration in THA and for early detection of potential failures. This section discusses why validation and phased implementation are essential, using bone cement and RSA/CT-RSA in THA as a case study, and highlights the risks of bypassing these safeguards.

6.7.2 THE NEED FOR VALIDATION OF NEW METHODS

Validating new measurement techniques and implant innovations is of paramount importance before they enter routine practice. Without validation, there lies a risk of relying on inaccurate data or unsafe devices, which can compromise patient outcomes [58–60]. History has shown that inadequate screening of orthopaedic innovations can lead to subsequent failures on a large scale. For instance, in the 1990s a new low-viscosity cement (Boneloc, Polymers Reconstructive A/S, Farum, Denmark; distributed by Biomet, Inc., Warsaw, IN, USA) was introduced without robust clinical evidence, which resulted in revision rates up to 14 times higher than normal, illustrating the dangers of adopting unproven methods [61,62]. Likewise, many hip and knee prostheses were historically approved via tolerant regulatory pathways with minimal pre-market testing, leading to some designs having failure rates 2–10 times the standard observed in joint registries [59,63]. These cases highlight why stepwise introduction and validation are needed to filter out suboptimal designs early [63]. Every new implant, fixation method, or surgical technique should be evaluated systematically to ensure that its benefits outweigh the risks. Methodological transparency is a key part of validation [63]. Researchers must clearly report

how a new method was tested, and any potential drawbacks or risks. Standardization efforts have greatly aided this transparency. In 2013, the first international standard on RSA (ISO 16087:2013) [2] was published to formalize how implant migration is assessed. This ISO standard defines uniform coordinate systems and metrics for measuring implant micromotion, ensuring that different studies speak the same "language" of micromotion. Following ISO 16087, updated RSA guidelines were issued to further standardize methodology and reporting, and adhering to these guidelines makes studies more transparent and reproducible [42,60,64]. Key recommendations include performing phantom experiments to determine accuracy (trueness) and precision of the measurement system, double examinations for precision assessment, and detailed reporting of marker configurations, calibration procedures, and analytical software. In theory, no single study should skip these steps. In reality, though, a recent systematic review of RSA/CT-RSA publications (between 2012 and 2024) found that none reported all recommended items, and on average only ~61% of the checklist items were fully addressed [65]. This gap indicates room for improvement in methodological reporting and why standards should be emphasized.

6.7.3 BONE CEMENT

Bone cement (polymethylmethacrylate, PMMA) is a critical load-bearing intermediary in total hip arthroplasty (THA), anchoring the prosthetic components to bone with proven long-term success (e.g. traditional cements like Palacos show ~90% 10-year survivorship [66]). Any modification to cement composition can have significant mechanical and clinical consequences, and rigorous validation and a phased introduction are essential. For example, adding antibiotics to cement is common for infection prophylaxis, and moderate doses generally preserve adequate strength, but high antibiotic loads or certain drugs (e.g. high-dose cefazolin) can weaken the cement matrix [34,35]. Similarly, cements are formulated with different viscosities for improved handling or penetration, however, their performance in vivo must be verified [66]. In contrast, poorly screened chemical alterations have led to failures, e.g. the Boneloc cement introduced in the 1990s, which was designed for lower exothermic polymerization, had inferior mechanical properties, resulting in early implant loosening [61]. This historical case underscored the need for stringent regulatory oversight and early-phase clinical monitoring of new cement formulations. Modern regulatory bodies support a stepwise, evidence-based introduction of orthopaedic innovations, combining thorough preclinical

testing with limited clinical release under surveillance. Radiostereometric analysis (RSA) has become a key tool in this phased introduction, as early implant migration (on the order of a few tenths of a millimetre) measured in the first 1–2 years strongly predicts long-term loosening, as already discussed. Micromotion monitoring of implants with RSA, has allowed precise in vivo tracking of implant stability. By requiring robust short-term RSA outcomes (typically 2-year migration data) before widespread adoption, and by maintaining close registry follow-up thereafter, the orthopaedic community aims to ensure that changes in cement composition (antibiotics, viscosity, or chemistry) translate into improved patient outcomes rather than repeating past failures [59,60].

6.7.4 RADIOSTEREOMETRIC ANALYSIS (RSA) AND EARLY IMPLANT MIGRATION

RSA has been used to detect implant migration in the order of tenths of a millimetre in the last decades. Numerous studies have shown that early implant migration measured by RSA is predictive of long-term outcomes. For example, distal femoral stem migration of about 0.2–1.0 mm within the first two postoperative years has been linked to high risk for future aseptic loosening [6,15,38,39]. Multiple studies confirm that excessive early migration is an alarming surrogate endpoint for failure, often preceding clinical symptoms. In another landmark case, the Charnley Elite-Plus hip stem showed rapid early migration on RSA [67] (particularly posterior head migration), foreshadowing an unacceptably high revision rate, while a follow-up study confirmed that all stems with early RSA-detected migration eventually failed [67,68]. This example highlights the importance of early RSA testing, which can detect high-risk designs well before clinical failures emerge. The ability to detect excessive migration in small patient cohorts (often <50) and short follow-up (1–2 years) makes RSA invaluable for screening new prostheses prior to mass deployment [42].

6.7.5 INTRODUCTION OF CT-RSA AND ITS VALIDATION

CT-RSA has been developed as a modern alternative to traditional RSA. The driving motivation for CT-RSA is to overcome drawbacks of MBRSA while preserving its benefits. Early concerns about radiation from CT have been mitigated by optimized protocols—studies report that modern low-

dose CT-RSA protocols can limit effective dose to around 0.8 mSv or less, although slightly higher than RSA exams [8,13,45]. With metal artefact reduction algorithms, metal implants can be reliably scanned with minimal image distortion. Despite these advantages, it is crucial to validate CT-RSA rigorously against the established RSA standard before embracing it in clinical research. Alongside validations in phantom models [10,69,70], initial clinical studies were conducted in a stepwise fashion. Early pilot studies applied CT-RSA in small patient cohorts to evaluate its performance in vivo [71]. By 2025 the accumulated evidence, spanning phantom studies, systematic reviews, and clinical trials [8,10,11,14,45,51,56,72], indicates that CT-RSA can achieve accuracy and precision that is essentially matching the performance of traditional RSA. A recent meta-analysis concluded that CT-RSA has "comparable accuracy and precision to standard RSA" and is a promising alternative for migration measurement [56]. This growing body of validated research has paved the way for CT-RSA to be adopted more widely. Crucially, the methodological validation of CT-RSA has to follow a transparent, stepwise path. Each new variant of CT-based analysis (different software algorithms, marker-less approaches, AI-based analysis etc.) has to be introduced via pilot studies with concurrent RSA comparison, rather than directly replacing RSA in clinical trials. It also exemplifies how new imaging modalities should be introduced: first by bench testing, then limited clinical validation against the gold standard, and only then broader dissemination once equivalence is proven. By following this phased approach, CT-RSA has gradually been proposed as a method to expand migration monitoring beyond the limitations of traditional RSA.

6.7.6 METHODOLOGICAL TRANSPARENCY AND STANDARDS

The RSA community has long emphasized standardization and openness, formalized in the ISO 16087:2013 standard, which defines consistent procedures for measuring and reporting implant migration. These guidelines help ensure critical details—such as calibration cage type, marker model, and measurement precision—are fully reported, enabling reproducibility and proper assessment of study quality [1,42,65].

As new methods like CT-RSA emerge, methodological transparency is vital for scientific credibility, why more recent RSA guidelines include even a section on CT-RSA [42]. Transparency is essential: without clear documentation of methodology, new imaging methods risk scepticism from

clinicians and regulatory bodies. Journals and reviewers increasingly expect adherence to these standards.

6.7.7 THE STEPWISE INTRODUCTION PROCESS

Rather than releasing a new implant or technique directly to the market (or using a new measurement tool in pivotal trials without prior testing), a step-by-step approach in theory typically follows a hierarchy:

1. Bench testing or in vitro validation
2. Cadaveric or phantom studies
3. Early clinical studies in small cohorts using validated endpoints (e.g., RSA)
4. Controlled trials with functional and patient-reported outcomes
5. Long-term registry-based surveillance

In clinical practice regarding THA, though, the following step-by-step approach is more often used:

1. Preclinical and pilot phase: In vitro evaluation and simulations (e.g. implant fatigue tests, FEA, cadaver studies, phantom RSA studies) establish basic safety and performance [73]. If feasible, relevant and ethical, first-in-human pilot studies use highly accurate monitoring (such as RSA) on a small patient group to detect any early issues. At this stage, warning signs can halt development before many patients are exposed.

2. Controlled clinical trials: If pilot and in vitro results are promising, the method or product to be tested is submitted to formal clinical trials [38,74–76] (often randomized) in a controlled setting. RSA or CT-RSA is often employed here as a sensitive endpoint to compare the new implant/technique against the standard. Early outcome measures (e.g. 1–2 year migration, early complications) serve as surrogates for long-term success. Clear performance thresholds derived from prior evidence (for example, “femoral stem subsidence >0.2mm-1mm at 2 years is unacceptable”) can be used to evaluate the new device.

3. Multi-centre or registry studies: Once efficacy and safety are demonstrated in a single-centre or limited trial, larger multi-centre studies or registry-based studies can be initiated. At this point, having a broadly deployable measurement method is invaluable. Multi-centre studies can feed into arthroplasty registries or create parallel early-warning systems for new implants [60].

4. Post-market registry monitoring: Even after a device is approved and in use, continued monitoring via national joint registries and selective RSA studies is recommended. If an implant shows higher-than-expected failure in registry data, targeted RSA studies can unveil the mechanism of failure (e.g. excessive wear or migration). Conversely, if early RSA surveillance flags a problem (as with the Elite-Plus stem or certain knee designs), action can be taken to limit use of that implant and monitor how the already implanted devices perform in the long term. This feedback loop, then, closes the evidence-based introduction cycle [59].

Adopting this phased approach dramatically reduces the risk of prematurely adopting a harmful innovation. It mirrors the pharmaceutical field, where new drugs undergo Phase I–III trials before approval. In orthopaedics, due to historically looser device regulations, many costly failures have occurred that might have been averted by proper phased testing.

The benefits of stepwise introduction are now increasingly recognized: patients avoid exposure to unsafe implants and methods, manufacturers can correct or abandon flawed designs early, and successful innovations build credibility by accumulating evidence at each step. Migration monitoring, thus, plays an important role in this process and has been called a "small investment with big returns", given how small RSA studies can protect patients from a bad implant design down the line.

Today, regulatory and research bodies encourage using RSA or similar tools during pre-market evaluation of new THA designs, as these early surrogate outcomes correlate with long-term performance. Multi-centre trials of a new THA implant could incorporate RSA or CT-RSA follow-up at 3, 6, 12 and 24 months post-op to quickly gather migration data from multiple centres. This proactive surveillance would catch problematic designs far sooner than waiting for high failure rates to appear in registries years or decades later.

6.7.8 RISKS OF PREMATURE ADOPTION WITHOUT ROBUST EVIDENCE

By contrast, bypassing validation and stepwise introduction carries significant risks. Premature adoption of unvalidated methods can mislead research or jeopardize patients. If a measurement tool has unknown accuracy, studies using it might draw false conclusions (e.g. underestimating true implant migration or missing a failure mechanism) [42].

In clinical practice, adopting a new implant or technique based on marketing hype or limited data can lead to widespread patient harm [59]. Orthopaedic history has unfortunately sobering examples: the early 2000s saw a surge of new hip designs and bearing materials introduced with minimal clinical evidence, followed by implant recalls and high revision rates (e.g. certain metal-on-metal hips). As noted, the Boneloc cement case [61] underlines failures that occurred because clinical practice embraced a new product without independent trials, resulting in many early loosening failures. The Elite-Plus stem mentioned earlier made it to market and into patients, only for RSA and registry data later to reveal its high failure – knowledge that a small RSA study could have provided much earlier. These scenarios illustrate the cost of skipping steps: the “evidence gap” was filled by unfortunate real-world outcomes. Therefore, the research community has become more vigilant. Innovations now are more likely to undergo a probationary period – often referred to as a "safe introduction" period – where enhanced monitoring (RSA studies, controlled rollout, etc.) is mandated. Research bodies have called for implants to be treated akin to new pharmaceuticals, requiring phased clinical trials and regulatory scrutiny rather than following marketing hype.

The goal is to intercept any design or method that does not demonstrate clear benefit and safety. In summary, the importance of validation and stepwise introduction in THA (and orthopaedics broadly) cannot be overstated. Ultimately, robust validation and phased implementation protect patients, improve the quality of research, and ensure that innovation in THA delivers on its promise of improved patient outcomes without compromising safety.

7 AIM

7.1 KNOWLEDGE GAPS

I. MBRSA has been the gold-standard in measuring implant micromotion in orthopaedic surgery. CT-RSA has been identified as a possible alternative method that can overcome some of the drawbacks of MBRSA. Although research on CT-RSA has been evident, it consists mostly of experimental in vitro or studies with a small number of patients. Specifically, for cemented acetabular cups in total hip arthroplasty, previous studies on this subject are few and, for the most part, retrospective. Thus, prospective studies with a larger number of patients are needed to evaluate any clinical differences between the two methods.

II. In 2005, Refobacin Bone Cement R and Palacos R + G bone cement were introduced as replacements for the original Refobacin Palacos R cement, with the assumption that both new cements would exhibit biomechanical properties similar to the original. However, earlier in vitro studies suggested that these new cements might not share the same properties as their predecessor. Furthermore, their introduction did not follow the evidence-based, stepwise approach recommended for new implants and techniques including Radiostereometric Analysis (RSA) as described by previous research. In 2016, Refobacin Bone Cement R was further modified by replacing certain raw materials in its powder component. This updated version, now commercially available, has not been thoroughly investigated for its migration properties.

III. As noted in point 7.1.I for acetabular cups, the same is true even for cemented femoral stems. Moreover, the intra- and interobserver reliability of the CT-RSA method has yet to be tested thoroughly in order to investigate whether the method is assessor independent.

IV. Although there are some experimental studies regarding the precision and accuracy of CT-RSA in measuring implant migration, those often include a small number of experiments that could conceal a proportional bias. Additionally, there is to this date no study evaluating intra- and interobserver reliability of CT-RSA in an experimental setting regarding femoral stems.

7.2 AIMS

I. To investigate whether CT-RSA can detect proximal migration in cemented acetabular cups and has precision comparable to that of MBRSA.

II. To investigate whether Refobacin Bone Cement R (2016 formula) is performing equivalent to Palacos R+G in terms of stable fixation by measuring distal stem migration as a surrogate of future aseptic loosening. Moreover, two mixing systems, Optivac and Optipac, were used together with Refobacin Bone Cement R in order to evaluate presence of any influence of mixing systems on migration.

III. To investigate whether CT-RSA can measure distal stem migration in cemented femoral stems in a way comparable to that of MBRSA. Moreover, to evaluate the intra- and interobserver reliability of the CT-RSA method.

IV. To evaluate the precision and accuracy of the CT-RSA method against known actual micromotions in measuring migration of femoral stems. In addition, to evaluate the inter- and intraobserver reliability of CT-RSA in an experimental setting.

8 PATIENTS AND METHODS

For the purpose of this thesis 4 studies were conducted. Study I, II and III were a part of a larger study entitled ''Cement Study''. Study IV was a phantom in vitro study.

8.1 CEMENT STUDY: OVERVIEW

Location, Time Settings and Patient Selection

The Cement Study was a single-centre, prospective, randomized trial conducted at the Department of Orthopaedics, Sahlgrenska University Hospital, Mölndal, Sweden. Recruitment took place between September 2018 and October 2020. The inclusion criteria were:

- Age 60–75 years.
- Diagnosis of primary hip osteoarthritis.
- ASA classification class I–II.
- BMI between 18 and 35 kg/m².
- Charnley classification A.
- All patients were able to understand Swedish and complete standardized questionnaires.

Exclusion criteria included:

- Cognitive impairment.
- Bone loss requiring grafting or cages.
- Cases deemed unsuitable for cemented fixation.

Of 90 initially screened patients, 75 underwent surgery, and 71 in total completed the two-year follow-up.

Randomization

Patients were randomized preoperatively to receive one of three combinations of cement and mixing system: Palacos R+G with Optivac (Heraeus Kulzer, Heraeus Medical, Germany), Refobacin Bone Cement R with Optivac, or Refobacin Bone Cement R with Optipac (Zimmer Biomet, Warsaw, IN, USA). Randomization was performed using sealed envelopes and block randomization. The entire cohort was included in Study II, which investigated implant migration and clinical outcomes. A predefined

subgroup underwent additional CT-RSA and formed the study populations for Study I and III.

Surgery and Follow-up

All patients underwent cemented total hip arthroplasty using a polished, collarless, triple-tapered MS-30 femoral stem and a cemented Exceed acetabular component with a vitamin E-infused highly cross-linked polyethylene liner (Zimmer Biomet, Warsaw, IN, USA). A 32 mm femoral head was used in all cases. Surgery was performed by experienced hip surgeons using either a direct lateral (Gammer)[77,78] or posterior approach (Moore)[80]. Cementation followed a standardized third-generation technique, including vacuum mixing, pulsatile lavage, retrograde injection, and pressurization. Tantalum markers (0.8 mm) were inserted into the proximal femur and acetabulum and 1.0 mm markers into the cement restrictor. Patients were followed postoperatively at 3, 6, 12, and 24 months with radiographic and clinical assessment.

Radiologic Assessment

Implant micromotion was evaluated using MBRSA, with double examinations performed postoperatively to assess precision within 1–3 days and then single examinations at 3, 6, 12, and 24 months. MBRSA was conducted on all patients using a uniplanar calibration cage and analysed with UmRSA software (RSA Biomedical, Umeå, Sweden).

In the CT-RSA subgroup, double low-dose CT scans were also performed postoperatively within 1–3 days and single examinations at one year using a standardized protocol. CT data were analysed using CT-RSA software (CTMA, Sectra Corp., Linköping, Sweden). Micromotion was measured along and around the three orthogonal axes (X, Y, Z), as defined by previous RSA studies [1] (Figure 6). Migration results from MBRSA and CT-RSA were thereafter compared.

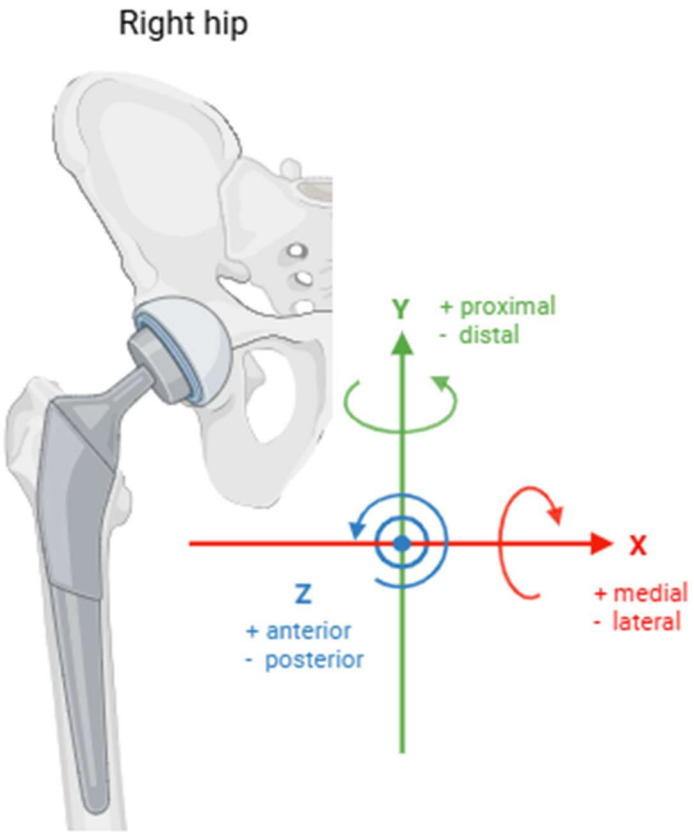

*Figure 6 The orthogonal, usual RSA coordinate system is shown. The **X-axis** (red) runs medial–lateral, with positive values toward the **medial** side. The **Y-axis** (green) runs proximal–distal, with positive values toward the **proximal** direction. The **Z-axis** (blue) runs anterior–posterior, with positive values toward the **anterior** direction. Curved arrows indicate rotations about each axis (following the right-hand rule): rotation about the **X-axis** corresponds to anterior/posterior tilt, rotation about the **Y-axis** to internal/external rotation (ante-/retroversion) and rotation about the Z-**axis** to varus/valgus tilt for the femoral stem and increased/ decreased inclination for the acetabular cup.*

Radiostereometric Analysis (RSA)

MBRSA was conducted for all patients in the parent study to assess micromotions about the three orthogonal axes (X, Y, Z). Only radiographs with at least three identifiable tantalum markers per segment meeting predefined quality criteria (CN <125 and ME <0.35 mm) were included. MBRSA acquisition used the Adora radiography system (NRT-Nordisk Røntgen Teknik, Denmark), uniplanar calibration cage (cage 77), and was analysed using UmRSA Digital Measure and UmRSA Analysis software v. 7.0 (RSA Biomedical, Umeå, Sweden).

Computed Tomography Radiostereometric Analysis (CT-RSA)

CT scans were performed on the subgroup of patients included in Studies I and III. All CT scans were acquired using a Discovery CT 750 HD scanner with a low-dose protocol. Analyses were performed with CT-RSA software (CTMA, Sectra Corp., Linköping, Sweden) by trained analysts using a predefined protocol. The DICOM axes were aligned to the RSA axes before calculating micromotions (Appendix B).

Minimal important difference

As already mentioned, prior research suggests that migration higher than 0.2–1.0 mm of cemented hip components within the first two years predicts later aseptic loosening [6,38]. Accordingly, in Studies I and III we predefined a minimal important difference (MID) of 0.2 mm between the measurements of RSA and CT-RSA regarding early acetabular cup and femoral stem migration as a threshold of comparability.

8.1.1 STUDY I

Questions to be answered by the hypothesis

A detailed summary of methods can be found in the corresponding publication [8]. In this study the following questions were posed: 1) Is the precision of CT-RSA comparable to that of MBRSA? and 2) does CT-RSA measure proximal acetabular cup migration in a comparable way to MBRSA in cemented THA? We hypothesized that CT-RSA has precision comparable to MBRSA and can be used as an alternative for measuring proximal acetabular cup migration.

Study design and patient selection

This study was a prospective agreement sub-study embedded within the larger randomized Cement Study, conducted at the Department of Orthopaedics, Sahlgrenska University Hospital, Mölndal, Sweden. The aim was to evaluate the performance of CT-RSA for detecting implant migration of cemented acetabular components in total hip arthroplasty (THA), using conventional MBRSA as reference.

A total of 30 patients were consecutively recruited from the parent study cohort and constituted the basis for this analysis. Eligibility required successful completion of the one-year follow-up and availability of both MBRSA and CT imaging of sufficient quality to allow for comparative analysis. Patients were blinded to study allocation, and selection was performed without knowledge of clinical or radiographic outcomes to reduce selection bias. All patients had previously been randomized in the Cement Study to receive either Refobacin Bone Cement R or Palacos R+G, and all received the same implant configuration: a cemented Exceed cup with a vitamin E-infused highly cross-linked polyethylene liner and a cemented MS-30 femoral stem. Marker insertion in the periacetabular bone and cement mantle had been performed at the index procedure to facilitate RSA evaluation.

Outcomes

The primary outcome of the study was to determine the precision of CT-RSA for assessing acetabular cup migration, specifically along the proximal–distal (Y) axis, by comparing repeated CT scans (double examinations) postoperatively. The secondary outcomes included CT-RSA precision along the orthogonal X and Z axes, evaluation of 3D translation

vectors, and comparison of CT-RSA-derived migration results with those obtained using MBRSA.

Participant flow

One patient was lost due to the Covid-19 pandemic and had no RSA or CT-RSA data available. Another patient was excluded because of inadequate CT scan quality. In three additional cases, RSA analysis was not possible due to high condition numbers (CN), caused by suboptimal marker placement; however, CT-RSA analysis could still be performed for these patients. As a result, complete one-year data was obtained for 26 patients using RSA and for 28 patients using CT-RSA.

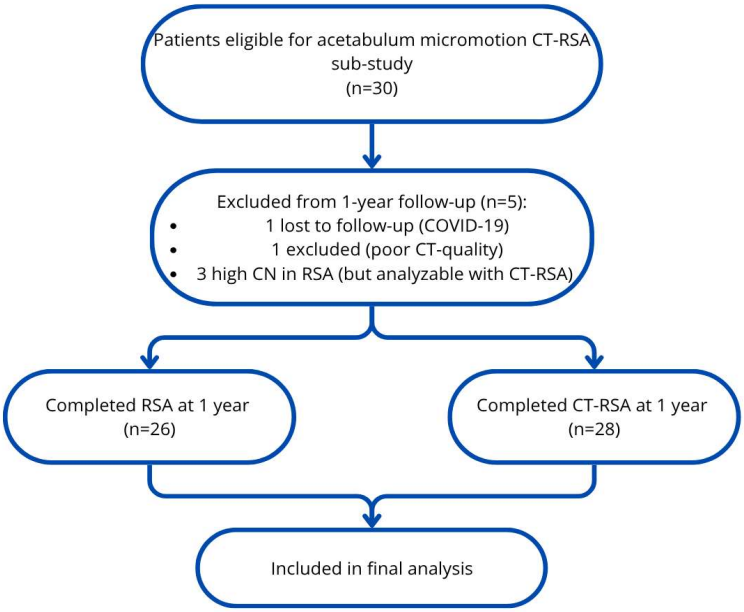

Figure 7 Participant flow in Study I

8.1.2 STUDY II

Questions to be answered by the hypothesis

A detailed description of the methodology is publicly available [79]. Study II sought to address the following questions: 1) Are there any differences in the migration pattern of the triple tapered polished MS30 femoral stem over a 2-year period, when Refobacin Bone Cement R or Palacos R+G are used? 2) Does the mixing system (Optivac or Optipac) have any impact on the migration of the femoral stem? 3) Are there any differences in PROM between patients operated with Refobacin Bone Cement R or Palacos R+G with either of the mixing systems? Our hypothesis was that there are no differences in either femoral migration or PROM between the two cements and mixing systems.

Study design and patient selection

This was a prospective, randomized, single-centre study conducted at the Department of Orthopaedics at Sahlgrenska University Hospital, Mölndal, Sweden between September 2018 and October 2020. The study aimed to compare the radiographic and clinical outcomes of femoral stem migration, cement mantle characteristics, and PROM in patients receiving THA using two different cement types, Palacos R+G and Refobacin Bone Cement R using two different mixing systems, Optivac and Optipac.

Outcomes

The primary outcome of this study was defined as the proximal-distal migration of the femoral stem, corresponding to translation along the Y-axis. Secondary outcomes included assessment of the cement mantle, stem alignment, and PROM.

Participant flow

The whole cohort of the ''Cement Study'' was included in this study, with inclusion and exclusion criteria as described above in section 8.1. Initially, 90 patients fulfilled the inclusion criteria. However, 15 were excluded prior to or during surgery for reasons such as anatomical incompatibility with the smallest available cup size (n = 6), unsuitability for cemented fixation (n = 3), implant availability issues (n = 2), oversized acetabula (n = 1), or voluntary withdrawal (n = 3). Thus, 75 patients were randomized using block randomization to receive either Refobacin Bone Cement R or Palacos R+G, in combination with the Optivac or Optipac vacuum mixing systems. Randomization was conducted on the day of surgery using sealed

envelopes. All participants underwent surgery using a standardized third generation cementing technique using the implant configuration already discussed on section 8.1. RSA bead implantation followed ISO16087:2013 guidelines [2]. After surgery, additionally four patients were excluded: two due to insufficient marker configuration for RSA (n=2), one declined participation in follow-up (n=1), and one missed the two-year examination (n=1). This left 71 patients available for analysis. The patient who did not complete the two-year follow-up was nonetheless included in the analysis of RSA setup precision.

Follow-up

Postoperative follow-up included MBRSA imaging, conventional radiographs, and PROM at 3 months, 6 months, 1 year, and 2 years postoperatively.

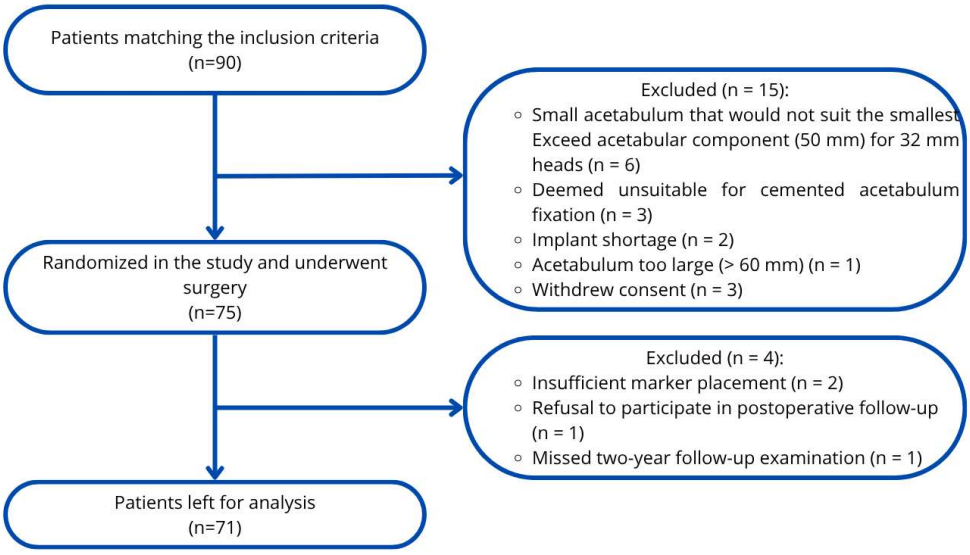

Figure 8 Participant flow in Study II

8.1.3 STUDY III

Questions to be answered by the hypothesis

A detailed description of the methodology is available on the corresponding published article [45]. Study III aimed to address the following research questions: 1) Is CT-RSA comparable to MBRSA in measuring femoral stem subsidence? 2) Is the intra- and interobserver reliability of CT-RSA high, making it assessor independent? We hypothesized that CT-RSA is comparable to MBRSA in measuring femoral stem subsidence and that the intra- and interobserver reliability of CT-RSA is high.

Study design and patient selection

This study was designed as a prospective, agreement sub-study within the framework of the Cement Study conducted at Sahlgrenska University Hospital, Mölndal, Sweden. The study focused on comparison of MBRSA and CT-RSA of femoral head translations at one year postoperatively, as well as the intra- and interobserver reliability of the CT-RSA method. One observer performed two separate analyses of all cases with a minimum interval of 14 days to assess intraobserver reliability. A second, independent observer performed the same analyses to assess interobserver reliability. The study population consisted of the same predefined subgroup of 30 patients as in Study I plus one pilot patient from the parent study who fulfilled the radiological inclusion criteria, yielding in total 31 eligible patients who had previously been enrolled and randomized in the ''Cement Study''. These patients had undergone cemented THA and completed the one-year follow-up, including both MBRSA and low-dose CT imaging and received the same implant configuration as every other patient in the parent study: a cemented MS-30 femoral stem and an Exceed acetabular component with a vitamin E-infused, highly cross-linked polyethylene liner The cement type (Refobacin Bone Cement R or Palacos R+G) was assigned according to the original study randomization.

Patients were eligible for this sub-study if they had analysable CT scans and a complete MBRSA marker setup that allowed for reliable migration measurement. Exclusion criteria included poor-quality CT imaging or RSA configurations exceeding acceptable thresholds for condition number (CN) or mean error (ME).

Outcomes

The primary outcome was defined as the proximal–distal migration of the femoral head at one year, corresponding to translation along the Y-axis. Secondary outcomes were the intra- and interobserver reliability of CT-RSA.

Participant flow

Three patients were excluded from the one-year follow-up due to low image resolution and motion artefacts on their CT scans (n=3). Additionally, one patient who did not attend any postoperative follow-up visits was excluded from the analysis (n=1). As a result, a complete evaluation at the one-year follow-up was available for 27 patients.

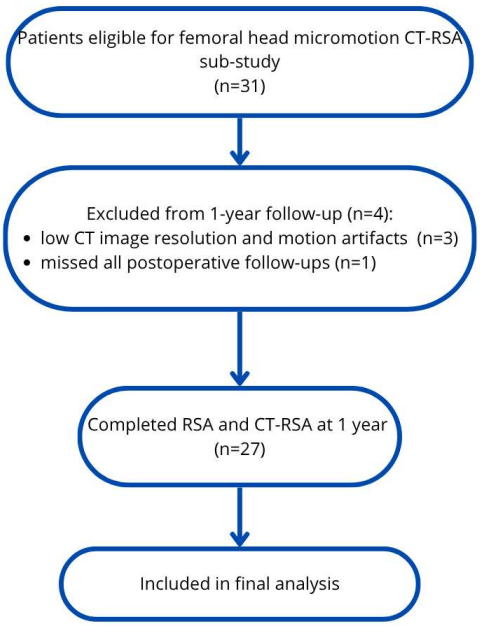

Figure 9 Participant flow in Study III

8.2 STUDY IV

Questions to be answered by the hypothesis

A detailed description of the methodology is available in the ‘’Methods’’ section of Study IV, which is submitted as a manuscript. Study IV sought to address the following questions: 1) What is the precision and accuracy of CT-RSA measuring femoral stem micromotions along the X-, Y- and Z-axes in an in-vitro setup? and 2) Does CT-RSA demonstrate acceptable intraobserver and interobserver reliability for femoral stem micromotion measurements in an experimental model?

Study design

This study was designed as an in-vitro experimental investigation with the primary aim of evaluating the precision and accuracy of CT-RSA in quantifying known micromotions of a femoral stem using a standardized and reproducible phantom model. The secondary aim was to assess the intra- and interobserver reliability of the CT-RSA method.

Experimental Setup

The hip model consisted of a synthetic femoral bone (Sawbones, USA, Pacific Research Laboratories, Inc., Vashon, WA, USA) into which a cementless femoral stem (Avenir Complete, Zimmer Biomet, Warsaw, IN, USA) was implanted in a manner that allowed free motion within the prepared canal. The bone model was rigidly mounted on a micrometre-controlled translation stage capable of applying controlled displacements in three orthogonal directions (X, Y, and Z). The stem was connected via the femoral neck to a femoral head that was in turn anchored to the moving plate of the micrometre platform. Due to the 135° CCD angle of the femoral stem neck and the orthogonal fixation to the platform, the coordinate system of the applied displacements was offset by 45° relative to anatomical and previously used RSA coordinates. To account for this discrepancy, all measured translations were later transformed into a rotated coordinate system (X′, Y′, Z′) to facilitate interpretation within a clinically relevant frame of reference.

The micrometre platform (Parker Hannifin, USA, Irwin, Pennsylvania USA) allowed controlled translations with a resolution of 2 µm. Displacement steps of 0 µm, 25 µm, 50 µm, 75 µm, 100 µm, and 150 µm were applied along each axis, simulating clinically relevant micromotions of the stem within the femoral canal. Five independent measurement series

were conducted, with the platform returned to the zero position (X, Y, Z: 0, 0, 0) between series and axes, yielding 90 paired measurements in total (N=90) and 60 double examinations as described in detail in the submitted manuscript (n=60).

Imaging Protocol and CT-RSA Analysis

All imaging was performed at a dedicated radiological unit using a low-dose CT protocol tailored for implant imaging and optimized for metal artefact reduction using the same CT-apparatus and scanning protocol. The CT datasets were uploaded to the CT-RSA software and analysed. Each CT series contained a reference scan (point zero X, Y, Z: 0, 0, 0) and a subsequent scan corresponding to a known displacement. The femoral bone and femoral head were defined as the fixed and moving rigid bodies, respectively. The software's chromatic overlay tool was used for visual confirmation of alignment during registration. The centre of the femoral head was manually defined by selecting 5–12 surface points across the head contour using the multi-planar reconstruction (MPR) view, allowing for the creation of a best-fit sphere. The centre of this sphere served as the reference point for migration measurements. All translations were measured in three degrees of freedom, with rotations disabled in order to isolate translational micromotions.

Data Transformation

Given the angled fixation of the femoral stem relative to the micrometre platform, a mathematical transformation was applied to all measurements to enable comparison with anatomical axes. A 2D rotation matrix corresponding to a 45° counterclockwise transformation was used to convert raw displacements along the X and Y axes into clinically interpretable X′ and Y′ values, respectively. The Z axis remained unchanged.

Reliability testing

To assess intraobserver reliability, one investigator repeated all analyses after a 14-day interval, blinded to the results of the first analysis. Interobserver reliability was evaluated by a second investigator, who independently analysed the same data using identical segmentation protocols and was blinded to the first observer's results.

Statistics

Precision of the CT-RSA was calculated from repeated measurements under identical displacement conditions. Accuracy was quantified using the differences between measured and known displacements. Intra- and interobserver reliability were analysed by calculating Intraclass Correlation Coefficient (ICC). All measurements were thereafter transformed into a clinically relevant coordinate system using a 45° rotation matrix. For more details, please see the Statistics section 8.3.IV.

8.3 STATISTICS

All statistical analyses were performed using SPSS v. 27.0.0 (IBM Corp, Armonk NY, USA). All statistical tests were two-sided, and the level of significance was set to α=0.05. Any complex pure mathematical analysis was performed using Python v. 3.11 (Python Software Foundation, Wilmington, DE, USA).

Study I

Precision of the MBRSA and CT-RSA was evaluated using postoperative double examinations, with the SD of the differences multiplied by the critical value from the Student's t-distribution at 95% confidence interval (CI) with n-1 degrees of freedom (Appendix A). Descriptive statistics and Bland–Altman plots were used to assess respectively comparability and agreement between methods.

Study II

With a sample size of 25 hips per group and a follow-up period of two years, the study was powered to detect a difference in stem subsidence of 0.5 mm, assuming a standard deviation of 0.65 mm in each group. This corresponded to a statistical power of 85%. The calculation was based on mean values and variability either observed in the current dataset or derived from previously published studies. Descriptive data were reported as means with standard deviations or medians with interquartile ranges, as appropriate. Group differences were analysed using Kruskal-Wallis, one-way ANOVA or chi-squared tests depending on data type and distribution.

Study III

Precision of the MBRSA was evaluated using postoperative double examinations, with the SD of the differences multiplied by the critical value from the Student's t-distribution, as described above (Appendix A). Intra- and interobserver reliability were analysed by calculating ICCs. Descriptive statistics and Bland–Altman plots were used to assess respectively comparability and agreement between methods.

Study IV

Precision was defined as the consistency of repeated measurements under identical conditions, reflecting random error. It was assessed by comparing double examinations across series for each axis. Precision was calculated as SD x t, where SD is the standard deviation of paired differences and t is the critical value from the Student's t-distribution at 95% confidence interval with n-1 degrees of freedom and n=60 (Appendix A).

Accuracy was defined as the closeness of CT-RSA measurements to the known displacements applied by the micrometre platform. It was calculated as RMSE x t where RMSE is the root mean square error of the differences between measured and true values and t is the critical value from the Student's t-distribution at 95% confidence interval with N-1 degrees of freedom and N=90 (Appendix A).

To enable interpretation in the usual RSA coordinate system, a coordinate transformation was applied. The X and Y axes were rotated counterclockwise by 45°, while the Z-axis remained unchanged. A standard 2D rotation matrix was used to compute the transformed axes (X′, Y′), and precision and accuracy were recalculated accordingly (Appendix A).

Intraobserver reliability was assessed by repeated measurements with a 14-day interval by the same observer, and interobserver reliability by independent analysis from a second observer, both blinded. Agreement was expressed using intraclass correlation coefficients (ICC), based on a two-way mixed-effects model with absolute agreement.

8.4 ETHICAL CONSIDERATIONS

Study I-III

All three studies were conducted as subprojects within a larger prospective clinical trial approved by the Regional Ethics Review Board in Gothenburg, Sweden (entry number 801-17). Written informed consent was obtained from all participants prior to inclusion. In accordance with national regulations and the Declaration of Helsinki, data were anonymized and handled confidentially throughout all phases of the research.

Due to the inclusion of low-dose CT imaging in Study I and III, a complementary ethical amendment was obtained to ensure compliance with current standards regarding additional radiation exposure in clinical research. The ethical review board assessed the CT radiation dose to be minimal and within acceptable risk thresholds. No external funding bodies influenced the study design, data collection, analysis, or interpretation.

Study IV

As the study involved no human subjects, patient data, cadaveric material, or animal models, ethical approval was not required. The experimental work was conducted using synthetic femoral bone models in a controlled laboratory setting. Data collection and analysis were performed independently, and no external funding bodies influenced the study design, data collection, analysis, or interpretation.

8.5 FUNDING

Financial support has been received from Zimmer Biomet (Warsaw, IN, USA) covering the additional costs of follow-ups and MBRSA radiography in the parent study, but had no part in the collection, preparation or interpretation of the data.

Sectra Corp (Linköping, Sweden) has provided access to the CTMA software, as well as financial support covering the cost of the CT-scans performed during Study IV, but had no part in the collection, preparation or interpretation of the data.

Västra Götalands Region (The Region of West Götaland) has provided financial support to buy the materials needed for Study IV as well as with research funding to conduct three months of research.

Göteborgs Läkaresällskap (The Gothenburg Society of Medicine) has supported the PhD candidate with generous funds in order to conduct three months of research and write the dissertation.

Guldbyxan Stiftelse (The Golden Trousers Foundation) has supported the PhD candidate with generous funds in order to conduct research, especially regarding Study IV.

9 RESULTS

9.1 STUDY I

Clinical precision of CT-RSA and cup migration measurements at the 1-year follow-up

Clinical Precision

The precision of RSA for cup migration was 0.06 to 0.15 mm for translations and 0.21º to 0.63º for rotations. Correspondingly, the CT-RSA method showed precision ranging from 0.06 to 0.13 mm for translations and from 0.23º to 0.35º for rotations. The precision for total migration was 0.18 mm for RSA and 0.16 mm for CT-RSA (Table 1). For total rotation, the precision was 0.46º for RSA and 0.38º for CT-RSA.

Cup migration at 1-year follow-up

The median (range) translation along the Y-axis at one year, measured using RSA, was 0.13 mm (-0.10 to 1.75). Corresponding measurements using CT-RSA were 0.11 mm (-0.15 to 2.00). The median (range) total migration was 0.21 mm (0.05 to 2.50) for RSA and 0.22 mm (0.04 to 2.23) for CT-RSA (Table 2). The median cup rotations at one year were minimal (-0.11˚ to 0.06˚). Detailed values for cup translation and rotation at 1 year for RSA and CT-RSA on the three orthogonal axes (X, Y, and Z) are outlined in Table 2. Regarding Bland-Altman analysis, the 95% Limits of Agreement (LoA) on the Y-axis ranged from -0.22 mm to 0.25 mm, capturing approximately 95% of all paired measurements on the Y-axis. Bland-Altman plots at 1 year (Figures 10 and 11) indicated that the discrepancies between the methods, particularly for translations on the Y-axis (which is the primary outcome measure of this study), fell within clinically important limits (0.2-1 mm for proximal/distal translations) and the margin of error for RSA. On the other axes, the measured discrepancies were generally below or within the clinically important limits for translation and within the RSA margin of error, as well as under or within the precision values for rotation for both methods (Table 1). The Bland-Altman plots showed that the best agreement between the methods was observed in the proximal/distal axis (Y) and total translation (3D) measurements.

Table 1 Precision of the two methods measuring cup migration based on 20 double examinations (n=20) per method, expressed as SD x t, where SD: standard deviation and t: critical value from the Student's t-distribution for n-1 degrees of freedom.

	RSA		***CT-RSA***	
	SD	Precision	SD	Precision
Cup migration (mm)				
X-axis (medial/lateral)	0.04	**0.08**	0.03	**0.06**
Y-axis, (proximal/distal)	0.03	**0.06**	0.06	**0.13**
Z-axis, (anterior/posterior)	0.07	**0.15**	0.04	**0.08**
Total translation	0.09	**0.18**	0.08	**0.16**
Cup rotations (degrees)				
X-axis, (anterior/posterior)	0.20	**0.42**	0.16	**0.33**
Y-axis, (internal/external)	0.30	**0.63**	0.17	**0.35**
Z-axis, (increased/decreased inclination)	0.10	**0.21**	0.11	**0.23**
Total rotation	0.22	**0.46**	0.18	**0.38**

Table 2. Median (range) translations and rotations of the acetabular cup at the 1-year follow-up measured with RSA and CT-RSA.

	RSA (n=26)	***CT-RSA (n=28)***
	Median (range)	Median (range)
	Cup migration (mm)	
X-axis (medial/lateral)	0.06 (-0.38 - 0.90)	0.00 (-0.39 - 0.83)
Y-axis, (proximal/distal)	0.13 (-0.10 - 1.75)	0.11 (-0.15 - 2.00)
Z-axis, (anterior/posterior)	-0.01 (-1.50 - 0.39)	-0.08 (-0.90 - 0.22)
Total translation	0.21 (0.05 - 2.50)	0.22 (0.04 - 2.23)
	Cup rotations (degrees)	
X-axis, (anterior/posterior)	0.00 (-1.21 - 0.54)	-0.01 (-1.15 - 0.55)
Y-axis, (internal/external)	-0.11 (-0.62 - 1.42)	0.06 (-0.41 - 2.04)
Z-axis, (increased/decreased inclination)	-0.04 (-1.92 - 2.38)	-0.11 (-1.96 - 5.65)
Total rotation	0.67 (0.06 - 2.81)	0.53 (0.10 – 5.68)

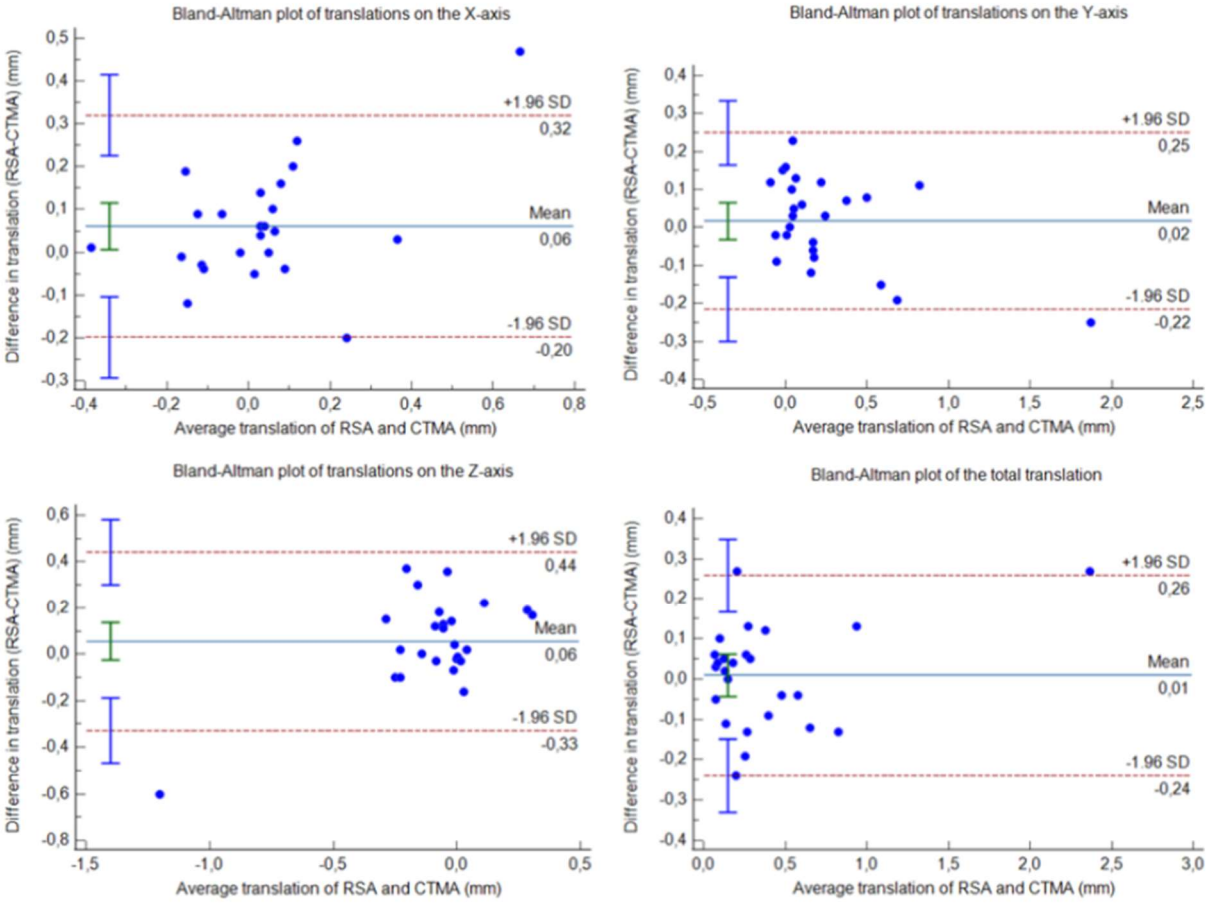

Figure 10 Bland–Altman plots for translations on each axis and for total translation: Limits of Agreement (red, dotted) with 95% CIs in light blue; bias (blue, solid) with 95% CI in green.

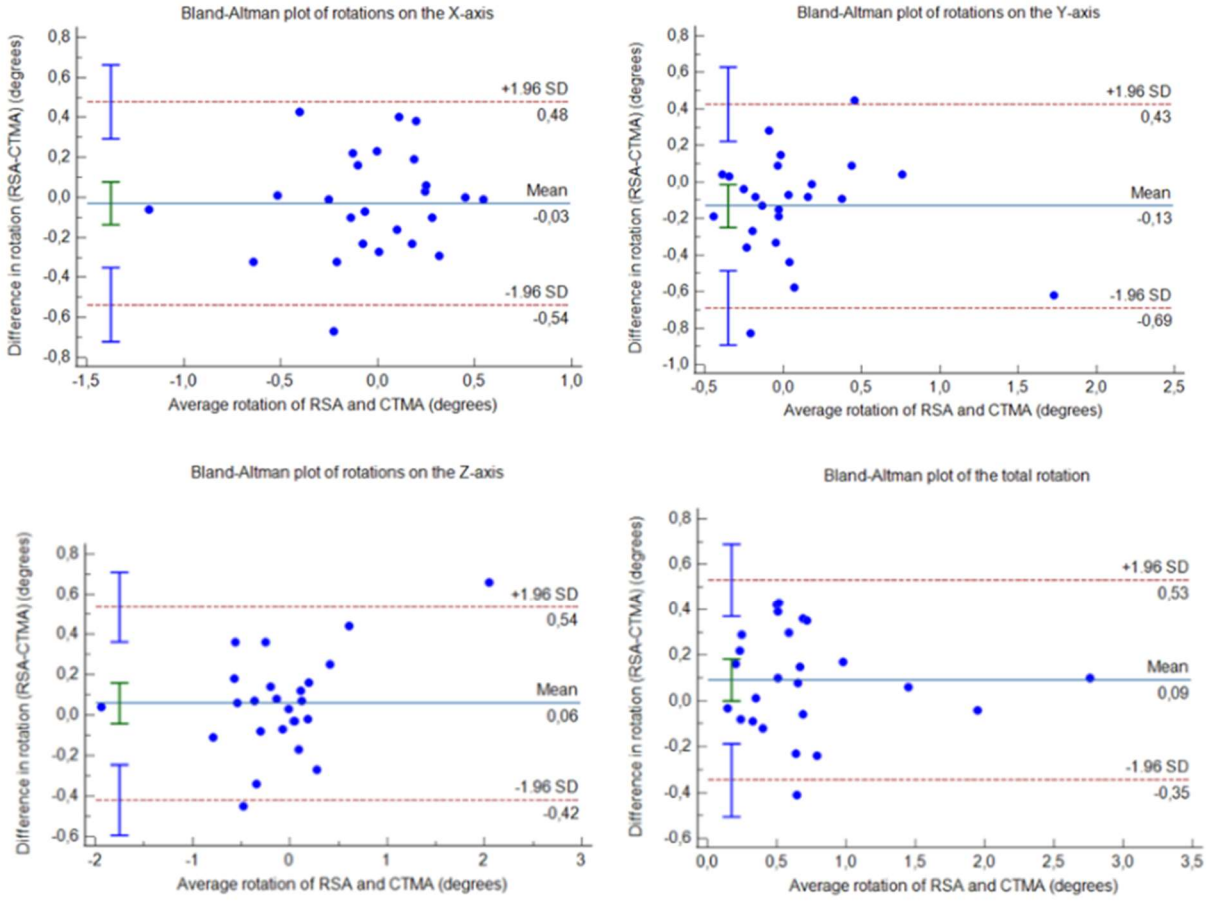

Figure 11 Bland–Altman plots for rotations about each axis and for total rotation: Limits of Agreement (red, dotted) with 95% CIs in light blue; bias (blue, solid) with 95% CI in green.

9.2 STUDY II

Refobacin Bone Cement R vs Palacos R+G: Femoral stem migration and PROM at the 2-year follow-up

Demographics

The complete demographics of this patient cohort are reported in Table 3.

Clinical precision of RSA

In this setup, the precision of RSA for translations along the Y-axis was 0.17 mm, with precision values for the other axes listed in Table 4.

Cement penetration and stem positioning at baseline

Cement mantle quality was assessed in the 14 Gruen Zones, as well as mean varus/valgus positioning of the femoral stem, with no statistically significant differences among the three groups ($p = 0.127$ and $p = 0.196$, respectively). All values are summarized in Tables 5 and 6.

Femoral stem migration

The median (range) translations along the Y-axis at 2 years in mm were: for the Refobacin Optivac system, -0.79 mm (-2.01 to -0.09); for the Refobacin Optipac system, -0.75 mm (-2.16 to 0.20); and for the Palacos Optivac system, -1.01 mm (-4.31 to -0.29). Detailed values for translations along all three orthogonal axes, as well as total translation at all five time points, are provided in Table 7.

No significant differences were observed in stem migration and subsidence along the Y-axis among the three groups at 2 years post-operatively ($p = 0.111$). Proximal-distal migration of the stem followed a similar trend over time in all three groups. Stems cemented with Palacos R+G showed a slightly higher median distal migration at all time points, but this was not statistically significant at 2 years (Figure 12).

PROM

PROM improved across all three groups (Table 8). No significant differences were detected in clinical outcomes at the 2-year follow-up ($p > 0.05$).

There were no complications or adverse effects recorded during the study or follow-ups. No revisions were performed in this cohort for any reason to date.

Table 3 Patient demographics were comparable across the three study arms: the number of participants (N), mean age, and mean BMI did not differ meaningfully between groups.

Cement Type	***N***	***Mean Age (SD)***	***Mean BMI (SD)***
Palacos R + G (Optivac)	22	68 (4.1)	26.5 (4.2)
Refobacin Bone Cement R (Optivac)	23	68.7 (4.2)	26.3 (4.2)
Refobacin Bone Cement R (Optipac)	26	69 (5)	27 (4.2)
Sum	**71**	**68.6 (4.5)**	**26.6 (4.1)**

Table 4 Based on 72 paired examinations, MBRSA precision in measuring stem migration was calculated. Precision in millimeters is defined as the standard deviation (SD) x t, where t is the critical value from the t-table for 95% CI with n-1 degrees of freedom (n=72).

	RSA	
Axes of translation	**SD**	**Precision**
X-axis (medial/lateral)	0.07	**0.13**
Y-axis, (proximal/distal)	0.09	**0.17**
Z-axis, (anterior/posterior)	0.21	**0.43**
Total translation	0.17	**0.35**

Table 5 Cement penetration at baseline graded per Barrack et al. across the three cement groups is reported as percentages and absolute counts by grade in a cross-tabulation; the Chi-square test shows no significant group differences.

Cement penetration according to Barrack et al.

	Palacos Optivac	**Refobacin Optivac**	**Refobacin Optipac**
A	63.6% (14)	52.2% (12)	34.6% (9)
B	36.4% (8)	47.8% (11)	65.4% (17)
C	0% (0)	0% (0)	0% (0)
D	0% (0)	0% (0)	0% (0)
Chi-Square = 4.13, P=0.127			

Table 6 Femoral stem varus/valgus alignment at baseline is reported in degrees as mean and SD for each of the three groups. No statistical difference in alignment was noted across the groups.

Cement type	***Varus/valgus position of the femoral stem***
Palacos Optivac	1.25 (0.77)
Refobacin Optivac	1.85 (1.50)
Refobacin Optipac	1.39 (1.19)
P=0.196	

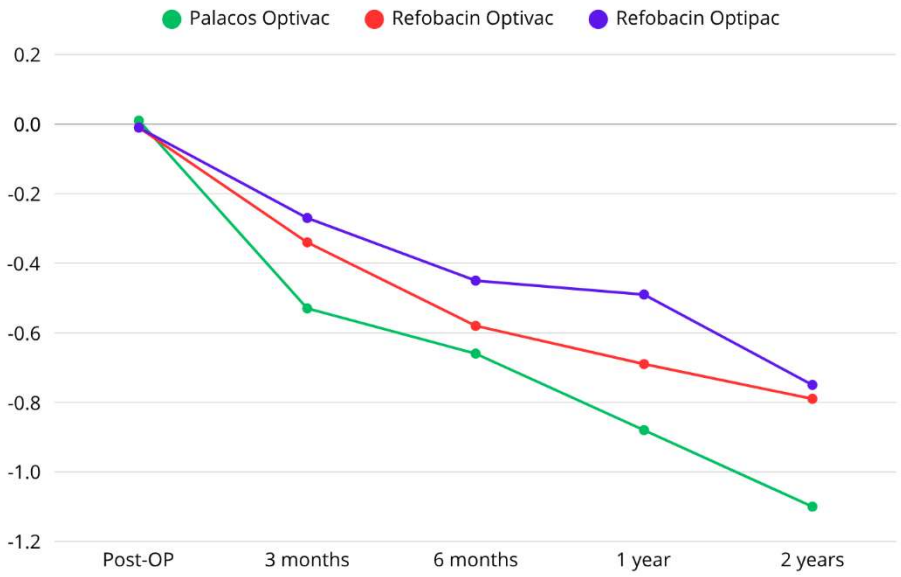

Figure 12 Median stem migration along the Y-axis for all three groups at the five follow-up time points presented in mm. Each follow-up time point is represented with a dot of corresponding colour, please see legend.

Table 7 Femoral stem migration across the three cement groups is reported in millimetres as median (range) at five follow-up time points.

Palacos Optivac

	Post-OP	**3 months**	**6 months**	**1 year**	**2 years**
X-axis	0.02 (-0.14 – 0.18)	-0.09 (-0.34 –0.63)	0.01 (-0.53 – 0.64)	-0.04 (-0.36 – 0.60)	-0.03 (-0.61 – 0.74)
Y-axis	0.01 (-0.20 – 0.18)	-0.53 (-1.84 – -0.11)	-0.66 (-2.49 – -0.13)	-0.88 (-3.25 – -0.28)	-1.01 (-4.31 – -0.29)
Z-axis	0.03 (-0.52 – 0.33)	-0.31 (-2.07 – 0.54)	-0.50 (-1.46 – 0.89)	-0.48 (-1.89 – 0.04)	-0.65 (-2.53 – 0.45)
Total Translation	0.17 (0.05 – 0.58)	0.71 (0.29 – 2.10)	0.94 (0.35 – 2.68)	1.12 (0.47 – 3.69)	1.34 (0.60 – 4.63)

Refobacin Optivac

	Post-OP	**3 months**	**6 months**	**1 year**	**2 years**
X-axis	-0-01 (-0.06 – 0.13)	-0.08 (-0.28 – 0.20)	-0.04 (-0.48 – 0.64)	-0.07 (-0.47 – 0.44)	-0.05 (-0.29 – 0.80)
Y-axis	-0.01 (-0.10 – 0.09)	-0.34 (-1.34 – 0.03)	-0.58 (-1.45 – -0.04)	-0.69 (-1.80 – -0.04)	-0.79 (-2.01 – -0.09)
Z-axis	0.01 (-0.46 – 0.21)	-0.28 (-1.25 – 0.43)	-0.42 (-1.66 –0.15)	-0.45 (-1.70 – 0.53)	-0.64 (-2.91 – -0.25)
Total Translation	0.09 (0.02 – 0.46)	0.54 (0.17 – 1.80)	0.74 (0.37 – 2.23)	0.93 (0.47 – 2.49)	1.12 (0.38 – 3.04)

Refobacin Optipac

	Post-OP	**3 months**	**6 months**	**1 year**	**2 years**
X-axis	0.01 (-0.13 – 0.12)	-0.02 (-0.28 – 0.58)	-0.05 (-0.59 – 0.95)	0.02 (-0.32 – 1.05)	0.06 (-0.44 – 1.18)
Y-axis	-0.01 (-0.32 – 0.17)	-0.27 (-1.19 – 0.20)	-0.45 (-1.16 – -0.01)	-0.49 (-1.85 – -0.16)	-0.75 (-2.16 – 0.20)
Z-axis	0.03 (-0.95 – 0.89)	-0.21 (-0.93 – 0.62)	-0.41 (-1.54 – 0.48)	-0.56 (-1.79 – 0.86)	-0.74 (-2.53 – 0.45)
Total Translation	0.13 (0.02 – 0.96)	0.62 (0.21 – 1.23)	0.81 (0.32 – 1.89)	1.05 (0.34 – 2.21)	1.48 (0.22 – 2.97)

Table 8 Patient reported clinical outcomes. HHS (Harris Hip Score), OHS (Oxford Hip Score), UCLA Activity Scale and FJS (Forgotten Joint Score) are presented preoperatively and at the 2-year follow-up as median and range.

Cement combination		***Preoperatively***	***2-year follow-up***
Palacos Optivac	**HHS**	51 (20-69)	86.5 (0-91)
	OHS	18.50 (8-38)	46.50 (19-48)
	UCLA	4.5 (2-9)	6 (3-8)
	FJS	4.2 (0-31.3)	78.15 (0-100)
Refobacin Optivac	**HHS**	50 (23-73)	80 (0-91)
	OHS	21 (10-34)	45 (14-65)
	UCLA	3 (2-8)	6 (3-9)
	FJS	6.3 (0-54.2)	64.6 (0-100)
Refobacin Optipac	**HHS**	48.5 (23-81)	82.5 (0-91)
	OHS	18.5 (10-40)	46 (25-48)
	UCLA	3 (2-8)	6 (4-9)
	FJS	8.3 (0-62.5)	72.9 (8-100)

9.3 STUDY III

CT-RSA measurements of femoral stem migration and corresponding intra- and interobserver reliability

Femoral Head Migration at 1-Year Follow-Up

The precision of MBRSA for translations along the Y-axis was 0.06 mm, with precision values for the other axes detailed in Table 9. At 1-year, the median (IQR) translations along the Y-axis measured using MBRSA were -0.86 mm (-1.10 to -0.37), compared to -0.83 mm (-1.11 to -0.48) with CT-RSA. The median (IQR) total migration was 1.11 mm (0.61 to 1.38) for MBRSA and 1.12 mm (0.79 to 1.55) for CT-RSA. Comprehensive data for femoral head migration on the X, Y, and Z axes are summarized in Table 10.

The median difference (95% CI) between the two methods on the Y-axis was -0.03 mm (-0.08 to 0.18). Importantly, the 95% CI of differences in translation measurements did not include the minimal important difference of 0.2 mm for any axis, supporting the comparability of the two methods in assessing translation (Table 10).

Bland-Altman analysis for the Y-axis (proximal/distal femoral head translation), revealed no proportional bias and demonstrated a bias (LoA) of 0.05 mm (-0.62 to 0.73) between the methods. All paired measurements on the Y-axis were contained within the LoA and their corresponding 95% confidence intervals (CI) (Figure 13). Similar analyses across the remaining axes (Figure 13) confirmed minimal discrepancies between the methods, with no proportional bias detected.

Intra- and Interobserver Reliability

The CT-RSA method demonstrated excellent intra- and interobserver reliability for translations along the Y-axis, with ICC (95% CI) of 1 (0.99–1) and 0.99 (0.99–1), respectively. Interobserver reliability on the X-axis was good, while intra- and interobserver reliability for the other axes were excellent (Table 11).

Table 9 Bias, standard deviation and precision of MBRSA in measuring stem migration are presented below in mm, based on 27 double examinations. Precision is expressed as SD x t, where SD: standard deviation and t: critical value from the Student's t-distribution for n-1 degrees of freedom (n=27).

	RSA		
Axes of translation	Bias	SD	**Precision**
X-axis (medial/lateral)	0.010	0.04	**0.08**
Y-axis, (proximal/distal)	0.001	0.03	**0.06**
Z-axis, (anterior/posterior)	-0.003	0.07	**0.14**
Total translation	0.080	0.04	**0.08**

Table 10 Median (IQR) femoral stem migration at 1-year measured by MBRSA and CT-RSA (n=27) reported in mm. Median differences between the methods (Δ) with 95% CI are also presented. X-, Y-, and Z-axes represent medial/lateral, proximal/distal, and anterior/posterior directions, respectively.

	RSA	***CT-RSA***	***Δ RSA – CT-RSA***	
	Median (IQR)	Median (IQR)	Median	95% CI
		Stem migration (mm)		
X-axis	-0.02 (-0.22 to 0.14)	-0.05 (-0.27 to 0.09)	0.03	[-0.40 to 0.27]
Y-axis	-0.86 (-1.10 to -0.37)	-0.83 (-1.11 to -0.48)	-0.03	[-0.08 to 0.18]
Z-axis	-0.45 (-0.59 to -0.18)	-0.44 (-0.70 to -0.21)	-0.01	[-0.32 to 0.18]
Total translation	1.11 (0.61 to 1.38)	1.12 (0.79 to 1.55)	-0.01	[-0.32 to 0.03]

Table 11 Intra- and interobserver reliability of CT-RSA, presented as intraclass correlation coefficients (ICC) with corresponding 95% CI.

	Intraobserver reliability		***Interobserver reliability***	
Axis	**Mean**	**95%CI**	**Mean**	**95%CI**
X-axis	0.91	[0.81 to 0.96]	0.82	[0.80 to 0.83]
Y-axis	1	[0.99 to 1]	0.99	[0.99 to 1]
Z-axis	0.94	[0.86 to 0.97]	0.91	[0.80 to 0.96]
Total translation	0.98	[0.97 to 0.99]	0.97	[0.93 to 0.98]

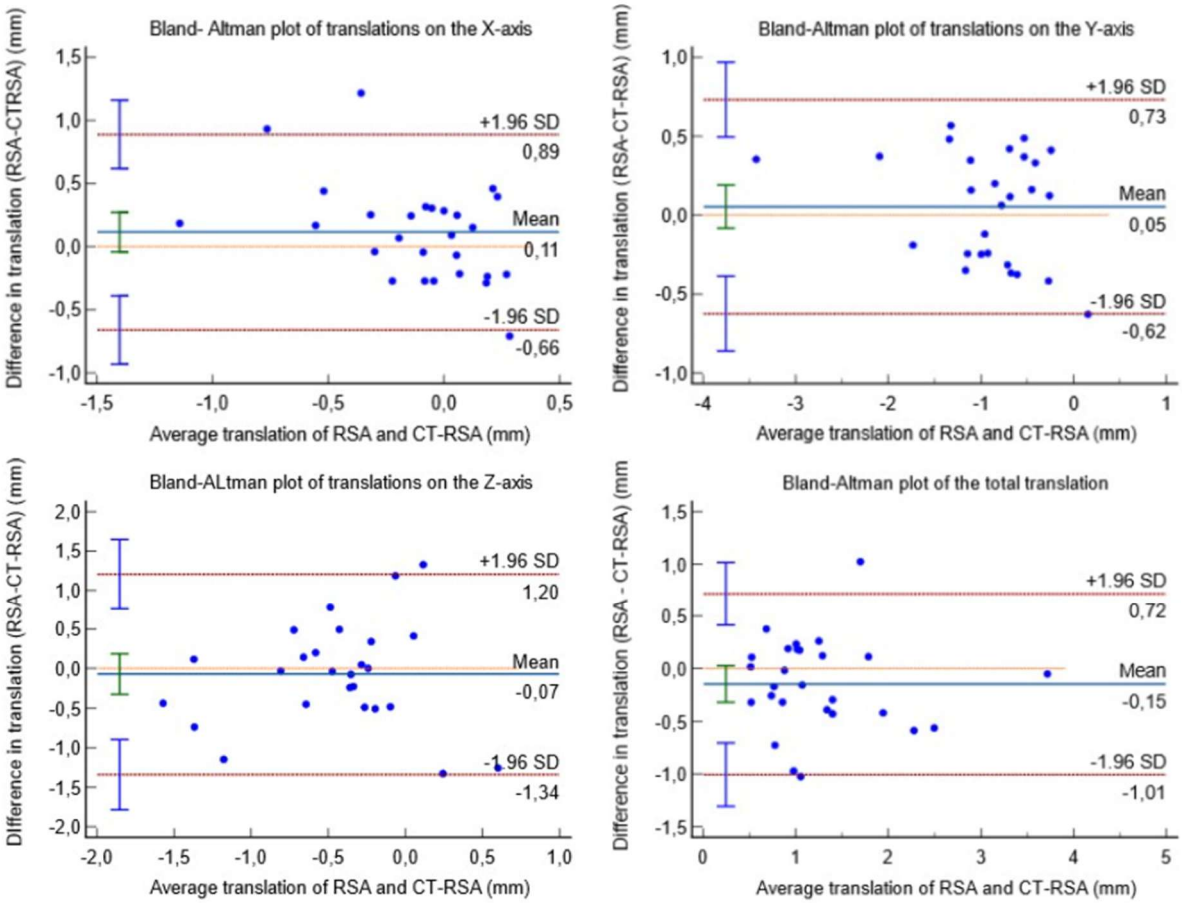

Figure 13 Bland-Altman plots for translations along the three orthogonal axes, as well as for total translation. Limits of Agreement (LoA) are shown as dotted, red lines with their 95% confidence intervals in light blue. Bias is shown as a solid, blue line with 95% confidence intervals (CI) in green.

9.4 STUDY IV

Precision, accuracy, and reliability of the CT-RSA method in an experimental setting

Precision

The precision of CT-RSA in the actual coordinate system was 0.08 mm for the X-axis, 0.06 mm for the Y-axis, and 0.07 mm for the Z-axis. After applying a 45° counterclockwise coordinate transformation to account for the platform's/implant's orientation, the precision was 0.06 mm along both the X′- and Y′-axes and remained 0.07 mm along the Z′-axis. Detailed values can be found in Table 12.

Accuracy

Accuracy of CT-RSA on the actual coordinate system was 0.09 mm for the X-axis, 0.13 mm for the Y-axis, and 0.11 mm for the Z-axis. In the transformed coordinate system, accuracy was 0.03 mm for the X′-axis, 0.14 mm for the Y′-axis, and 0.11 mm for the Z′-axis. Detailed values can be found in Table 13.

Intra- and interobserver reliability

Intraobserver reliability was excellent, with ICC (95% CI) 0.99 (0.98–0.99) for both the X- and Y-axes, and 0.99 (0.97–0.99) for the Z-axis. Interobserver reliability was also high, though slightly more variable, with ICCs of 0.91 (0.74–0.97) for the X-axis, 0.98 (0.93–0.99) for the Y-axis, and 0.96 (0.88–0.99) for the Z-axis. Detailed values can be found in Table 14.

Table 12 CT-RSA precision based on 60 double examinations reported along three orthogonal axes: X, Y, Z (original translation axes) and X', Y', Z' (transformed). Mean and SD of the differences between double examinations, as well as the corresponding precision (SD x t) for each axis are presented in millimetres.

Precision Estimates

Actual data				**Transformed**			
Axis	Mean	SD	**Precision**	Axis	Mean	SD	**Precision**
X	0.015	0.041	**0.08**	**X´**	0.001	0.031	**0.06**
Y	0.001	0.030	**0.06**	**Y´**	0.011	0.031	**0.06**
Z	-0.014	0.034	**0.07**	**Z´**	-0.014	0.034	**0.07**

Table 13 CT-RSA accuracy based on 90 paired measurements reported along three orthogonal translation axes: original (X, Y, Z) and transformed (X', Y', Z'). mean signed differences (Bias) and Root Mean Square Error (RMSE) of the differences between CT-RSA and micrometre platform readings, as well as the corresponding accuracy (RMSE x t) for each axis are presented in millimetres.

Accuracy Estimates

Actual data				**Transformed**			
Axis	Bias	RMSE	**Accuracy**	Axis	Bias	RMSE	**Accuracy**
X	0.011	0.05	**0.09**	**X´**	0.002	0.02	**0.03**
Y	0.008	0.07	**0.13**	**Y´**	0.013	0.07	**0.14**
Z	-0.035	0.06	**0.11**	**Z´**	-0.035	0.06	**0.11**

Table 14 Intra- and interobserver reliability is presented as mean intraclass correlation coefficients (ICC) with 95% CIs on the original X, Y, and Z translation axes.

Reliability

	Intraobserver reliability		**Interobserver Reliability**	
Axis	**Mean**	**95% CI**	**Mean**	**95% CI**
X	**0.99**	0.98-0.99	**0.91**	0.74-0.97
Y	**0.99**	0.98-0.99	**0.98**	0.93-0.99
Z	**0.99**	0.97-0.99	**0.96**	0.88-0.99

10 DISCUSSION

10.1 STUDY I

Interpretation of own results

The findings of Study I showed that CT-RSA achieves precision comparable to the MBRSA for assessing early acetabular cemented cup migration. The precision values obtained for CT-RSA were in the range of 0.06 to 0.13 mm for translations and 0.23° to 0.35° for rotations, which closely paralleled those of RSA (0.06 to 0.15 mm for translations and 0.21° to 0.63° for rotations). The primary outcome focused on proximal–distal translations along the Y-axis, the most clinically relevant migration direction for predicting aseptic loosening. The precision of 0.13 mm achieved by CT-RSA for Y-axis translations is below the clinically important threshold of 0.2-1.0 mm for proximal cup migration [6]. The total migration precision of 0.16 mm for CT-RSA versus 0.18 mm for RSA further indicates comparability of the two methods. This suggests that CT-RSA has a level of precision that could facilitate its adoption as an alternative method for assessing early acetabular cup migration and can reliably detect clinically meaningful migration patterns that may predict long-term implant survival [6].

The Bland-Altman analysis showed good agreement between CT-RSA and RSA measurements, with 95% LoA for Y-axis translations of -0.22 mm to 0.25 mm. This narrow range suggests that the two methods produce clinically comparable results for migration on the Y-axis (proximal-distal).

An additional advantage of CT-RSA is its marker-free workflow: three patients excluded from RSA analysis due to suboptimal marker placement were successfully analysed with CT-RSA. This demonstrates CT-RSA's capacity to include cases otherwise lost to follow-up.

Limitations and methodological considerations

Several limitations need to be acknowledged. First, CT-RSA lacks objective quality metrics analogous to RSA's CN and ME. Instead, it relies on software-based colour maps and overlays subject to analyst interpretation, which may introduce variability.

Another limitation was that the study's sample size, while adequate for precision analysis based on established RSA research guidelines, was relatively small with only 30 patients enrolled and complete evaluation possible for 26-28 patients depending on the analysis method. The exclusion of five patients from the one-year follow-up (one due to COVID-19 pandemic, one due to poor CT image quality, and three due to inadequate RSA marker placement), although clearly documented, inevitably reduced statistical power.

The radiation dose consideration represents another important limitation. While the mean effective dose of 0.8 mSv for CT-RSA was within acceptable limits, it was approximately four times higher than the 0.2 mSv dose for RSA. This difference becomes more significant when considering long-term longitudinal studies requiring multiple CT examinations over several years. However, advances in low-dose CT protocols [80–82] have demonstrated the potential to reduce radiation exposure to levels approaching those of RSA while maintaining adequate image quality [64].

Generalizability is limited by the exclusive use of cemented acetabular cups; uncemented components, femoral stems, or other joints may yield different precision due to varying implant designs and fixation interfaces. Interobserver reproducibility was not assessed, as all measurements were performed by a single analyst, precluding evaluation of user-to-user consistency. Finally, coordinate system alignment required an adjustment in CT-RSA to match RSA axes, introducing a minor source of uncertainty.

Synthesis of own results with literature

This study is the first clinical comparison of MBRSA and CT-RSA for cemented acetabular components. Prior CT-RSA investigations have been largely in vitro or used markers in vivo, often with heterogeneous implants and small cohorts, limiting direct comparison. For example, Brodén et al. [12,13] evaluated CT-RSA for acetabular cups and reported precision values around 0.1 mm, consistent with our findings. Similarly, Olivecrona et al.[10] found high correlation and similar precision between CT-RSA and RSA in an experimental setting. Our clinical results corroborate these findings, confirming that CT-RSA attains comparable precision in clinical scenarios.

Early proximal–distal migration exceeding 0.2–1.0 mm within two years is a well-established predictor of aseptic loosening [6,7,41], as already discussed. The close agreement between CT-RSA and RSA within these thresholds

supports CT-RSA as a robust clinical alternative capable of detecting migration predictive of long-term implant survival.

It is noteworthy that prior studies [14,71] have shown variable precision with CT-RSA depending on the implant type and anatomical region. In comparison, our findings consistently showed higher precision, possibly attributable to current optimized image acquisition protocols, standardized patient positioning, and preceding analyst training. Furthermore, previous studies have often not included the stringent double examinations and/or pilot intraobserver reliability tests as part of the analyst training regime that were part of our protocol. This methodological rigor may explain why our precision values are at the upper end of what has been reported previously.

Radiation dose remains the major trade-off between image quality and patient safety. Although CT-RSA's susceptibility to metal artefacts has been noted [69], a recent study suggests that higher radiation dosages do not improve resolution in implant micromotion measurements [83], likely reflecting advances in modern low-dose acquisition protocols. Contemporary protocols achieve sub-1 mSv hip CT-scans while preserving image quality for migration analysis [83], removing a major barrier to wider CT-RSA adoption.

Clinical implications

CT-RSA offers a marker-free, prospective and retrospective option for postoperative surveillance of cemented acetabular implants. Its compatibility with standard clinical CT scanners facilitates implementation in multicentre trials and registry studies lacking RSA infrastructure. Despite a modest increase in radiation dose, optimized low-dose protocols can minimize exposure, supporting CT-RSA's broader clinical adoption. Further interobserver validation and long-term studies are recommended before CT-RSA fully substitutes RSA in implant migration research.

10.2 STUDY II

Interpretation of own results

The main finding of this randomized controlled trial was that, at two years no significant differences in early femoral stem migration were evident between the Palacos Optivac, Refobacin Optivac, and Refobacin Optipac groups. Palacos R+G cement exhibited slightly greater median distal migration at two years, although statistically insignificant. All three cohorts demonstrated subsidence within the expected range for force-closed, polished, triple-tapered stems [18,84]. RSA measurements confirmed minimal variation in migration patterns across cement types and mixing systems, indicating comparable early mechanical stability and good early fixation of the femoral stem for both cement types and mixing systems.

Moreover, our secondary outcome measures revealed consistent stem alignment and satisfactory cement mantle quality across all groups. Although approximately half of the cases were classified as Barrack score B [3] (indicating less optimal cement mantle), this result might reflect the learning curve associated with the introduction of a new femoral stem design at our institution rather than inherent issues with cement or mixing systems. Importantly, no Barrack C or D mantles were observed. Additionally, all PROM demonstrated postoperative improvement without statistically significant differences between the three groups at the two-year follow-up.

Limitations and methodological considerations

Several methodological factors must be considered when interpreting the findings of this study. First, our relatively small sample size restricts the ability to detect outcomes such as infection or early implant failure, which typically require much larger cohorts and longer follow-ups [85]. Additionally, we did not investigate rotational migration along the longitudinal stem axis because our implants lacked pre-embedded tantalum beads by the manufacturer. This decision aimed to avoid restricting implant choices, thus enhancing optimal biomechanical reconstruction possibilities. Although not directly assessed, slight posterior translation of the femoral head (slightly above 0.5 mm) observed at two years could indirectly indicate stem retroversion. Previous literature, however, suggests that detailed retroversion measurements add limited additional value when

subsidence data are available for force-closed designs, such as MS-30 and Exeter stems [18,84]. Another methodological limitation was the absence of intra- and interobserver reliability measurements, which we recommend including in future RSA studies of this type. Furthermore, surgical approaches—either the direct lateral (Gammer) [77] or posterior (Moore) [78] approach—were chosen according to individual surgeon preference, reflecting common practice in Sweden. We deliberately avoided standardizing surgical approach to prevent introducing a potential surgical confounder that could affect clinical outcomes.

Synthesis of own results with literature

Earlier research by Olerud et al. reported a mean distal migration of 1.28 mm at two years for the MS-30 stem using Refobacin Bone Cement R cement [86]. Our observed distal migration across all three investigated groups was notably lower compared to their findings. One of the potential reasons for this difference could be the fact that Olerud et al [86] employed only two predetermined stem sizes (8 and 10), each with standard and lateral offsets. In contrast, our study individualized stem size and offset selections based on preoperative planning tailored to each patient's anatomy. Furthermore, Olerud et al. [86] reported mean values assuming a normal distribution, whereas our data, presented as medians, reflected non-normal distribution. Nevertheless, both studies demonstrated a similar trend characterized by a gradual decrease in the rate of distal subsidence over time.

In agreement with our findings, van der Voort et al. [29] found no significant differences between Refobacin Bone Cement R and Palacos R+G during two-year follow-up using model-based RSA. However, they reported substantially lower median distal migration (0.37 mm) compared to our study. This discrepancy could be attributed to differences in implant design; van der Voort et al. utilized a collared Stanmore femoral component, categorized as a shape-closed design, inherently less prone to subsidence. In contrast, the collarless MS-30 femoral stem that we used, is a force-closed design, and naturally allows distal migration [87]. Prior studies confirm that force-closed designs, such as MS-30 and Exeter stems, demonstrate continued distal migration extending beyond ten years postoperatively [18,84].

All PROM demonstrated expected postoperative improvements, with no significant differences among groups at two-year follow-up, corroborating findings from earlier studies assessing these cement types [29,86].

Clinical implications

Refobacin Bone Cement R with either mixing system and Palacos R+G, perform similarly in terms of femoral stem fixation and PROM at the two-year endpoint, according to our data. Our results indicated slightly greater, although statistically insignificant, median distal migration with Palacos R+G cement. Thus, extending RSA and clinical follow-up beyond two years (potentially up to five or ten years) could clarify the clinical importance of this numerical difference and provide deeper insights regarding long-term performance and potential implications for clinical practice.

10.3 STUDY III

Interpretation of own results

Our results demonstrated that CT-RSA is comparable to MBRSA for evaluating early distal migration of the femoral head, effectively serving as a surrogate measure of femoral stem subsidence. Furthermore, excellent intra- and interobserver reliability was found, suggesting minimal user dependency, provided analysts have received appropriate training with the CT-RSA software.

Limitations and methodological considerations

Several methodological limitations need consideration. Firstly, a notable constraint of CT-RSA compared to MBRSA, as already mentioned in the discussion of Study I, is the absence of quantitative metrics such as CN and ME. Instead, CT-RSA segmentation and registration accuracy relies heavily on a software-generated colour-coding system [8,12,88] combined with subjective analyst judgment. Thus, the results depend partially on the analyst's experience, though previous research indicates that even relatively inexperienced users can achieve high repeatability and reliability after adequate training [57].

Additionally, our study was unable to directly evaluate the precision of the CT-RSA method due to technical issues during immediate postoperative double examinations, specifically movement artefacts and omission of artefact reduction protocol in the second CT-scan. While we successfully estimated the precision for the RSA setup, future studies should proactively address similar technical concerns to reliably assess CT-RSA precision as precise measurement is critical for distinguishing methodological errors from true implant migration.

Another limitation arose from the femoral components not being pre-marked with tantalum beads by the manufacturer, precluding MBRSA measurements of rotations around the three axes. The decision to avoid marking the implants aimed at preserving the flexibility of implant selection for optimal biomechanical reconstruction, given that patients were participants in a larger RSA migration study. Although small posterior translations of the femoral head centre (slightly exceeding 0.4 mm) observed after one year might imply stem retroversion, existing literature

suggests detailed rotational analysis may offer limited additional insights when subsidence data is available for force-closed stem designs, including the MS-30 stem [18,84], as already discussed. While rotations could theoretically be measured using CT-RSA, rotations were deliberately set to zero to maintain comparability with MBRSA, which did not have available data on rotations. Hence, a comparison of rotations between the methods was not feasible.

Furthermore, using femoral head migration to represent femoral stem migration might be considered as a limitation. However, the direct anatomical and functional relationship between the femoral head and stem supports its appropriateness as a practical surrogate for detecting femoral stem migration in clinical practice.

Technical problems led to the exclusion of three patients from the CT-RSA analysis at one year, primarily due to poor resolution and patient movement artefacts. Sandberg et al. [64] previously addressed these issues and recommended proactive measures such as pilot scans, extended CT-scales, and optimization of CT protocols before patient enrolment. We suggest that future studies adopt these guidelines to mitigate resolution-related exclusions.

Lastly, our study exclusively evaluated polished cemented femoral stems, potentially limiting the applicability of these results to other fixation methods employed in THA.

Synthesis of own results with literature

Our findings align with previous clinical and experimental studies evaluating CT-RSA for measuring femoral stem migration [51,57]. For instance, Christensson et al. [51] recently reported strong concordance between AI-based CT-RSA and model-based RSA for measuring stem and cup migration at five-year follow-up, with mean differences falling within RSA precision ranges, thus supporting methodological comparability. Furthermore, Christensson et al. [51] observed no detectable intra- or interobserver variability, underscoring the consistency and user-independent nature of AI-based CT-RSA. Unlike their study, our investigation utilized conventional rather than AI-based CT-RSA but similarly confirmed strong comparability between CT-RSA and MBRSA in evaluating femoral head translation.

Recent literature includes clinical trials, pilot studies, and phantom experiments demonstrating that low-dose CT-RSA can deliver precision

levels comparable to and radiation doses slightly higher than those of RSA [10,12,13,51,69,70]. Previous studies reported effective doses ranging from 0.33 mSv in experimental settings [10] to between 0.2–2.3 mSv in clinical THA studies [8,13]. The mean effective dose measured in our study (0.8 mSv; range 0.5–1.2 mSv) adheres to guidelines recommended by the European Commission's "Radiation protection 99" (1998) [52]. Although CT examinations involve greater radiation exposure than RSA, we argue that the advantages of CT-RSA—such as eliminating the need for implanted markers, specialized RSA facilities, and reducing patient exclusion due to inadequate marker visibility or poor marker configurations—outweigh radiation concerns.

A recent experimental study by Øhrn et al. [89], involving porcine cadaveric tibial implants, demonstrated comparable precision between very low-dose CT scans (0.02 mSv) and standard-dose scans. Though Øhrn et al.'s research was not clinical and performed on tibial components rather than femoral, it implies potential for further dose reductions without compromising CT-RSA resolution. Thus, optimizing CT-scan protocols to reduce radiation exposure appears feasible and necessary for long-term clinical follow-up studies, as previously suggested [50].

Additionally, two different cement types were utilized in femoral stem fixation in this study. However, we assumed that the cement type had no influence on femoral head and stem segmentation, and thus it was not taken into account in the radiological and statistical analysis.

Clinical implications

Our results suggest that CT-RSA is a reliable alternative to MBRSA for assessing femoral stem subsidence following cemented THA. The method's high intra- and interobserver reliability further supports its clinical applicability, showing minimal observer dependency when users are appropriately trained. Future longitudinal RSA and clinical evaluations extending beyond one year could further validate whether observed migration differences hold clinical significance over extended periods. Given its methodological advantages, CT-RSA represents a valuable technique, particularly in clinical environments lacking specialized RSA infrastructure or for retrospective studies where implanted markers are unavailable.

10.4 STUDY IV

Interpretation of own results

In this in-vitro study we evaluated the precision, accuracy and observer reliability of CT-RSA for femoral stem micromotion under controlled conditions. Precision for translations was 0.06–0.08 mm on the actual axes and 0.06–0.07 mm after aligning the coordinate system to the conventional RSA frame. Accuracy ranged from 0.03 to 0.14 mm depending on axis and intra- and interobserver reliability were excellent. Taken together, these findings show that CT-RSA can detect micromotions below or near one-tenth of a millimetre with little observer dependence when imaging and analysis follow a standardized protocol. The effective dose in this experimental setting was very low (0.08 mSv per scan), indicating a low radiation burden suitable for method development, although clinical protocols may use different doses.

Limitations and methodological considerations

Several constraints temper direct extrapolation to clinical practice. First, an in-vitro phantom lacks soft-tissue interference, patient motion, and metal-related artefacts typical of actual patient imaging. These factors generally degrade imaging quality compared to an experimental setup. Second, the migration analysis was performed in the platform's/phantom's plane and subsequently rotated counterclockwise by 45° to match the anatomical RSA frame. While such a rigid rotation does mathematically not alter the data, it remains a derived construct rather than a direct physical measurement. Any segmentation or registration error present before the transformation remains, though, unchanged afterwards. Third, accuracy was referenced to micrometre platform readings and although the platform was calibrated and has a high nominal linear accuracy, small mechanical inaccuracies are still possible residual error sources. Fourth, rotations were set to zero by design to harmonize with point-motion analyses; rotational precision and accuracy—relevant for some stem designs—were therefore not assessed. Finally, although radiation in the experimental protocol was negligible, clinical CT-RSA typically entails higher (yet still low) doses, and dose optimization remains an issue for longitudinal trials.

Synthesis of own results with literature

Our in-vitro evaluation of CT-RSA for femoral stem migration demonstrated sub-tenth-millimetre precision (0.06–0.07 mm) and accuracy (0.03–0.14 mm) on the RSA reference axes, with excellent intra- and interobserver agreement. These results position CT-RSA performance in our study within, and in several respects at the favourable end of, the performance spectrum reported for both experimental and clinical applications of CT-RSA. The precision we observed match or exceed prior CT-RSA studies [56,71,90], a difference that is plausible given our controlled experimental setting, where patient motion, soft-tissue interference, metal artefacts, and image acquisition were not an issue compared to clinical imaging.

When contrasted with earlier experimental work, the accuracy profile of CT-RSA in our study shows the expected axis-specific variability: X′ and Y′ accuracy compared favourably with previous phantom and cadaveric studies [69,90], while Z′ accuracy was less favourable than one isolated report citing ≈0.04 mm [90]. Such discrepancies likely arise from heterogeneity in phantoms (foam bone vs synthetic femur vs cadaver), reference standards (bead-based [90] vs marker-free registration [69]), segmentation thresholds, and—crucially—the choice of error metric and software used for registration and analysis. For example, prior studies have used non-dedicated software (e.g., generic segmentation suites [90]) or alternative accuracy definitions (e.g., signed errors [69]), each of which can shift point estimates independent of true method performance.

Observer reliability in our experimental study was uniformly excellent. This strengthens a growing body of evidence that CT-RSA can be used with high repeatability when analysts have received training and apply predefined segmentation thresholds and registration protocols. Notably, in vivo femoral stem migration studies have likewise reported excellent intra-/interobserver reliability using CT-RSA, supporting the generalizability of our reliability findings beyond the laboratory [45,57].

Radiation performance in our setup (mean effective dose = 0.08 mSv per scan) is well below typical clinical ranges reported for low-dose CT-RSA protocols, which span roughly 0.2–2.3 mSv, with several clinical implementations around ~0.8 mSv [8,45]. The lower dose in our phantom context is expected, but the broader literature indicates that clinically acceptable exposures can be achieved while maintaining precision [81–83]. This underscores the feasibility of longitudinal CT-RSA surveillance in

trials, provided dose-optimization and standardized acquisition are enforced.

Clinical implications

In an in-vitro setting, CT-RSA achieved high measurement precision and accuracy for femoral stem translations, with excellent intra- and inter-observer reliability. These results indicate that, under controlled conditions, CT-RSA provides robust estimates of femoral stem migration. Clinical implementation should be coupled with standardized image acquisition and analysis protocols, structured analyst training, and radiation dose optimization. Under such conditions, CT-RSA is suitable for longitudinal surveillance of implant migration. However, further in-vivo validation is needed to confirm performance in clinical practice.

10.5 CROSS-STUDY SYNTHESIS

Across four complementary studies, low-dose CT-RSA demonstrated measurement performance comparable to MBRSA for both cups and stems, while the randomised cement trial found no clinically meaningful differences in early stem migration or PROM between Refobacin Bone Cement R and Palacos R+G, and no mixing-system effect. These findings support CT-RSA as a validated, marker-free alternative for early migration surveillance in cemented THA and reaffirm RSA-based stepwise introduction for assessing new cements and measurement methods.

11 CONCLUSION

Paper I: CT-RSA is comparable to MBRSA in terms of precision and in measuring proximal cemented cup migration postoperatively up to 1 year. This suggests that CT-RSA is a viable method for assessing early acetabular cup migration in cemented THA.

Paper II: At the 2-year follow-up, the cemented MS-30 femoral stem demonstrated a similar distal migration pattern when comparing Palacos R+G mixed with Optivac to Refobacin Bone Cement R mixed with either the Optivac or Optipac mixing systems. No significant differences were observed in PROM at the 2-year follow-up. Moreover, no adverse events or revisions were reported in this cohort to date. Our data suggest that both Refobacin Bone Cement R and Palacos R+G provide comparable stable stem fixation in THA, when using a force-closed stem design.

Paper III: Our findings support the use of the CT-RSA method as a reliable alternative to MBRSA for measuring femoral head subsidence in cemented THA. Furthermore, the CT-RSA method demonstrates excellent intra- and interobserver reliability in a clinical setting, indicating that it is assessor-independent, provided the assessor has received appropriate training in the CT-RSA software.

Paper IV: CT-RSA has good accuracy and precision in detecting the migration of femoral stems in an experimental setting, using very low-dose CT imaging. Additionally, both intraobserver and interobserver reliability were found to be excellent, indicating minimal dependence on the assessor.

Despite these promising results, careful consideration of radiation exposure and image-quality optimization remains essential before widespread clinical adoption. Clinical studies are warranted to determine whether CT-RSA represents a suitable alternative to traditional RSA for migration measurements in total hip arthroplasty.

12 FUTURE PERSPECTIVES

Study I

Future research should include larger patient cohorts and longer follow-up periods to fully establish CT-RSA's clinical relevance and confirm its long-term comparability with RSA. It would also be valuable to explore automated segmentation and analytical software solutions, aiming to enhance reproducibility and reduce potential observer variability. Additionally, further optimization of CT protocols is necessary to minimize radiation exposure, thereby promoting broader clinical adoption. Expanding this method into multicentre studies could validate its robustness across different clinical settings and enhance the generalizability of the results.

Study II

Long-term follow-up studies beyond the current two-year horizon are warranted to assess whether the observed minor differences in femoral stem migration between different cement types and mixing systems become clinically significant over time. Extended clinical outcomes such as implant survival rates, revision frequency, and PROM should be monitored to clarify potential long-term implications. Additionally, future investigations could benefit from a multicentre approach with larger cohorts to increase generalizability and address possible rare outcomes not detected in smaller single-centre studies.

Study III

Future studies should aim to address technical limitations related to image quality and patient movement artefacts by incorporating suggested improvements such as pilot CT scanning, extended imaging scales, and optimized scanning protocols. Furthermore, it is essential to evaluate the applicability of CT-RSA across various femoral stem designs and fixation methods to enhance the method's clinical versatility. Comprehensive assessments including rotational migration analyses are also recommended, as this could further strengthen the validity of CT-RSA. Ultimately, additional research involving larger patient populations will be crucial for confirming the method’s reliability, accuracy, and robustness compared to traditional MBRSA.

Study IV

This in-vitro study confirmed that CT-RSA can detect small, controlled micromotions with high precision and accuracy. However, the findings are constrained by the use of a synthetic bone model and an idealized experimental environment. Future studies should involve clinical validation in patients, preferably comparing CT-RSA data against long-term implant survival outcomes. Additionally, optimizing CT protocols for radiation minimization and standardizing segmentation workflows are key to advancing CT-RSA as a practical clinical tool for follow-up of implant migration in THA.

13 THE PHD CANDIDATE'S CONTRIBUTION TO THE THESIS

The PhD candidate actively participated in the design and methodological planning of all four studies included in this thesis. Additionally, the candidate independently conducted all statistical analyses for each study and was responsible for drafting, writing and revising all manuscripts. Furthermore, in studies III and IV, the candidate performed all primary CT-RSA analyses, ensuring methodological consistency throughout these studies.

14 RELATED ARTICLES NOT INCLUDED IN THE THESIS

1. Angelomenos, V., Björkman, A., Shareghi, B., Andreasson I., Ullman M. Bone substitute in distal radius osteotomy: a prospective randomized double-blinded study on micromotion and outcomes in 42 patients up to one year. *Archives of Orthopaedic and Trauma Surgery* 145, 178 (2025).

2. Angelomenos, V., Sandberg, O., Shareghi, B., Ullman, M. Comparison of marker-based RSA and CT-RSA for analyzing micromotions after distal radius osteotomy: a 1-year retrospective study of 24 patients. *Journal of Orthopaedic Research* 43: 660-670 (2025).

15 ACKNOWLEDGEMENTS

I would like to thank the following for their direct or indirect support during my voyage of research and writing of the thesis:

My main supervisor **Maziar Mohaddes** and co-supervisors **Raéd Itayem** and **Bita Shareghi** for guiding me from scratch to dissertation. Their support at every step from the beginning and beyond has been invaluable.

My co-authors, professors **Johan Nils Kärrholm** and **Henrik Malchau** for their invaluable contribution in these studies, both in technical terms and advice. A great thank you to you both.

My wife **Daryna** and my daughter **Eva Lydia** for their support when morale was down and for putting up with me with love.

My parents in Greece, for their emotional support and raising me as child to have grit and overcome obstacles in life.

Olof Sandberg, engineer and employee at Sectra Corp., for his technical support, insightful advice, and solution-oriented approach to resolving the technical challenges encountered during studies I, III, and IV.

Sectra Corp. (Linköping, Sweden) for providing access to the CTMA software and financial support for the CT scans performed during Study IV.

Zimmer Biomet Corp. (Warsaw, IN, USA) for their generous financial contribution covering the additional follow-up costs and MBRSA radiography in the parent study.

Göteborgs Läkaresällskap (The Gothenburg Society of Medicine) and **Guldbyxans Stiftelse** (The Golden Trousers Foundation) for generously supporting the PhD candidate's research activities and the writing of this dissertation.

Västra Götalands Region (The Region of West Götaland) together with **Sahlgrenska University Hospital** for their financial support in study IV and funding to conduct three months of research.

My colleagues at **The Hand Surgery Department in Gothenburg,** where I work now permanently, for their support, understanding and for further employing my research skills in future hand and wrist arthroplasty studies.

The heads of the Hand Surgery Department **Martin Byström** and **Dag Vikingsson** for their understanding, support and time provided to complete my research in time.

Professor **Anders Björkman** for creating an excellent research environment at the Hand Surgery Department, that allowed me to complete my dissertation in time.

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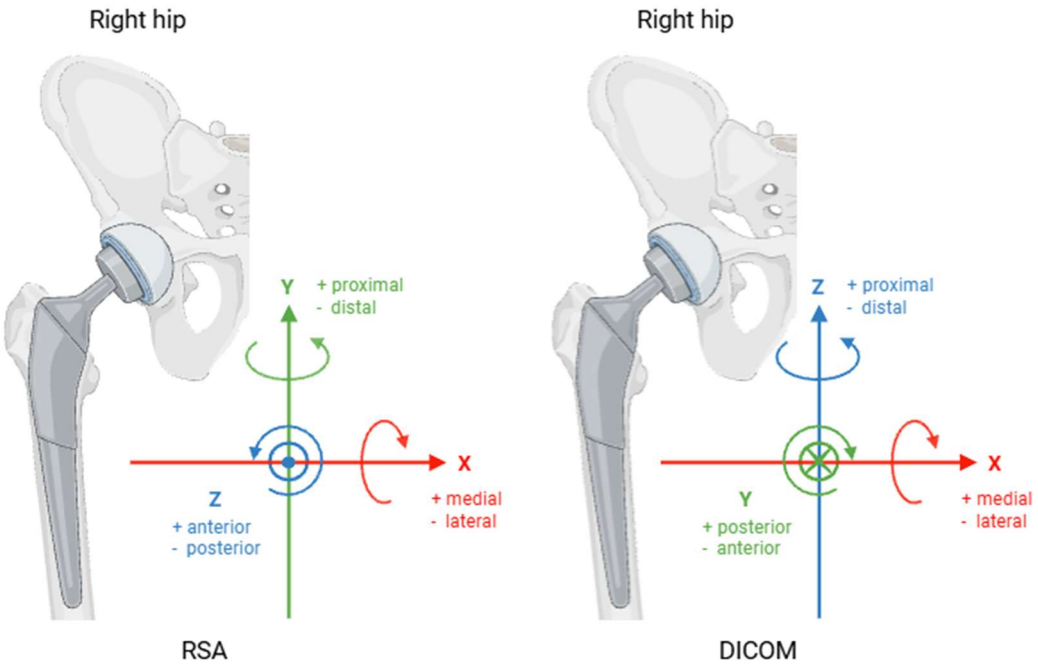
17 APPENDIX

A. EQUATIONS

- $Precision = \mathrm{SD}_\Delta \times t_{n-1}$, $\mathrm{SD}_\Delta = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}\left(d_i - \bar{d}\right)^2}$
  where d_i are the paired differences from repeated measurements under identical conditions (double examinations) and t_{n-1} the critical t value from Student's t-table for a two-sided 95% CI for n-1 DOF, and n the number of paired measurements.

- $Accuracy = \mathrm{RMSE} \times t_{n-1}$, $\mathrm{RMSE} = \sqrt{\frac{1}{n}\sum_{i=1}^{n} e_i^2}$
  where RMSE is the root square mean error of the differences between known and observed measurements, t is defined as above and n the number of observations.

- $\mathrm{R}_z(\theta) = \begin{bmatrix} \cos\theta & -\sin\theta & 0 \\ \sin\theta & \cos\theta & 0 \\ 0 & 0 & 1 \end{bmatrix}$
  was the rotation matrix around the Z-axis used to transform the data in Study IV, where θ is the wanted rotation angle.

B. COORDINATE SYSTEMS

- The DICOM CT coordinate system and the conventional RSA coordinate system differ in orientation. Before extraction of migration numerical values in CT-RSA, the DICOM coordinate system needs to be adjusted to match that of RSA.