Radiostereometric Analysis in Unicompartmental Knee Arthroplasty

An Analysis of Marker Placement

IMKE ANNA MARIA GEVERS

A thesis submitted to
Delft University of Technology,
Erasmus University Rotterdam
and Leiden University

In partial fulfillment of the
requirements for the degree of

MSc. Technical Medicine
Track Imaging & Intervention

17 MAY 2022

THESIS REPORT

[This page intentionally left blank]

RADIOSTEREOMETRIC ANALYSIS IN UNICOMPARTMENTAL KNEE ARTHROPLASTY

- An Analysis of Marker Placement -

Imke Gevers

Student number: 4375343

17 May 2022

Thesis in partial fulfilment of the requirements for the joint degree of Master of Science in

Technical Medicine

Leiden University ; Delft University of Technology ; Erasmus University Rotterdam

Master thesis project (TM30004 ; 35 ECTS)

Dept. of Biomechanical Engineering, TUDELFT

September 2021 – May 2022

Supervisor(s):

dr. ir. Bart Kaptein

drs. Hennie Verburg

dr. ir. Jantsje Pasma

Thesis committee members:

Prof. dr. ir. Jaap Harlaar, TU Delft (chair)

dr. ir. Bart Kaptein, LUMC

dr. Gerald Kraan, TU Delft / RHOC

dr. ir. Jantsje Pasma

Universiteit Leiden

TU Delft Delft University of Technology

Erasmus Universiteit Rotterdam

[This page intentionally left blank]

Preface

Before you lies my graduation thesis, containing the result of research conducted in the Reinier Haga Orthopedisch Centrum from September – May 2022. With this research I'm able to obtain my Master of Science by fulfilling the graduation requirements of the Master degree of Technical Medicine.

Almost eight years ago I started my academic journey as one of the first 100 students that were able to attend the bachelors of Klinische Technologie. Not knowing where I would get into, I moved to the 'big' city with an open mind. If you would have told me what kind of person I would have become just a couple of years later and all the memories I would have obtained, I would not have believed it. It has been an amazing, hectic, stressful but most importantly fulfilling journey of finding myself and gaining a lot of knowledge in the field that I love.

The last two years of internships in the clinical field have shown me the possibilities that we have as a 'Klinisch Technoloog'. Just one week after starting my first clinical internship, the most unexpected thing happened when the COVID pandemic put the entire world to a stop. Showing the flexibility of a real TM student, we started a non-profit student organization to develop an emergency ventilator. After the summer, I was ready to try again and officially kick-off my clinical internships. Starting at the department of invertention radiology and nuclear medicine in the LUMC, where I was fortunate to work with a lot of Technical Physicians that should me the ropes of working in a hospital. My second internship at the department of sportsmedicine and orthopaedics in the EMC showed me my real passion for the musculoskeletal systems. At my third internship at the transplantation department of the LUMC I regained my love for coding and creating my own programs. Lastly, a very different internship at Stryker fulfilled my international curiosity.

Now that my time as a student has come to and end, I can be thankful for all the amazing opportunities that I got. Not only from our study department but also all the extra-curricular roles I was able to perform. It is a time of reminiscing of the wonderful experience, but also a time to look into the future and be excited for all the opportunities that are still to come.

Acknowledgements

I would like to express my sincere appreciation to my supervisors for their contributions and continued support throughout this thesis. Jantsje, thank you for being involved with my research on a daily basis and giving me the feeling your door was always open for a good intellectual discussion. Our contradicting personalities where I sometimes want to move fast and possibly act before thinking and you being more of a contemplator really pushed me to improve myself. I am also very thankful for your positive attitude and open mindedness which helped me to push through the tougher times. When it was needed you were very flexible in providing a new timeline because of sickness or help me in changing the scope of my research. Bart, thank you for taking the time to project all your extensive knowledge on radiostereometric analysis on me. I really appreciated all the effort you put in to giving me the information and data needed to perform this research. When my research needed to take a completely different route, you helped me to regain my focus and find a new subject to delve into. Also, I would like to thank all orthopaedic surgeons and residents from the RHOC for being so open and welcoming me in your daily clinical tasks. I really enjoyed myself with all the fun conversations in the operating room and cups of coffee during the outpatient clinic. I have never been in a clinical environment that was more accessible than this centre and it really helped to involve myself as a clinical professional. In specific, I would like to thank Hennie Verburg and Gerald Kraan for their involvement in my research. From the occasional walk by to ask how it was going, to the eventful MAKO surgeries.

Lastly, I would to thank my loving friends and family who have supported me continuously. You were there during the entire process and gave me a good balance between helping me with substantive questions but also knowing when to help me blow of some steam. The unconditional support I felt from you and the limitless of believe in my capabilities truely make you the best company I could have ever wished for.

Imke Gevers
Delft, May 2022

[This page intentionally left blank]

Table of Contents

List of Abbreviations

Abbreviation	Meaning
OA	Osteoarthritis
TKA	Total Knee Arthroplasty
UKA	Unicompartmental Knee Arthroplasty (also known as; Unicondilar Knee Arthroplasty / Partial Knee Arthroplasty)
RSA	Radiostereometric Analysis
CN	Condition Number
NSAID	Nonsteriodal Antiinflammatory Drugs
ACL	Anterior Cruciate Ligament
PCL	Posterior Cruciate Ligament
PPK	Persona® Partial Knee implant
DE	Double Examination
AP	Anterior-Posterior
ML	Medial-Lateral

I

TM Literature Study

Migration of Unicompartmental Knee Replacements; a Systematic Review

Imke A.M. Gevers[1], Jantsje H. Pasma[2], Bart L. Kaptein[3], Hennie Verburg[2]

[1] Student MSc Technical Medicine, Delft University of Technology; Erasmus Medical Centre Rotterdam; Leiden University Medical Centre, the Netherlands. [2] Research Department, Reinier Haga Orthopaedic Centre, Zoetermeer, The Netherlands. [3] Department of Orthopedics, Leiden University Medical Centre, Leiden, The Netherlands

Abstract

Background: Studies have shown inconsistent results regarding the long-term survival of unicompartmental knee arthroplasty (UKA). Radiostereometric analysis (RSA) can be used to assess early migration which has shown high predictive value for later aseptic component loosening.

Objective: Systematically review the initial and continuing migration of unicompartmental knee replacements. The secondary aim was to review clinical outcome and RSA functionality.

Method: A systematic literature search was performed using PUBMED and Cochrane Library on October 4th, 2021. The primary outcome was translation, rotation and maximum total point motion (MTPM) of the tibial and femoral component at 1.5, 3, 6, 12 and 24 months (longer if available). The clinical outcome was evaluated using the revision rate and mean revision time. The RSA functionality was evaluated using the cut-off value for condition number, precision interval of double examination and RSA success rate.

Results: The literature search yielded 502 hits of which 13 studies were included, comprising 16 study populations reviewing 442 knees. The initial mean migration values at 12 months follow-up ranged from 0.47mm to 1.58mm for MTPM, <0.01mm to 0.53mm for translation and 0.06° to 2.08° for rotations. The continuing migration between 12 and 24 months ranged from <0.01mm to 0.50mm for MTPM, <0.01mm to 0.13mm for translation and <0.01° to 0.35° for rotation. The mean revision rate at 2 years follow-up was 1.3%. The CN cut-off value ranged from 95-150. The maximum precision intervals were 0.37mm for translation and 0.77° for rotation. The mean RSA success rate was 93% for the initial post-operative analysis and 79.9% for the follow-up periods.

Interpretation: This systematic review shows that there are few RSA studies for UKA. Adherence to existing international standards and guidelines is low regarding migration outcome measures, consistent follow-up intervals, CN cut-off values and precision measurements. Hence, it is difficult to evaluate the quality of the RSA studies and compare results. The majority of the studies reported a mean MTPM that stabilizes after 12 months and translations and rotations that stabilize after 3 months. Further research is recommended to create adherence in RSA guidelines, provide long-term follow up and improve RSA functionality regarding precision interval and RSA success rate.

Keywords: Unicompartmental Knee Arthroplasty · Radiostereometric Analysis · Migration · Systematic Review

Introduction

Osteoarthritis (OA) is a degenerative joint disease which is characterized by the deterioration of joint cartilage. The most common symptom is pain, followed by stiffness and swelling, which leads to activity restrictions.[1,2] It constitutes a leading cause of disability in the adult population, with the knee as the most affected joint. Approximately 10% of the population above the age of 55 suffer from knee osteoarthritis and 25% of them are severely disabled by their disease.[3,4] Treatment of knee osteoarthritis commonly starts with non-operative treatment modalities which include nonsteroidal antiinflammatory drugs (NSAIDs), intra-articular injections, activity modification, physical therapy and knee bracing. In case non-operative treatments are not sufficient, osteo arthritis can be treated with knee arthroplasty.[4]

The knee consists of three separate compartments; the medial, lateral and patella-femoral compartment. In 85% of the knees presented with clinical OA, the disease is isolated in the medial compartment of the knee.[5,6] This discovery revolutionized knee replacement surgery through the development of unicompartmental knee arthroplasty (UKA).[7] UKA offers several potential benefits in comparison with total knee arthroplasty (TKA) including less-invasive surgical exposure, preservation of native bone stock, retention of crucial ligaments, lower perioperative morbidity, enhanced postoperative recovery and improved patient satisfaction.[8–10] However, studies have shown inconsistent results regarding the long-term survival of UKA compared to TKA. With

data from the UK and Australian registries showing a much higher revision rate in UKA but independent studies with the Oxford UKA showing comparable results with the TKA.[5,11,12] The most common failure modes for UKA are instability, progression of disease to another compartment and aseptic loosening of the tibial component. Along with revision for unexplained pain and infection, these are the most frequent reasons for revision.[13,14] An explanation for the varying revision rates for UKA is a difference in the threshold for the revising surgeon for conversion of UKA to TKA, where some believe the revision is simple and comparable to a primary TKA.[13,15] In addition, research is showing a correlation between the experience of UKA surgeons and the revision rate. Where it indicates that low volume UKA surgeons, performing often less than 15 UKAs per year, have higher rates of revision.[12,13,16] The widespread performance of UKA has been limited by the technical difficulty of performing the procedure. In particular, UKA has less tolerance for acceptable component positioning when compared to TKA.[17] Evidence suggests that increased usage (>20%) is associated with decreased revision rate. To achieve this usage rate, surgeons could either change their indications for UKA resulting in more UKAs performed, or refer the patients eligible for UKA to specialized high volume UKA surgeons.[12,18] Another possible solution is the use of robotic-assisted technology which has made performing UKA technically less demanding.[17] Both increase of usage rates, specializations in UKA and the upcoming robotic-assisted technology could indicate better performance of UKA over time.

Aseptic loosening is one of the common reasons for revision of UKA.[19] Radiostereometric analysis (RSA) has shown a high predictive value for later aseptic component loosening.[20,21] RSA is the assessment of early migration by analyzing the motion of the implant using three-dimensional X-ray imaging.[22] This can be achieved by placing tantalum markers in the patients bone and either attaching markers (in)to the prosthesis, called marker-based RSA, or matching a virtual projection of a 3D model with the contours of the radiographic projection of the implant, called model-based RSA.[23] The quality of the RSA depends on the precision and accuracy of the measurement and the successful placement of the tantalum markers. The accuracy can be determined with an experimental saw-bone study and the precision by performing double examination during one of the follow-up periods.[24] The successful placement of the markers is dependent on their location, i.e. distribution, visibility and stability of the markers. The condition number (CN) is a measure for the distribution of markers in the bone and a high condition number results in less accurate analyses. It has been suggested that a CN below 100 for large joints will provide reliable results.[25,26] Visibility of the markers can be compromised by marker projection overlap or overlap with the implant. Stability is dependent on the density of the bone in which the marker is placed. The RSA images can not be analyzed sufficiently if there are not enough visible and stable markers or if the condition number is to high.

Over time there have been several RSA studies performed to investigate the migration of unicompartmental knee implants. However, as of now there is no systematic overview of the migration results of these studies. The objective of this research is to systematically review the migration reported in RSA studies of unicompartmental knee replacements. This will help new studies to compare there results to earlier performed research and determine if newer techniques (e.g. robotic-assisted surgery) improve the migration rate of UKA. In addition, the survival rate and their relation to migration will be reviewed. The second goal of this research is to review the RSA functionality, regarding condition number, precision and successful placement of markers.

Materials and Methods

This study is reported in accordance with the PRISMA 2020 (Preferred Reporting Items in Systematic Reviews and Meta-Analysis) statement.[27]

Literature Search

A systematic literature search was performed using PUBMED and Cochrane Library. The query was designed based on MeSH (Medical Subject Headings) terms combined with free text terms describing unicompartmental knee replacements (UKR) and implant migration.

The query used for the PUBMED search was:

"*((Unicompartmental Knee Arthroplast*) OR (Unicondylar Knee Arthroplast*) OR (Partial Knee Arthroplast*) OR (Unicondylar Knee Replacement) OR (Partial Knee Replacement) OR (Unicompartmental Knee Replacement)) AND ((Migration*) OR (Micromotion*) OR (Radiostereometric Analysis[Mesh]) OR (Radiostereometric Analys*) OR (Radiostereometry) OR (Roentgen Stereophotogrammetry))*".

The query used for the Cochrane Library search was:

"*(Unicompartmental Knee Arthroplast OR Unicondylar Knee Arthroplast OR Partial Knee Arthroplast OR Unicondylar Knee Replacement OR Partial Knee Replacement OR Unicompartmental Knee Replacement) AND (Migration OR Micromotion OR Radiostereometric Analysis OR Radiostereometric Analys OR Radiostereometry OR Roentgen Stereophotogrammetry)*".

For both searches no additional filters or language restrictions were used. The date of final literature search was October 4$^{\text{th}}$, 2021.

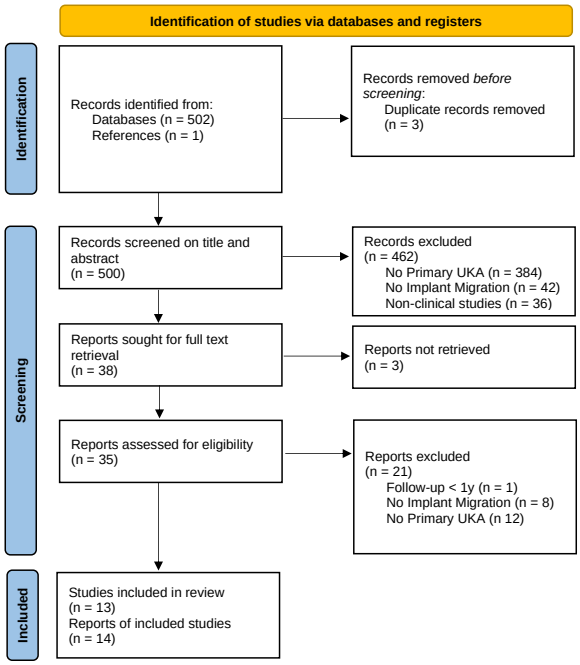


Figure 1: PRISMA flowdiagram of study selection[27]

Selection and Eligibility Criteria

Inclusion criteria specified any study measuring the migration of the tibial and/or femoral component of primary unicompartmental knee implants with a minimal follow-up of 12 months. Re-operations (revision prosthesis), non-clinical studies and articles not written in English or Dutch were excluded. One author (I.A.M. Gevers) reviewed all articles upon the search strategy and uncertainties were resolved by discussion with a second author (J. Pasma). All articles were screened using the PRISMA Flowdiagram guidelines.[27] Afterwards the references of the included articles were reviewed to check for other eligible studies. The entire selection flowdiagram can be seen in Figure 1. At the end of the literature search 14 articles reporting 13 studies were enrolled for analysis.

Outcomes

For study demographics the following data is extracted: author, year of publication, number of patients, number of knees, patient age at time of surgery, male-female ratio, implant type, medial-lateral implant ratio, number of surgeons, RSA method and mean follow-up.

The primary outcome measure was the micromotion of the tibial and/or femoral component of the unicompartmental knee implants. The two most common used presentations of micromotions are the translations and rotations as described in Figure 2 or the Maximum Total Point Motion (MTPM) which is the total three-dimensional vector displacement of the prosthesis marker with the greatest motion.[25] MTPM, translations and rotations will be described as the mean value in millimeters or degrees over the following follow-up periods: 1.5, 3, 6, 12 and 24 months. If there are longer follow-up periods they will be reported annually. The mean MTPM after the first 12 months of follow-up will be compared to the thresholds for initial migration where implants with a mean MTPM $<$0.5mm are described as promising and a mean MTPM $>$1.6mm as associated with an increased revision rate.[20,28,29] The absolute difference in mean migration between 12 and 24 months of follow-up will be compared to the thresholds for continuing migration where the implant is marked unstable (at risk of implant loosening at 10 years follow-up) if the absolute difference exceeds the following thresholds; MTPM $>$ 0.2mm, translation $>$ 0.2mm in any direction and rotation $>$ 1.0 degree in any direction.[22,30,31]

The secondary outcome measures are related to implant survival and RSA functionality. The implant survival is described with the revision rate and compared to the continuing migration thresholds. RSA functionality is described by the condition number, the precision of the RSA (measured with double examinations) and the RSA success rate determined by the amount of images that were not applicable for analysis due to a insufficiently amount of stable tantalum markers.

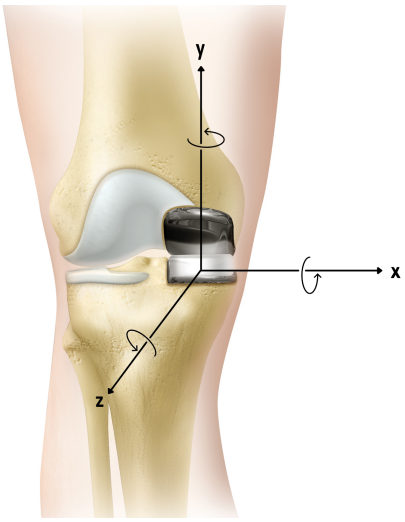


Figure 2: Orientation of translation and rotation axes. Translations are directed along the medial-lateral axis (Tx), distal-proximal axis (Ty) and posterior-anterior axis (Tz). Rotations are directed over the flexion-extension angle (Rx), internal-external rotation angle (Ry) and abduction-adduction angle (Rz).[22,32]

Data Extraction and Quality Assessment

All randomized clinical trials are assessed using the Cochrane risk-of-bias (ROB) tool to evaluate data on study demographic, quality, radiological outcome and clinical outcome.[44] All cohort studies are assessed using the Methodological Index for Non-Randomized Studies (MINORS) tool to evaluate the methodological quality

regarding eight questions .[45] All data necessary for the assessment tools was extracted and evaluated by one author (I.A.M. Gevers) and any questions in data extraction or scoring were settled by discussion with a second author (J. Pasma).

Results

Study Demographics

The literature search yielded 502 hits and 13 studies were included, covering a total of 435 patients with 442 knee replacements. Four studies were randomized clinical trials and two of them scored for the Risk of Bias Assessment an overall score of 'low risk' and the other two scored 'some concerns'. The remaining nine cohort studies had a mean MINORS score of 10.3 out of 16 with a range between 8 and 13. The detailed scoring can be found in supplementary data Section 1.1 and 1.2. The patients mean age at surgery ranged from 63 to 81 years with a median age of 69. The percentage of male patients was 47% and ranged from 0% to 88%. Eight studies had a mean follow-up period of 24 months, the remaining five studies had a longer follow-up with a maximum of 120 months. Of the four randomized control trials, three compared two different unicompartmental knee implants and one compared a unicompartmental knee implant with a total knee implant. This resulted in 16 reported RSA study populations with a total of 7 different types of knee implants of which one had cementless fixation. Eleven study populations only consisted of

Table 1: Study demographics

Study ID	Author	Year of publication	RCT	Number of Patients	Patient Age *Mean (Range)*	% Male Patients	Mean Follow-Up (Months)
1[33]	Bragonzoni et al.	2005	No	16	71 (62-82)	38	36
2[31]	Bruni et al.	2014	No	15	81 (74-87)	33	120
3[26,34]	Campi et al.	2021	Yes	39	66 (49-79)	51	60
4[35]	Carlsson et al.	2006	Yes	41	64 (49-80)	32	24
5[36]	Ensini et al.	2013	No	20	69 (53-86)	35	24
6[37]	Hyldahl et al.	2001	Yes	38	68 (NA)	45	24
7[38]	Koppens et al.	2018	No	45	64 (45-88)	49	24
8[39]	Koppens et al.	2019	Yes	62	63 (47-79)	50	24
9[40]	Linde et al.	2019	No	53	65 (63-68)	49	24
10[41]	Lindstrand et al.	2000	No	46	72 (60-91)	NA	24
11[32]	Ryd et al.	1983	No	6	69 (65-73)	0	24
12[42]	Ryd et al.	1992	No	34	69 (62-78)	88	72
13[43]	Soavi et al.	2002	No	20	72 (62-83)	30	60

Table 2: Implant information per study population

Study ID	Number of Knees	Implant	Cemented	% Medial Implants	Number of Surgeons	RSA Method*
1[33]	18	Duracon UNI	Yes	94	NA	Marker
2[31]	15	Duracon UNI	Yes	NA	NA	Marker
3a[26,34]	19	Oxford UKA	Yes	100	4	Model
3b[26,34]	20	Oxford UKA	No	100	4	Model
4[35]	41	Miller-Galante UKA	Yes	100	3	Marker
5[36]	20	Optetrak UKA	Yes	100	1	Model
6a[37]	18	Miller-Galante UKA Metal-Backed	Yes	100	5	Marker
6b[37]	20	Miller-Galante UKA All-polyethylene	Yes	100	5	Marker
7[38]	45	Sigma Medial UKA	Yes	100	2	Model
8a[39]	31	Mobile Bearing Oxford UKA	Yes	100	2	Model
8b[39]	31	Fixed Bearing Sigma UKA	Yes	100	2	Model
9[40]	53	Oxford UKA	Yes	100	3	Model
10[41]	49	Duracon UNI	Yes	89	4	Model
11[32]	6	Richard Modular Knee Prosthesis	Yes	83	NA	Marker
12[42]	36	Marmor UKA	Yes	86	NA	Marker
13[43]	20	Duracon UNI	Yes	100	NA	Marker

* Marker = marker-based RSA ; Model = model-based RSA

medial unicompartmental implants, four included both lateral and medial implants and for one study population the information was not applicable. The number of surgeons performing the arthroplasty differed between 1 to 5 surgeons. The RSA method used was eight times marker-based and eight times model-based. The complete study and implant demographics can be found in Table 1 and 2.

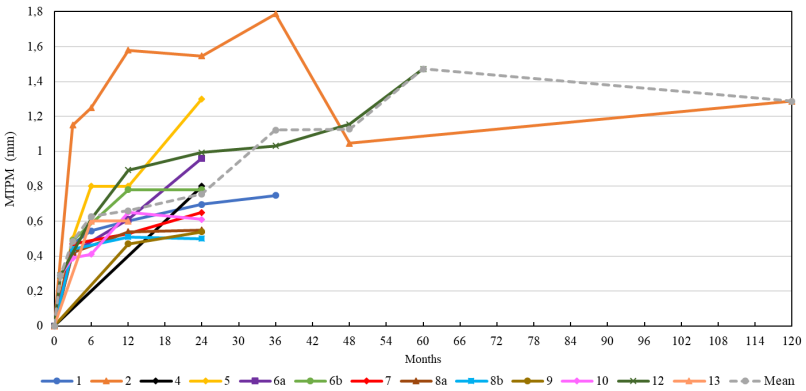
Migration Results

The maximal total point motion (MTPM) of the tibial component had been described in 11 studies for 13 different study populations with a maximum mean follow-up between 24 and 120 months.[31,33,35–43] The MTPM of the femoral component had been described in 2 studies for 3 different study populations and all had a mean follow-up of 24 months.[38,39] The results of the mean MTPM per follow-up period per study are shown in Figure 3a for the tibial component and Figure 3b for the femoral component. In addition the weighted mean MTPM, adjusted for the number of patients per study population, is plotted in these figures.

The mean MTPM of the tibial component at 12 months follow-up ranged from 0.47mm to 1.58 mm with a weighted mean of 0.66mm. The study population of Linde et al.[40] had a mean MTPM below the initial migration threshold of 0.5mm and no studies had mean MTPM values above the threshold of 1.6mm. The mean MTPM difference between 12 and 24 months follow-up of the tibial component ranged from <0.01mm to

Figure 3: Mean Maximum Total Point Motion (MTPM) per study

a. Tibial component



b. Femoral component

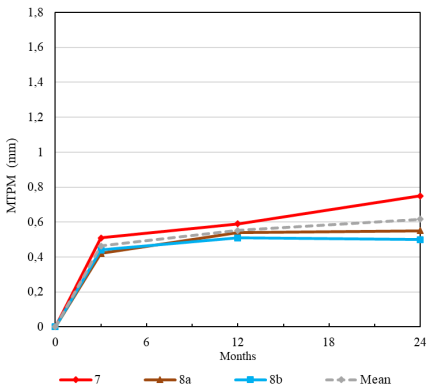


Table 3: Mean migration of tibial component

Study ID	Tx (mm)			Ty (mm)			Tz (mm)			Rx (°)			Ry (°)			Rz (°)		
	12m	24m	diff	12m	24m	diff	12m	24m	diff	12m	24m	diff	12m	24m	diff	12m	24m	diff
3a[26,34]	0.01	0.06	0.05	-0.09	-0.13	-0.04	0.00	0.03	0.03	-0.10	-0.17	-0.07	-0.02	0.03	0.05	-0.29	-0.31	-0.02
3b[26,34]	-0.04	0.01	0.05	-0.28	-0.34	-0.06	-0.01	-0.02	-0.01	-0.38	-0.40	-0.02	0.16	0.24	0.08	0.1	-0.01	-0.11
6a[37]		NA			NA			NA		0.42	0.73*	0.31	0.27	0.34*	0.07	0.71	1.00*	0.29
6b[37]		NA			NA			NA		0.48	0.53	0.05	0.31	0.26	-0.05	1.1	1.25	0.15
7[38]	0.08	0.08*	0.00	-0.04	-0.04*	0.00	0.01	0.04*	0.03	0.06	0.05*	-0.01	-0.16	-0.08*	0.08	-0.28	-0.56*	-0.28
8a[39]	0.09	0.02	-0.07	0.03	0.06	0.03	-0.11	-0.08	0.03	-0.37	-0.49	-0.12	0.02	0.02	0.00	-0.18	-0.18	0.00
8b[39]	0.04	0.05	0.01	0.04	0.04	0.00	0.03	0.03	0.00	-0.19	-0.28	-0.09	-0.28	-0.25	0.03	0.06	0.01	-0.05
11[32]	0.53	0.53	0.00	-0.45	-0.48	-0.03	-0.15	-0.18	-0.03	-0.33	-0.40	-0.07	1.10	1.27	0.17	-2.08	-2.17	-0.08

*Revised patients excluded from analysis (see Figure 5)

Table 4: Mean migration of femoral component

Study ID	Tx (mm)			Ty (mm)			Tz (mm)			Rx (°)			Ry (°)			Rz (°)		
	12m	24m	diff	12m	24m	diff	12m	24m	diff	12m	24m	diff	12m	24m	diff	12m	24m	diff
3a[26,34]	0.05	0.03	-0.02	-0.12	-0.05	0.07	0.24	0.22	-0.02	0.16	0.23	0.07	-0.05	0.32	0.37	0.25	-0.06	-0.31
3b[26,34]	-0.18	-0.05	0.13	-0.12	-0.04	0.08	0.26	0.21	-0.05	0.22	0.20	-0.02	0.24	0.23	-0.01	-0.26	0.00	0.26
7[38]	0.02	0.06*	0.04	0.06	0.11*	0.05	0.02	0.00*	-0.02	-0.08	0.11*	0.19	0.07	0.07*	0.00	0.12	0.47*	0.35
8a[39]	0.05	-0.02	-0.07	0.02	0.01	-0.01	0.15	0.15	0.00	0.08	0.17	0.09	0.25	0.38	0.13	-0.06	-0.22	-0.16
8b[39]	-0.05	-0.06	-0.01	0.06	0.07	0.01	0.02	0.01	-0.01	0.27	0.40	0.13	0.42	0.53	0.11	-0.1	-0.14	-0.04

*Revised patients excluded from analysis (see Figure 5)

0.50mm with a weighted mean of 0.10mm. The study population of Ensini et al.[36] and the Metal-Backed study population of Hyldahl et al.[37] exceeded the MTPM threshold for continuing migration of 0.2mm which marks them as unstable implants.
The mean MTPM of the femoral component at 12 months follow-up ranged from 0.51mm to 0.59mm with a weighted mean of 0.55mm. All study populations had a mean MTPM between the initial migration thresholds of 0.5 and 1.6mm. The mean MTPM difference between 12 and 24 months follow-up of the femoral component ranged from 0.01mm to 0.16mm with a weighted mean of 0.07mm. None of the femoral components exceeded the threshold for continuing migration.

The translations of the tibial component had been described in 4 studies for 6 different study populations.[26,32,34,38,39] The rotations of the tibial component had been described in 5 studies for 8 different study populations.[26,32,34,37–39] The translations and rotations of the femoral components had been described in 3 studies for 5 different study populations.[26,34,38,39]
All study populations describing migration had a maximum mean follow-up between 24 and 60 months. The mean translations and rotations at 12 months follow-up, 24 months follow-up and their difference are listed in Table 3 for the tibial component and Table 4 for the femoral component. The migration results for all follow-up moments can be found in supplementary data Section 2.1 and 2.2.
The absolute difference in mean migration between 12 and 24 months follow-up of the tibial component ranged from <0.01mm to 0.07mm for Tx, <0.01mm to 0.06mm for Ty, <0.01mm to 0.03mm for Tz, 0.01° to 0.31° for Rx, <0.01° to 0.17° for Ry and <0.01° to 0.29° for Rz. None of the tibial components exceeded the translation or rotation threshold for continuing migration.
The absolute difference in mean migration between 12 and 24 months follow-up of the femoral component ranged from 0.01mm to 0.13mm for Tx, 0.01mm to 0.08mm for Ty, <0.01mm to 0.05mm for Tz, 0.02° to 0.19° for Rx, <0.01° to 0.37° for Ry and 0.04° to 0.35° for Rz. None of the femoral components exceeded the translation or rotation threshold for continuing migration.

Clinical Outcome

The documented revision rates and their mean revision time can be seen in Table 5. Lindstrand et al.[41] did not report if there were any revisions during the follow-up period. Of the remaining 12 studies the maximum follow-up period for revision ranged from 2 to 10 years. The mean revision rate of all study populations at 2 years follow-up was 1.3% (5 revisions in a total of 393 knees). Five studies also reported revisions up to 3, 5, 6 or 10 years. Bragonzoni et al.[33] had a 3 year follow-up period and reported a revision rate of 6%. Campi et al.[26] and Soavi et al.[43] had a 5 year follow-up period and reported both a revision rate of 0%. Ryd et al.[42] had a 6 year follow-up period and reported a revision rate of 8%. Bruni et al.[31] had a 10 year follow-up period and reported a revision rate of 27%.

Eleven studies reported the amount of individual MTPM and/or migration values that exceeded the thresholds for continuing migration between 12 and 24 months of follow-up.[26,31–38,40,42,43] Of the implants that were revised after 24 months or more, 67% (6 out of 9) exceeded at least one of the thresholds for continuing migration. Of the implants that were not revised during the follow-up period, 11% (29 out of 275) exceeded at least one of the thresholds for continuing migration.

Table 5: Revision rates per study

Study ID	Number of Knees	Revised # (%)	Mean Revision Time (y)	Follow -Up (y)
1[33]	18	1 (6%)	3.0	3
2[31]	15	4 (27%)	6.3	10
3[26,34]	39	0	-	5
4[35]	41	1 (2%)	1.0	2
5[36]	20	0	-	2
6[37]	38	2 (5%)	1.6	2
7[38]	45	2 (4%)	1.7	2
8[39]	62	0	-	2
9[40]	53	0	-	2
10[41]	49	NA	-	2
11[32]	6	0	-	2
12[42]	36	3 (8%)	6.0	6
13[43]	20	0	-	5

RSA Functionality

There were six studies that reported the condition number (CN) and in those studies 5 different cut-off values were used; CN>90,[36] CN>95,[34] CN>105,[37] CN>120[38,39] and CN>150.[40] Linde et al.[40] excluded two patients because they exceeded the maximum condition number of 150. The remaining studies did not have any rigid body markers that exceeded the CN threshold. Furthermore, Campi et al.[26,34] and Linde et al.[40] measured the mean CN per follow-up period and it ranged from 35 to 58.

Three studies performed double examinations to determine the precision of RSA. Koppens et al. 2018[38] and Koppens et al. 2019[39] examined both the tibial and femoral component and Linde et al.[40] examined only the tibial component. The mean difference and precision interval (PI = 1.96 × SD) for all translation and rotation axes are shown in Table 6. The translations of the tibial component had a maximal mean difference of 0.01mm and the PI ranged from 0.04mm to 0.27mm. The rotations of the tibial component had a maximal mean difference of 0.06° and the PI ranged from 0.15° to 0.56°. The translations of the femoral component the maximal mean difference was 0.05mm and the PI ranged from 0.05mm to 0.37mm. The rotations of the femoral component had a maximal mean difference of 0.12° and the PI ranged from 0.31° to 0.77°.

Table 6: Precision of RSA by double examination; Mean Difference (Precision Interval)

Study ID	Tx (mm)	Ty (mm)	Tz (mm)	Rx (°)	Ry (°)	Rz (°)
			Tibia			
7[38]	0.00 (0.12)	0.01 (0.09)	0.00 (0.27)	0.02 (0.36)	0.04 (0.56)	0.06 (0.15)
8[39]	0.01 (0.10)	0.00 (0.07)	0.01 (0.18)	0.00 (0.36)	0.03 (0.32)	0.03 (0.27)
9[40]	0.00 (0.08)	0.00 (0.04)	0.00 (0.16)	0.01 (0.23)	0.01 (0.31)	0.01 (0.26)
			Femur			
7[38]	0.01 (0.05)	0.01 (0.08)	0.05 (0.29)	0.00 (0.45)	0.01 (0.31)	0.02 (0.45)
8[39]	0.03 (0.21)	0.00 (0.09)	0.02 (0.37)	0.00 (0.57)	0.05 (0.54)	0.12 (0.77)

Figure 4 shows the percentage of successfully executed radiostereometric analyses, in which a sufficient amount of stable markers were visible. In total, eight studies reported the RSA success rate.[32,35–40,42] Of these, three studies solely reported the success rate of the direct post-operative analyses and not at the subsequent follow-up periods. These studies had a post-operative success rate of 93%. The remaining five studies reported the success rate at every follow-up RSA. Their success rates varied between 68% - 100% with a mean success rate of 79.7%.

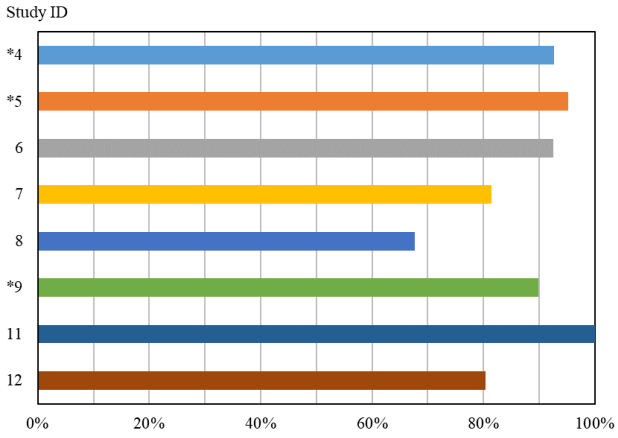


Figure 4: Percentage of successfully executed radiostereometric analyses
*Only based on post-operative analyses, not the follow-up.

Discussion and Conclusion

This systematic review described the migration results of 16 study populations containing 442 unicompartmental knee replacements. The mean MTPM of consecutively the tibial and femoral component were reported for 13 study populations containing 397 knees and 3 study populations containing 107 knees. The mean translation of consecutively the tibial and femoral component were reported for 6 study populations containing 152 knees and 5 study populations containing 146 knees. The mean rotation of consecutively the tibial and femoral component were reported for 8 study populations containing 190 knees and 5 study populations containing 146 knees.

The majority reported a mean MTPM of the tibial component that stabilized after 12 months with a weighted mean over all studies of 0.66mm at 12 months follow-up. The study population from Bruni et al.[31] showed a higher mean MTPM for all follow-up periods with a substantial decline after 48 months. This could be caused by several unstable implants that were revised between 36 and 48 months of follow-up. Other studies that investigated the same implant type[33,41,43] reported substantially lower mean MTPM results. The only difference that could be found between those studies and Bruni et al. is the difference in patient age at time of surgery. With a mean age of 81 years for Bruni et al. compared to 71, 72 and 72 years for the other studies. Literature showed that the annual revision rate of patients with an age above 75 years at time of surgery is higher compared to younger patients, this could potentially indicate that age has an influence on UKA performance.[46]
The study population from Ensini et al.[36] had the highest increase of mean MTPM between 12 and 24 months of follow-up. In the study no explanation is given for the high increase in MTPM during this follow-up period. In addition, based on the demographics no initial difference between this study and other included studies can be found besides the fact that this study is the only one that used the Optetrak UKA. Until this moment, no studies have been published comparing the migration or survival rates of the Optetrak UKA to another reviewed implant. However, a study from Catani et al.[47] reported lower clinical-functional scores for the Optetrak UKA compared to the Oxford UKA although those difference were not significant.
The mean MTPM of the femoral component had a maximum follow-up of 24 months. All studies reported a mean MTPM of the femoral component that stabilized after 12 months with a weighted mean over all studies of 0.55mm at 12 months follow-up. In the 24 months of follow-up no major differences between the study populations were noticeable.

The majority of translation and rotation of the tibial component occurs in the first 3 months and stabilizes after. The study population from Ryd et al. 1983[32] reported remarkably higher mean migration results for Tx, Ty, Tz, Ry and Rz at 12 months follow-up. This could potentially be explained by the publication year.

The UKA surgical techniques were less known in that time and surgeons were less experienced, this resulted in high failure rates when UKA was first introduced.[10,48] In addition, there were only 6 patients included which makes the mean migration very susceptible for the variety per patient.
The majority of the translation and rotation of the femoral component keep varying over the entire follow-up period of 24 or 60 months. This could indicate that the femoral component is less stable then the tibial component. This is similar to previous literature on TKA, which reported that 50%-75% of femoral components stabilize after 24 and 120 months after surgery.[49]
The direction of mean translations and rotations is varying per study for both the tibial and femoral component. This may indicate that there are no definitive directions in which the implant migrates or rotates.

Eight out of thirteen of the included studies had a mean follow-up period of 24 months. This is sufficient to investigate the initial and continuing migration given the thresholds for TKA.[21,29] However, this cannot confirm the presumption that after 24 months the implant is stabilized. All studies that reported migration for longer than 24 months show small ongoing migration in at least one of the outcome measures.[26,31,33,34,42] Bruni et al.[31] and Ryd et al. 1992[42] even showed a mean MTPM above the continuing migration threshold of 0.2mm between 24 and 60 months of follow-up. Therefore it is necessary to do more research on long term migration of both the tibial and femoral component and look into their relation to revision.

Regarding the migration and clinical outcome results there are no substantial differences between the 7 different implant types found in this systematic review as well as the included RCTs. It is not possible to perform a meta analysis on the significant differences since there are only 1-4 study populations per implant and their migration outcome measures are varying. The only cementless implant type is from study population 3b of Campi et al.[26,34] This study population reported the second highest initial translation and the highest continuing translation for Ty of the tibial component. The RCT of Campi et al.[34] also determined significantly more subsidising in the cementless components in the first 12 months. This could indicate that cementless UKA implants have higher initial and continuing subsidence compared to cemented UKA implants. Previous literature has indicated that subsiding is the main migration pattern for cementless TKAs.[50] In addition, the systematic review of Pijls et al. reported higher migration values for cementless total knee implants compared to cemented.[29] To provide the same evidence for UKA, it is required to further investigate the differences in migration and clinical outcome for different fixation types for unicompartmental knee replacements.

There is almost a 40 year gap between the first and last included report. During this period a lot of progress has been made in regards to unicompartmental knee surgery techniques.[5,51] If you compare the two earliest studies (Ryd et al. 1983[32] & 1992[42]) to the two most recent studies (Koppens et al. 2019[39] & Linde et al. 2019[40]), it can be seen that the earliest have the highest initial translation and one of the highest initial mean MTPM compared to the lowest initial and continuing mean MTPM for the most recent studies. This supports the idea that UKA techniques and outcomes have improved over time.[51]
As stated in the introduction, the experience of surgeons in performing UKA is important. Of all studies included in this systematic review none reported anything about the experience of the surgeon(s). For future research it would be of added value to have more information on surgeon UKA volumes.

The National Joint Registry reported a 4% revision rate of UKA at 2 years follow-up and a 12% revision rate at 8 years follow-up.[15] The RIPO registry reported 4% revision rate of UKA at 2 years follow-up and 13% at 10 years follow-up.[52] This indicates a longer follow-up period than two years is needed to sufficiently report clinical outcome. However, the revision rates shown in this systematic review are equivalent or even lower than stated in the literature.[15,52] Only Bruni et al.[31] reported a substantially higher revision rate than given in the literature of 27% at 10 years follow-up, which could potentially be associated with the high mean MTPM values. Furthermore, there is a noticeable relation between the continuing migration threshold and the revision rate, where 67% (6 out of 9) of the revised implants exceeded the thresholds and only 11% (29 out of 275) of the non-revised implants. However, to make the thresholds more accessible they should be adjusted to UKA to create a higher sensitivity. To make this possible, longer follow-up periods are needed. In the future, highly sensitive thresholds could potentially assist orthopedists to characterize patients that have a higher risk of revision.

The systematic review of Pijls et al.[29] showed mean precision intervals (PI = 1.96 × SD) for TKA of 0.14mm for Tx, 0.13mm for Ty, 0.20mm for Tz, 0.24° for Rx, 0.34° for Ry and 0.19° for Rz. The precision intervals reported by three of the included studies[38–40] are comparable to the mean PI of TKA for translations and slightly higher for rotations. Previous literature stated that a high condition number influences the precision of rotation more than of translation.[24,53] Future research should investigate if the condition number of UKA is usually higher than of TKA. For both TKA and UKA the translation precision interval is highest on the posterior-inferior axis (Tz). Koppens et al.[38,39] reported a PI of Tz for both components that was higher than the continuing threshold of 0.2mm. In addition, most of the mean migration results lay in the precision interval boundaries. To improve the precision one

should try to improve marker distribution, increase the redundancy of markers and standardize patient position throughout the follow-up periods.[25, 54]
A limitation of this review is the poor adherence to existing RSA guidelines.[25, 54] As recommended in the ISO standard, precision should be assessed in each clinical RSA study using double examinations. However, only three out of thirteen studies reported the precision interval. In addition, the exclusion criteria for high condition numbers (CN) should be mentioned and the standard cut-off value for large joints of CN>100 should be used.[54] Only six studies reported the CN exclusion criteria and three of them used CN cut-off values higher than recommended.
Furthermore, the number of visible markers and their stability is affecting the percentages of successfully executed radiostereometric analyses. In this systematic review this percentage has great variation between studies. Because of the small study population sizes used for RSA studies, it is important to have high success rates for the migration analyses. If different patients are excluded at each follow-up, it has a substantial influence on the mean migration values. In addition, marker placement is affecting the precision of the measurement as stated above. It is therefore recommended to do more research on marker placement for UKA RSA studies to improve marker visibility and stability.

This systematic review shows that there are few RSA studies conducted to evaluate the migration of unicompartmental knee arthroplasty. Only thirteen studies were eligible and had a minimum of 12 months follow-up on migration of the implant over a period of almost 40 years of research. Based on the quality assessment using the ROB and MINORS tools (Supplementary Data section 1.1 and 1.2) not all studies used standard protocols and thoroughly reported the methodology and results. In future research these tools should be taken into account when performing a RSA study and writing the report. In addition, the varying migration measures and follow-up periods make it more difficult to analyze the data. In line with the RSA International Standard all RSA studies should report migration with translation and rotation values and the addition of MTPM is optional.[54] Furthermore, the ISO states that the follow-up interval should at least consist of: 6 months, 1 year and 2 years. The guidelines of Valstar et al.[25] also state the importance of longer follow-up with measurements at 5, 10, 15 and 20 years. Future RSA studies of UKA should follow these international standards and guidelines to make better comparison and meta-analysis possible.

Future Recommendations for RSA in UKA

- Increase adherence to existing RSA international standard and guidelines on migration outcome measures and follow-up intervals to establish consistent and comparable results.[25, 54]
- Report longer annual follow-up periods to enable research on long term migration of the tibial and femoral component and their relation to revision.
- Report surgeon UKA volume in future RSA studies to evaluate affect of UKA volume on migration and clinical outcome.
- Further development and research on initial and continuing migration thresholds for UKA to assist orthopedists in characterizing patients at risk of revision.
- Further research on marker placement e.g. marker visibility, stability and distribution to improve precision and RSA success rate.
- Follow international standard and guidelines by using a condition number cut-off value of 100 and performing double examination for precision in every study.[25, 54]

References

[1] Mustafa Karahan. Diagnosis and management of unicompartmental knee osteoarthritis. *Marmara Medical Journal*, 16(3):228–235, 2003.

[2] Ingemar F Petersson, Torsten Boegård, Tore Saxne, Alan J Silman, and Björn Svensson. Radiographic osteoarthritis of the knee classified by the ahlbäck and kellgren & lawrence systems for the tibiofemoral joint in people aged 35–54 years with chronic knee pain. *Annals of the rheumatic diseases*, 56(8):493–496, 1997.

[3] A Dell'Isola, R Allan, SL Smith, SSP Marreiros, and Martijn Steultjens. Identification of clinical phenotypes in knee osteoarthritis: a systematic review of the literature. *BMC musculoskeletal disorders*, 17(1):1–12, 2016.

[4] Chetan Gohal, Ajaykumar Shanmugaraj, Patrick Tate, Nolan S Horner, Asheesh Bedi, Anthony Adili, and Moin Khan. Effectiveness of valgus offloading knee braces in the treatment of medial compartment knee osteoarthritis: a systematic review. *Sports health*, 10(6):500–514, 2018.

[5] Sim Johal, Naoki Nakano, Mark Baxter, Ihab Hujazi, Hemant Pandit, and Vikas Khanduja. Unicompartmental knee arthroplasty: the past, current controversies, and future perspectives. *The journal of knee surgery*, 31(10):992–998, 2018.

[6] Anurag Mittal, Prashant Meshram, Woo Hyun Kim, and Tae Kyun Kim. Unicompartmental knee arthroplasty, an enigma, and the ten enigmas of medial uka. *Journal of Orthopaedics and Traumatology*, 21(1):1–23, 2020.

[7] AA Shetty, A Tindall, P Ting, and FW Heatley. The evolution of total knee arthroplasty. part ii: the hinged knee replacement and the semi-constrained

knee replacement. *Current Orthopaedics*, 17(5):403–407, 2003.

[8] Jun W Lim, Gerard R Cousins, Benedict A Clift, David Ridley, and Linda R Johnston. Oxford unicompartmental knee arthroplasty versus age and gender matched total knee arthroplasty–functional outcome and survivorship analysis. *The Journal of arthroplasty*, 29(9):1779–1783, 2014.

[9] Adolph V Lombardi, Keith R Berend, Christopher A Walter, Jorge Aziz-Jacobo, and Nicholas A Cheney. Is recovery faster for mobile-bearing unicompartmental than total knee arthroplasty? *Clinical Orthopaedics and Related Research®*, 467(6):1450–1457, 2009.

[10] Jason M Jennings, Lindsay T Kleeman-Forsthuber, and Michael P Bolognesi. Medial unicompartmental arthroplasty of the knee. *JAAOS-Journal of the American Academy of Orthopaedic Surgeons*, 27(5):166–176, 2019.

[11] GG Jones, M Kotti, AV Wiik, R Collins, MJ Brevadt, RK Strachan, and JP Cobb. Gait comparison of unicompartmental and total knee arthroplasties with healthy controls. *The bone & joint journal*, 98(10_Supple_B):16–21, 2016.

[12] DW Murray and RW Parkinson. Usage of unicompartmental knee arthroplasty. *Bone Joint J*, 100(4):432–435, 2018.

[13] Emmanuel Thienpont. Conversion of a unicompartmental knee arthroplasty to a total knee arthroplasty: can we achieve a primary result? *The bone & joint journal*, 99(1_Supple_A):65–69, 2017.

[14] Stefan Lewold, Otto Robertsson, Kaj Knutson, and Lars Lidgren. Revision of unicompartmental knee arthroplasty: outcome in 1, 135 cases from the swedish knee arthroplasty study. *Acta Orthopaedica Scandinavica*, 69(5):469–474, 1998.

[15] DW Murray, AD Liddle, CAF Dodd, and Hemant Pandit. Unicompartmental knee arthroplasty: is the glass half full or half empty? *The bone & joint journal*, 97(10_Supple_A):3–8, 2015.

[16] Alexander D Liddle, Hemant Pandit, Andrew Judge, and David W Murray. Effect of surgical caseload on revision rate following total and unicompartmental knee replacement. *Jbjs*, 98(1):1–8, 2016.

[17] MD Mannava, Cara M Lorentzen, and Beth P Smith. Unicompartmental knee arthroplasty: Past, present, future. 2012.

[18] TW Hamilton, HG Pandit, A Inabathula, SJ Ostlere, C Jenkins, SJ Mellon, CAF Dodd, and DW Murray. Unsatisfactory outcomes following unicompartmental knee arthroplasty in patients with partial thickness cartilage loss: a medium-term follow-up. *The bone & joint journal*, 99(4):475–482, 2017.

[19] Kristian Horsager, Bart L Kaptein, Lone Rømer, Peter B Jørgensen, and Maiken Stilling. Dynamic rsa for the evaluation of inducible micromotion of oxford uka during step-up and step-down motion. *Acta orthopaedica*, 88(3):275–281, 2017.

[20] Bart G Pijls, Edward R Valstar, Klaas-Auke Nouta, Josepha WM Plevier, Marta Fiocco, Saskia Middeldorp, and Rob GHH Nelissen. Early migration of tibial components is associated with late revision: a systematic review and meta-analysis of 21,000 knee arthroplasties. *Acta orthopaedica*, 83(6):614–624, 2012.

[21] Leif Ryd, BE Albrektsson, Lars Carlsson, Finn Dansgard, Peter Herberts, Anders Lindstrand, Lars Regner, and Soren Toksvig-Larsen. Roentgen stereophotogrammetric analysis as a predictor of mechanical loosening of knee prostheses. *The Journal of bone and joint surgery. British volume*, 77(3):377–383, 1995.

[22] Edward R Valstar. Digital roentgen stereophotogrammetry: development, validation, and clinical application. *Proefschrift Universiteit Leiden*, 2002.

[23] Koen T Van Hamersveld, Perla J Marang-van de Mheen, Lennard A Koster, Rob GHH Nelissen, Sören Toksvig-Larsen, and Bart L Kaptein. Marker-based versus model-based radiostereometric analysis of total knee arthroplasty migration: a reanalysis with comparable mean outcomes despite distinct types of measurement error. *Acta orthopaedica*, 90(4):366–372, 2019.

[24] Trygve Holm-Glad, Ole Reigstad, Masako Tsukanaka, Magne Røkkum, and Stephan M Röhrl. High precision and accuracy of model-based rsa for analysis of wrist arthroplasty. *Journal of Orthopaedic Research®*, 36(11):3053–3063, 2018.

[25] Edward R Valstar, Richie Gill, Leif Ryd, Gunnar Flivik, Niclas Börlin, and Johan Kärrholm. Guidelines for standardization of radiostereometry (rsa) of implants. *Acta orthopaedica*, 76(4):563–572, 2005.

[26] S. Campi, B. J. L. Kendrick, B. L. Kaptein, E. R. Valstar, W. F. M. Jackson, C. A. F. Dodd, A. J. Price, and D. W. Murray. Five-year results of a randomised controlled trial comparing cemented and cementless oxford unicompartmental knee replacement using radiostereometric analysis. *Knee*, 28:383–390, 2021.

[27] Matthew J Page, Joanne E McKenzie, Patrick M Bossuyt, Isabelle Boutron, Tammy C Hoffmann, Cynthia D Mulrow, Larissa Shamseer, Jennifer M Tetzlaff, Elie A Akl, Sue E Brennan, et al. The prisma 2020 statement: an updated guideline for reporting systematic reviews. *Bmj*, 372, 2021.

[28] Bart G Pijls, Edward R Valstar, Bart L Kaptein, Marta Fiocco, and Rob GHH Nelissen. The beneficial effect of hydroxyapatite lasts: a randomized

radiostereometric trial comparing hydroxyapatite-coated, uncoated, and cemented tibial components for up to 16 years. *Acta orthopaedica*, 83(2):135–141, 2012.

[29] Bart G Pijls, José WM Plevier, and Rob GHH Nelissen. Rsa migration of total knee replacements: a systematic review and meta-analysis. *Acta orthopaedica*, 89(3):320–328, 2018.

[30] Rob GHH Nelissen, Edward R Valstar, and Piet M Rozing. The effect of hydroxyapatite on the micromotion of total knee prostheses. a prospective, randomized, double-blind study. *JBJS*, 80(11):1665–72, 1998.

[31] D. Bruni, L. Bragonzoni, M. Gagliardi, M. Bontempi, I. Akkawi, G. F. Raspugli, F. Iacono, S. Patella, and M. Marcacci. Roentgen stereophotogrammetric analysis: an effective tool to predict implant survival after an all-poly unicompartmental knee arthroplasty-a 10 year follow-up study. *Knee Surg Sports Traumatol Arthrosc*, 23(11):3273–80, 2015.

[32] L. Ryd, T. Boegård, N. Egund, A. Lindstrand, G. Selvik, and K. G. Thorngren. Migration of the tibial component in successful unicompartmental knee arthroplasty. a clinical, radiographic and roentgen stereophotogrammetric study. *Acta Orthop Scand*, 54(3):408–16, 1983.

[33] L. Bragonzoni, A. Russo, I. Loreti, L. Montagna, A. Visani, and M. Marcacci. The stress-inducible displacement detected through rsa in non-migrating ukr. *Knee*, 12(4):301–6, 2005.

[34] B. J. Kendrick, B. L. Kaptein, E. R. Valstar, H. S. Gill, W. F. Jackson, C. A. Dodd, A. J. Price, and D. W. Murray. Cemented versus cementless oxford unicompartmental knee arthroplasty using radiostereometric analysis: a randomised controlled trial. *Bone Joint J*, 97-b(2):185–91, 2015.

[35] L. V. Carlsson, B. E. Albrektsson, and L. R. Regnér. Minimally invasive surgery vs conventional exposure using the miller-galante unicompartmental knee arthroplasty: a randomized radiostereometric study. *J Arthroplasty*, 21(2):151–6, 2006.

[36] A. Ensini, P. Barbadoro, A. Leardini, F. Catani, and S. Giannini. Early migration of the cemented tibial component of unicompartmental knee arthroplasty: a radiostereometry study. *Knee Surg Sports Traumatol Arthrosc*, 21(11):2474–9, 2013.

[37] H. C. Hyldahl, L. Regnér, L. Carlsson, J. Kärrholm, and L. Weidenhielm. Does metal backing improve fixation of tibial component in unicondylar knee arthroplasty? a randomized radiostereometric analysis. *J Arthroplasty*, 16(2):174–9, 2001.

[38] D. Koppens, M. Stilling, S. Munk, J. Dalsgaard, S. Rytter, O. G. Sørensen, and T. B. Hansen. Low implant migration of the sigma(®) medial unicompartmental knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc*, 26(6):1776–1785, 2018.

[39] D. Koppens, S. Rytter, S. Munk, J. Dalsgaard, O. G. Sørensen, T. B. Hansen, and M. Stilling. Equal tibial component fixation of a mobile-bearing and fixed-bearing medial unicompartmental knee arthroplasty: a randomized controlled rsa study with 2-year follow-up. *Acta Orthop*, 90(6):575–581, 2019.

[40] K. N. Linde, F. Madsen, K. B. Puhakka, B. L. Langdahl, K. Søballe, I. Krog-Mikkelsen, and M. Stilling. Preoperative systemic bone quality does not affect tibial component migration in knee arthroplasty: A 2-year radiostereometric analysis of a hundred consecutive patients. *J Arthroplasty*, 34(10):2351–2359, 2019.

[41] A. Lindstrand, A. Stenström, L. Ryd, and S. Toksvig-Larsen. The introduction period of unicompartmental knee arthroplasty is critical: a clinical, clinical multicentered, and radiostereometric study of 251 duracon unicompartmental knee arthroplasties. *J Arthroplasty*, 15(5):608–16, 2000.

[42] L. Ryd, A. Lindstrand, A. Stenström, and G. Selvik. The influence of metal backing in unicompartmental tibial component fixation. an in vivo roentgen stereophotogrammetric analysis of micromotion. *Arch Orthop Trauma Surg*, 111(3):148–54, 1992.

[43] R. Soavi, I. Loreti, L. Bragonzoni, P. La Palombara, A. Visani, and M. Marcacci. A roentgen stereophotogrammetric analysis of unicompartmental knee arthroplasty. *The Journal of Arthroplasty*, 17(5):556–561, 2002.

[44] Jonathan AC Sterne, Jelena Savović, Matthew J Page, Roy G Elbers, Natalie S Blencowe, Isabelle Boutron, Christopher J Cates, Hung-Yuan Cheng, Mark S Corbett, Sandra M Eldridge, et al. Rob 2: a revised tool for assessing risk of bias in randomised trials. *bmj*, 366, 2019.

[45] Karem Slim, Emile Nini, Damien Forestier, Fabrice Kwiatkowski, Yves Panis, and Jacques Chipponi. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ journal of surgery*, 73(9):712–716, 2003.

[46] Harshvardhan Chawla, Hassan M Ghomrawi, Jelle P van der List, Ashley A Eggman, Hendrik A Zuiderbaan, and Andrew D Pearle. Establishing age-specific cost-effective annual revision rates for unicompartmental knee arthroplasty: a meta-analysis. *The Journal of arthroplasty*, 32(1):326–335, 2017.

[47] Fabio Catani, Maria Grazia Benedetti, Luca Bianchi, Valentina Marchionni, Sandro Giannini, and Alberto

Leardini. Muscle activity around the knee and gait performance in unicompartmental knee arthroplasty patients: a comparative study on fixed-and mobile-bearing designs. *Knee Surgery, Sports Traumatology, Arthroscopy*, 20(6):1042–1048, 2012.

[48] John Insall and Paolo Aglietti. A five to seven-year follow-up of unicondylar arthroplasty. *JBJS*, 62(8):1329–1337, 1980.

[49] Anders Henricson, Radek Wojtowicz, Kjell G Nilsson, and Sead Crnalic. Uncemented or cemented femoral components work equally well in total knee arthroplasty. *Knee Surgery, Sports Traumatology, Arthroscopy*, 27(4):1251–1258, 2019.

[50] M Therbo, B Lund, K-E Jensen, and HM Schrøder. Effect of bioactive coating of the tibial component on migration pattern in uncemented total knee arthroplasty: a randomized rsa study of 14 knees presented according to new rsa-guidelines. *Journal of Orthopaedics and Traumatology*, 9(2):63–67, 2008.

[51] Jeffrey A Geller, Richard S Yoon, and William Macaulay. Unicompartmental knee arthroplasty–a controversial history and a rationale for contemporary resurgence. *The journal of knee surgery*, 21(01):7–14, 2008.

[52] A Di Martino, Barbara Bordini, F Barile, Cristina Ancarani, Vitantonio Digennaro, and Cesare Faldini. Unicompartmental knee arthroplasty has higher revisions than total knee arthroplasty at long term follow-up: a registry study on 6453 prostheses. *Knee Surgery, Sports Traumatology, Arthroscopy*, pages 1–7, 2020.

[53] Leif Ryd, Xunhua Yuan, and Håkan Löfgren. Methods for determining the accuracy of radiostereometric analysis (rsa). *Acta Orthopaedica Scandinavica*, 71(4):403–408, 2000.

[54] ISO 16087: 2013 (E). Implants for surgery–roentgen stereophotogrammetric analysis for the assessment of migration of orthopaedic implants, 2013.

Supplementary Data

1.1 ROB Risk of Bias Assessment

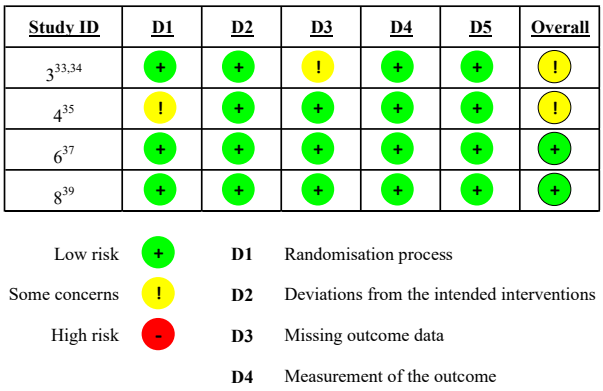


Figure 5: ROB2 results of randomized controlled trials[44]

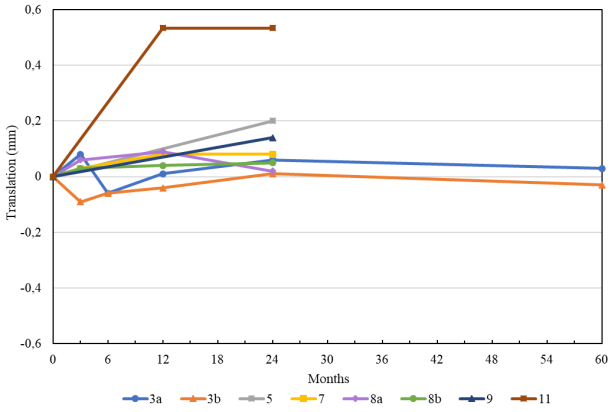
1.2 MINORS Methodological Quality Assessment

Study ID	A clear stated aim	Inclusion of consecutive patients	Prospective collection of data	End-points appropriate to the aim of the study	Unbiased assessment of the study enpoint	Follow-up period appropriate to the aim of the study	Loss to follow up less than 5%	Prospective calculation of the study size	Score/ (total possible)
1[33]	2	1	2	2	0	2	2	0	11/16
2[31]	2	1	2	2	1	2	1	2	13/16
5[36]	2	2	2	2	0	2	1	0	11/16
7[38]	2	2	2	2	0	2	1	0	11/16
9[40]	1	2	2	2	0	2	1	0	10/16
10[41]	1	1	1	2	1	2	0	0	8/16
11[32]	2	0	2	2	0	2	2	0	10/16
12[42]	2	0	2	2	0	2	1	0	9/16
13[43]	2	0	2	2	0	2	2	0	10/16

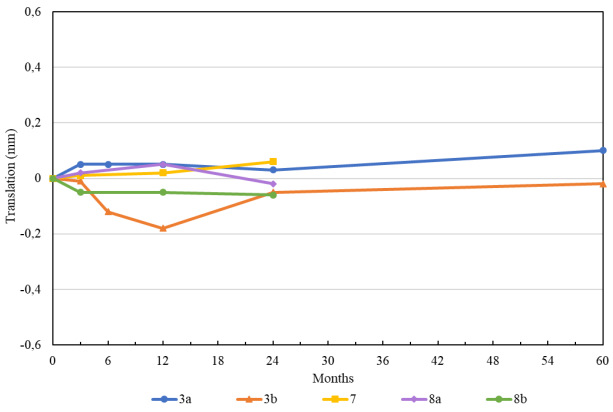
Table 7: MINORS results of cohort studies[45]

2.1 Translation Graphs

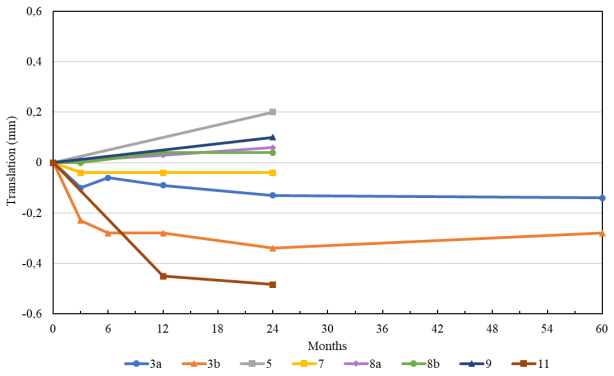
Figure 6: Translations of included studies



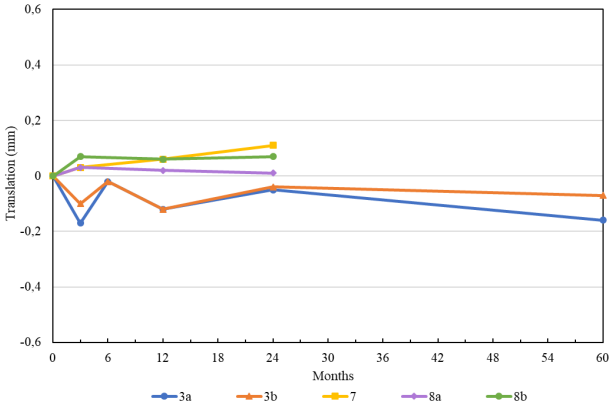
(a) Translation in X direction of tibial component



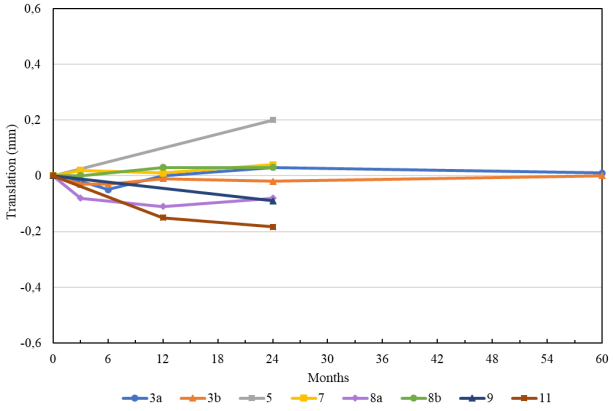
(b) Translation in X direction of femoral component



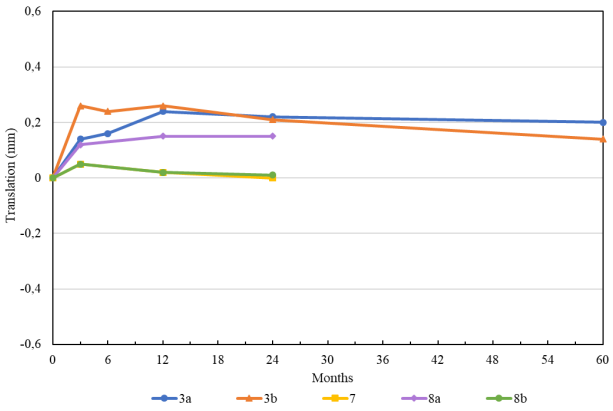
(c) Translation in Y direction of tibial component



(d) Translation in Y direction of femoral component



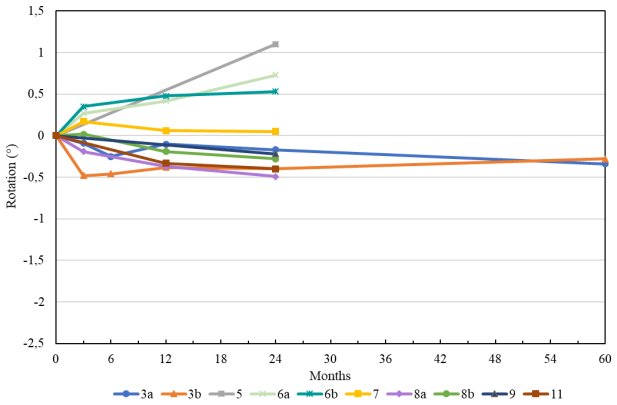
(e) Translation in Z direction of tibial component



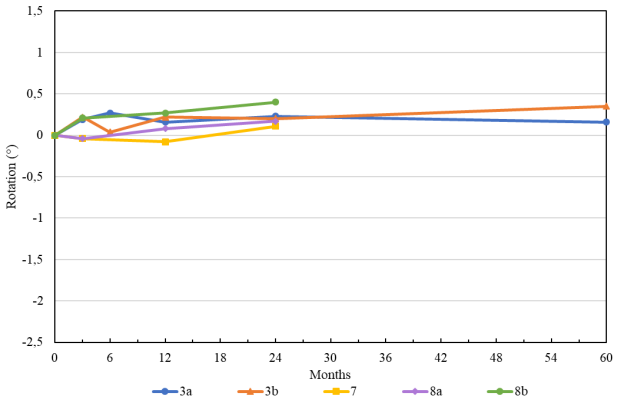
(f) Translation in Z direction of femoral component

2.2 Rotation Graphs

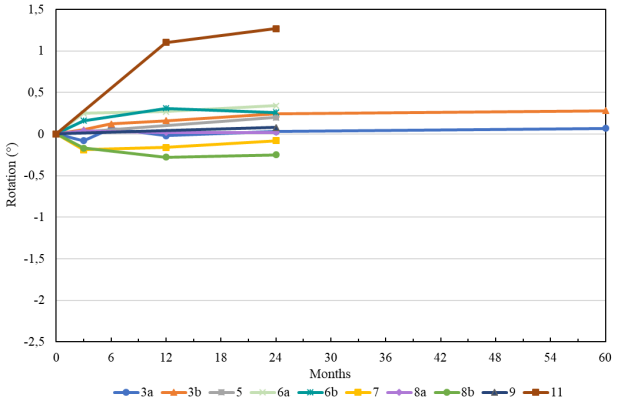
Figure 7: Rotations of included studies



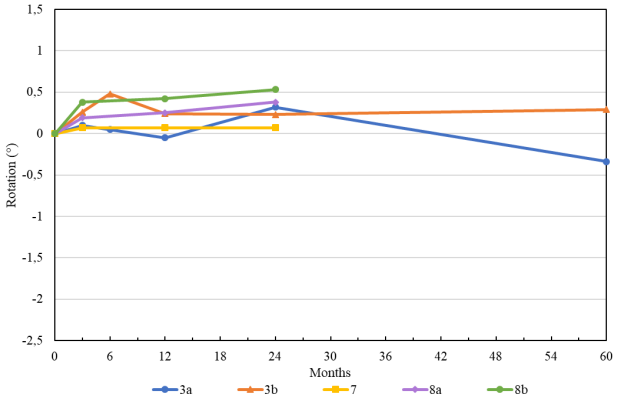
(a) Rotation in X direction of tibial component



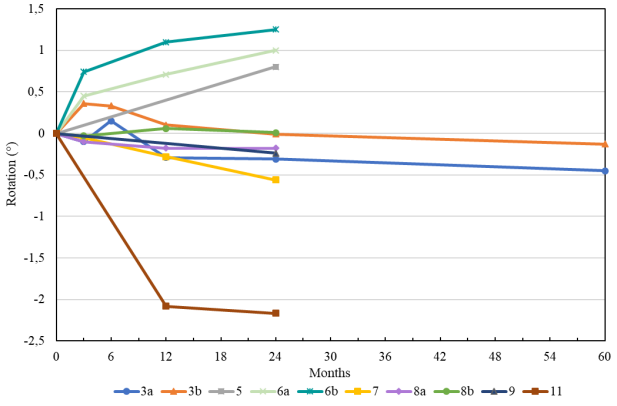
(b) Rotation in X direction of femoral component



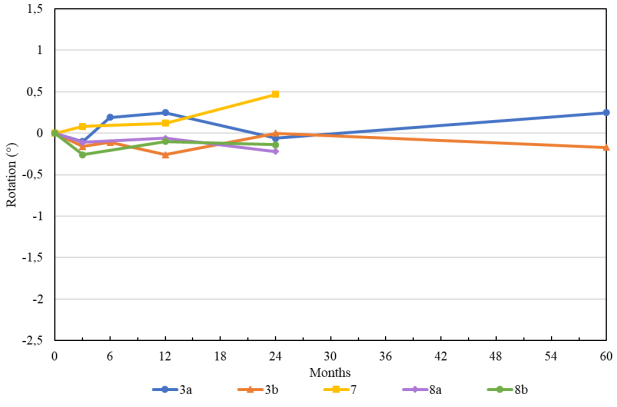
(c) Rotation in Y direction of tibial component



(d) Rotation in Y direction of femoral component



(e) Rotation in Z direction of tibial component



(f) Rotation in Z direction of femoral component

II

TM MSc Thesis

Abstract

Background: Radiostereometric analysis (RSA) is a technique to assess early migration, which has a predictive value for early failure of unicompartmental knee arthroplasty (UKA). To successfully analyze the RSA images it is important to have a sufficient amount of visible markers with an acceptable three-dimensional distribution.

Objective: To provide insights on marker location distribution by developing a method to analyse marker placement based on visibility and accessibility.

Method: Marker locations in RSA scenes of patients (N=25) from a previous study are used to assess marker placement and analyze marker density by performing a voxelization operation to divide the bone in a grid of 3x3x3mm bins. After spatial smoothing the hotspots with high marker fractions are determined and the four non-adjacent locations with the highest marker fraction are selected as the most favorable locations. Of these locations the distribution is analyzed by calculating the condition number (CN) of 1000 samples.

Results: The locations of a total of 635 3D markers in the femur and 917 3D markers in the tibia were assessed. After voxelization, the average marker density of non-empty bins was respectively 3.1 and 4.3 markers per bin. The four selected locations had a 47 times higher marker fraction compared to the average bin in the femur and 66 times higher for the selected locations in the tibia. Their mean condition number was 49.1 for the femur and 68.2 for the tibia.

Conclusion: The proposed method has proven to be sufficient for marker placement analysis. Placing the tantalum markers in the selected locations, which have a considerably higher marker contribution to the total amount of markers, would presumably increase the marker visibility during RSA and decrease patient exclusion due to an insufficient amount and/or distribution of visible markers.

1 Introduction

Osteoarthritis (OA) is the leading cause of disability in the adult population, with the knee as the most affected joint. Approximately one out of every ten adults above the age of 55 years suffer from knee osteoarthritis and 25% of them experience disability from their disease.[1, 2] In addition, OA is one of the most increasing diseases worldwide.[3] The deterioration of the joint cartilage, caused by OA, can occur in three different major compartments in the knee; the medial, lateral and patella-femoral compartment. In one-third of the cases OA is predominantly isolated in only one compartment of the knee.[4] Total Knee Arthroplasty (TKA) is the golden standard for treating patients with end-stage knee OA who exceed non-operative management.[5] Unicompartmental knee arthroplasty (UKA) is an alternative surgical option for patients who have OA limited to one compartment, which gives less invasive surgical exposure and potentially leads to higher patient satisfaction.[6, 7] Despite the benefits of UKA over TKA, the UKA utilization has remained relatively low compared to TKA.[8] Only 19.2% of all primary knee arthroplasties performed in 2020 where UKA as compared to 80.1% for TKA, as reported by the Dutch Arthroplasty Register (LROI).[9, 10]

The most important challenges of UKA are the patient inclusion criteria, the technically challenging surgical procedure, and the high variation in revision and re-operation rates per clinic or surgeon.[5, 11] Aseptic loosening is the most common cause of early failure of UKA.[12, 13] Early migration has shown a high predictive value for aseptic loosening in hip and knee arthroplasty.[9, 14, 15] Radiostereometric Analysis (RSA) is a technique to measure implant migration with high accuracy and precision.[16] Therefore, measuring the implant migration with RSA is a valuable technique to further assess the results of UKA performance. This could potentially give more insight in patient selection, performance of different implant types, and development of new surgical techniques. With RSA the relative implant positions is tracked by comparing it to small tantalum markers embedded in the bone. To successfully analyze the RSA images it is important to have a minimum of 3 tantalum markers visible with an acceptable three-dimensional distribution of the markers.[17] The most common reason for lack of visible markers is occlusion of markers by the implant or by other markers.[18] Up to 20% of patients with UKA had to be excluded from an RSA study due to an insufficient amount of visible markers.[19]

The goal of the present study is to develop a method to analyse marker positions and visibility to determine the most viable marker locations. This is done by retrospectively visualising and analysing the marker placement of an RSA study. The results can be used to give better insight on favorable marker locations which potentially decreases the exclusion rate of patients due to an insufficient amount of visible markers. Additionally, the developed method could be a first step for further research on marker placement for different joints and implant types.

2
Background

2.1 Unicompartmental Knee Arthroplasty

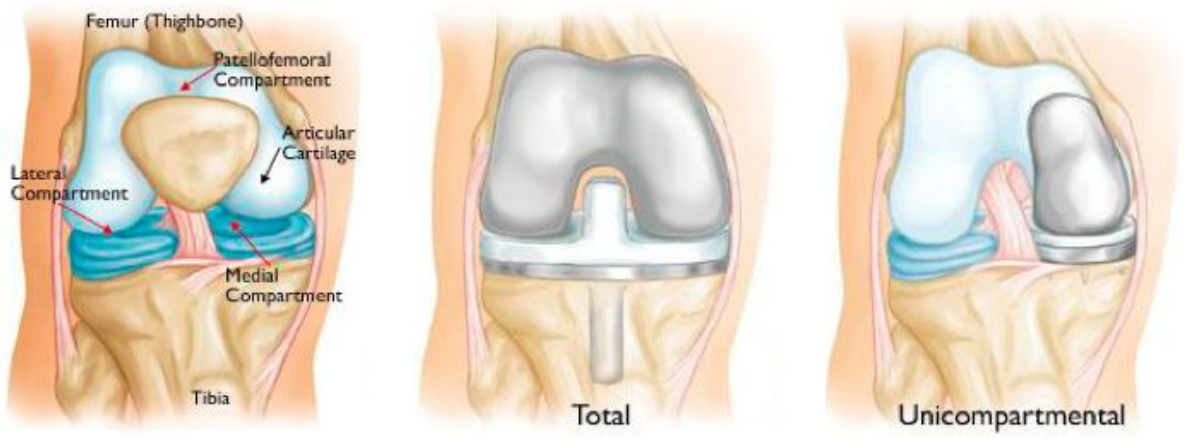
Osteoarthritis (OA) is a degenerative joint disease characterized by the deterioration of joint cartilage. Symptoms include pain, stiffness, and joint swelling which leads to activity restrictions.[20] The knee is divided in three major compartments: the medial, lateral, and patellafemoral compartment (Figure 2.1a). The stage of OA is determined with radiological imaging and can vary per compartment, where approximately one-third of patients have OA predominantly in only one compartment of the knee. [4, 21] Treatment of knee osteoarthritis usually starts with non-operative options including NSAIDs, physical therapy, activity modification, knee bracing, and intra-articular injections. In case the non-operative treatments prove to be insufficient for end-stage OA, knee replacement is the next step of treatment.[22]

The golden standard for surgical treatment of end-stage OA is total knee arthroplasty (TKA). TKA consists of resecting the diseased articular surfaces on the tibia and femur including the soft tissue from the knee joint (menisci and anterior cruciate ligament (ACL), possibly posterior cruciate ligament (PCL), depending on prosthesis type), followed by resurfacing with metal and polyethylene prosthetic components (Figure 2.1b).[23] For patients where knee OA is only present in one compartment, there is an alternative surgical option called unicompartmental knee arthroplasty (UKA). During this procedure only the medial or lateral side of the tibia and femur bone is removed and the ligaments are preserved, as shown in Figure 2.1c.[24] This leads to several advantages of UKA over TKA which include the preservation of normal knee kinematics, lower perioperative morbidity, less blood loss, and accelerated patient recovery.[13] Over the last years, the number of UKAs performed is rising globally. One of the reasons for the increasing usage of UKA, is the expanding indications. Where previously patients younger than 60 years or with obesity were excluded, the recent inclusion criteria are advanced unicompartmental OA, a functioning ACL and range of motion criteria.[24, 25]

Numerous studies demonstrate excellent clinical outcomes and implant survival of UKA.[27, 28] However, there is no established consensus regarding long-term survival of UKA compared to TKA.[25] The widespread performance of UKA has been limited by the technical difficulty of performing the procedure. Most importantly, UKA has less tolerance for acceptable component positioning when compared to TKA.[29] This could explain the correlation between the experience of UKA surgeons and the revision rates, where evidence suggests that increased surgical

Figure 2.1: Anatomy of the knee [26]

(a) Three major knee compartments (b) Total Knee Replacement (c) Unicompartmental Knee Replacement



volume is associated with decreased revision rate.[30–32] Besides increasing surgical volume and experience, another solution to overcome the technical difficulties is the new technology development of robotic-assisted surgery which has made performing UKA technically less demanding.[5]

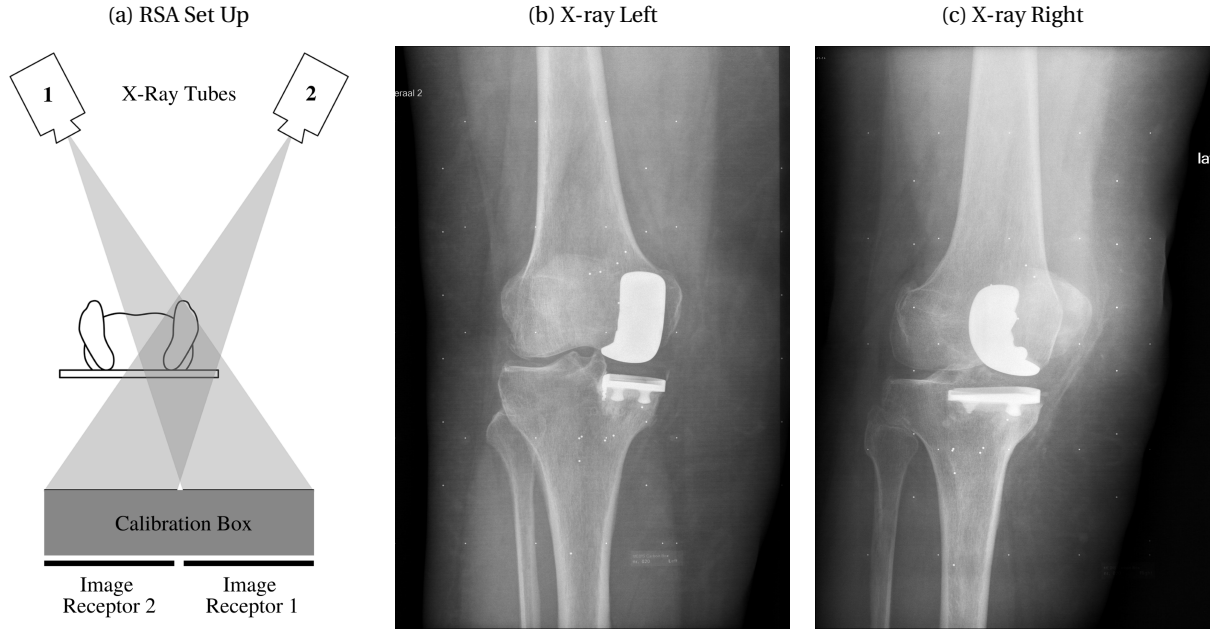
2.2 Radiostereometric Analysis

The golden standard for detection of implant wear and migration is currently radiostereometric analysis (RSA).[33] RSA is used to make accurate assessments of the relative position and orientation of bone structures and implants in vivo. Application of the technique allows the detection of clinically relevant motion. The measured migration with RSA can be used to predict long-term implant stability by studying its early behavior. For this technique, biplanar x-rays are taken in a specific angle through a calibration cage which has a fixed pattern of tantalum markers used for fiducial reference and control. A schematic overview of the set up is shown in Figure 2.2a and an example of the left and right X-ray where both the bone and fiducial markers are visible are shown in Figure 2.2b and 2.2c . In order to track the relative implant position compared to the bone, small tantalum markers are embedded into the patients femur and tibia during surgery.[14] The implant can be tracked using either tantalum markers in the prosthesis (marker-based RSA) or matching a virtual projection of a 3D model of the implant with the contours of the radiographic projection of the implant (model-based RSA).[18] This makes it possible to perform a three-dimensional rigid body movement analysis using the RSA software packages to measure migration in every direction, as can be seen in Figure 2.2d.[34] To evaluate the migration over time, the RSA is performed at several fixed follow-up points.

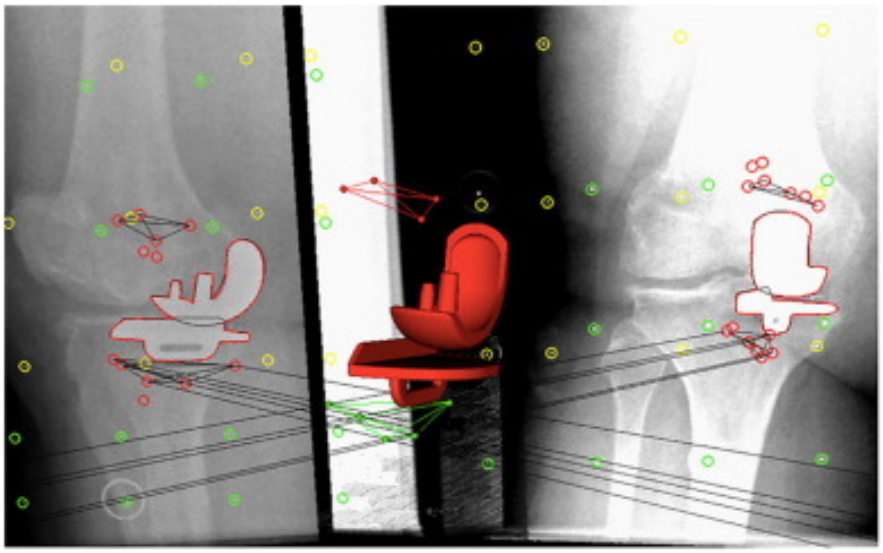
The assessment of early migration with RSA has shown a high predictive value for later aseptic loosening of knee implants.[36, 37] For total knee replacements there even is a threshold computed to determine implants at risk for revision. This contains a threshold for initial migration in the first year of follow-up and a threshold for continuing migration between the first and second year of follow-up.[38] Several systematic reviews and other literature indicate that RSA could also be a good method to determine risk of revision in UKA and to further understand the dependencies for the varying revision rates for UKA.[19, 39]

The migration measured by RSA is valued either by the translation and rotation in every direction or by maximum total point motion (MTPM). The MTPM is the total three-dimensional vector displacement of the prosthesis marker with the greatest motion.[40] The quality of the radiostereometric analysis depends on the precision and accuracy of the measurement. Accuracy is defined as the "trueness" of a measurement which is the closeness of agreement between a test result and an known value.[41, 42] This can be determined with an experimental saw-bone study using the specific set up and prosthesis that will be used in the in-vivo study. Precision is equal to the repeatability of the measurement and defined as the agreement between two test results under the same conditions.[40, 41] This

Figure 2.2: RSA for UKA set up, X-ray images and software [35]



(d) RSA Software. In the left and right X-rays the fiducial and control markers are denoted by green and yellow circles and bone markers are denoted by red circles. In the middle the 3D model and active markers are shown.



can be assessed performing double examinations at a certain follow-up measurement during an in-vivo RSA study. The migration between both examinations at the same follow-up moment is a representation of the precision.

Besides accuracy and precision, another important factor for a successful RSA measurement is the marker placement location. The location of the markers influences the marker visibility, distribution, and stability. Visibility can be compromised by projection overlap of the implant or other markers. As stated in the international standards for RSA, a minimum of three identical markers need to be visible on both radiographs at all examinations in order to assess translations and rotations with all six degrees of freedom.[17] Distribution of the markers is measured by the condition number (CN), which represents the three dimensional distance between the positions of the markers and their geometrical centre. It is believed that a CN below 120 for large joints will result in a reliable migration measurement.[40] Stability of the markers is dependent on the density of the surrounding bone in which the marker is placed. Because of the technical character of the radiostereometric analysis, patients can be excluded as a result of technical shortcomings such as poor bone marking or occluded markers where the necessary marker amount or CN is not met.[17]

2.3 Problem Statement

Unicompartmental knee arthroplasty (UKA) has the potential to treat medial and lateral knee osteoarthritis without replacement of the entire knee joint.[43] However, there is a high variation in treatment choice for TKA versus UKA and insufficient evidence to guide the selection.[44] To make better selection criteria regarding the patient characteristics and sufficient amount of surgeon volume, the success rate of UKA needs to be evaluated further. More RSA studies could be very useful to determine sufficient thresholds for implants at risk and to further investigate their clinical relevance compared to the results of TKAs.[39]

The systematic review of Gevers et al.[19] has shown that 7-20% of patients are excluded during an RSA study for UKA because of an insufficient amount of stable markers visible on the radiographs. In addition, patients need to be excluded because of a CN exceeding the threshold of 120. This could be caused by the small operating area when performing UKA surgery, which makes it harder to successfully place the markers compared to other hip or knee arthroplasties. In order to minimize the number of patients that need to be included to achieve the desired study size, it should be more defined where to correctly place the tantalum markers in the tibia and femur bone. In addition, a proper marker placement with more visible markers and a better marker distribution could potentially lead to the improvement of the quality of RSA in UKA.[35, 40]

2.4 Goal of the research

More research on migration in UKA is indicated. However, because of lack of experience in performing RSA studies in UKA most surgeons struggle with proper marker placement. The lack of a sufficient amount of visible tantalum markers in the tibia or femur bone in UKA RSA studies lead to an increase of exclusion of patients. The main goal

of this thesis is:

To provide insights on marker location distribution by developing a method to analyse marker placement based on visibility and accessibility. This will be achieved by visualising and evaluating previous marker locations in tibia and femur bone for RSA in UKA.

Subgoals of this thesis are:

- To identify the range of marker locations based on a previous UKA RSA study
- To investigate the effect of spatial smoothing on the marker density
- To create a heatmap that reveals marker density hotspots
- To select four favorable locations based on their marker density and interspatial distribution
- To approximate the condition number of the favorable locations

We hypothesize that there is a significant difference in marker density depending on their location and by evaluating placement of previous tantalum markers it is possible to develop a method to indicate favorable marker locations with high visibility and accessibility rates. This could be translated to marker placement instructions to use in general practice when placing markers to perform RSA.

3 Method

3.1 Data Acquisition

3.1.1. Study Population

The marker placement analysis was created using RSA data from an existing study containing patients that received a unicompartmental knee replacement. The primary goal of that RSA study was to evaluate the performance of the Persona® Partial Knee (PPK) implant (Zimmer Biomet)[45]. The PPK is a cemented medial fixed-bearing unicompartmental knee replacement system. All patients with an indication for UKA were eligble for inclusion. The exclusion criteria were; infection, rheumatoid arthritis or other inflammatory joint diseases, revision surgery and an allergy for one of the implant materials. Accordingly, a total of 26 patients were included between April 2017 and May 2018 and received a PPK at the Reinier de Graaf Hospital, Delft, The Netherlands.

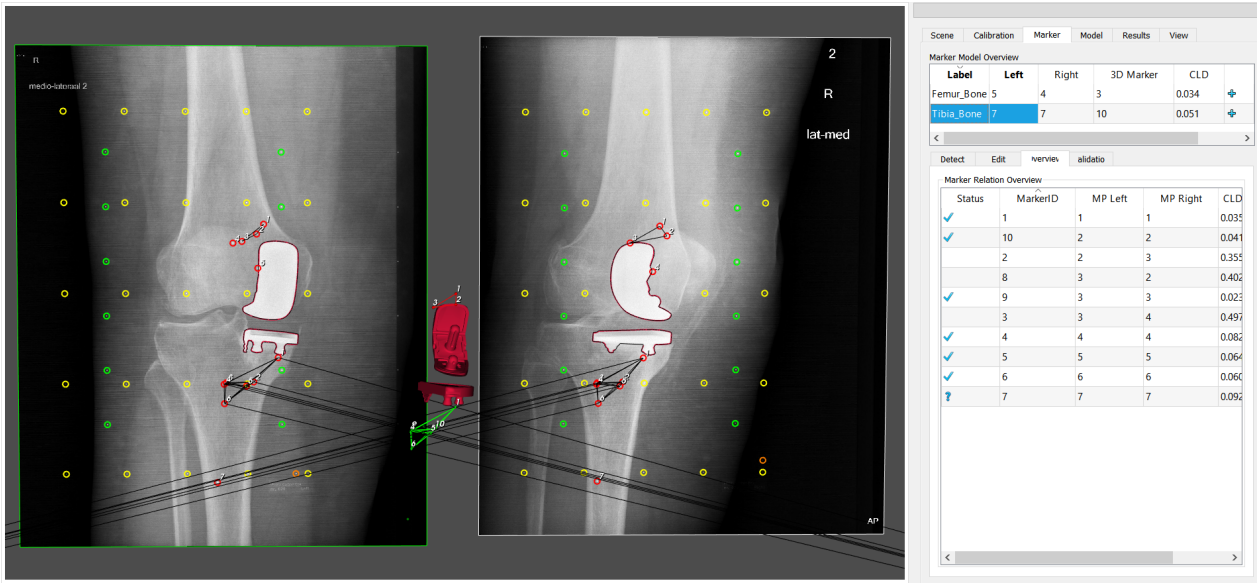
3.1.2. Study Design

During surgery the tantalum markers were inserted after bone preparation. In both the femur and tibia of the operated knee 6-9 markers with a diameter of 1.0mm were placed, which resulted in a maximum total of 18 markers per patient. The uniplanar radiographs for the RSA were obtained direct postoperatively after weight bearing and at 6 weeks, 6 months, 12 months, and 24 months after surgery. At 12 months follow-up a double examination was performed to assess the precision (repeatability of the measurement). The uniplanar radiographs were made using a standardized RSA protocol with the patient in supine position with a minimum endorotation of the leg of 20 degrees. The anatomical axis of the leg was parallel to the y-axis of the calibration box. Two X-ray tubes were positioned at an angle of 40 degrees and 120 centimeter from the patient table.

3.1.3. Radiostereometric Analysis of Included Patients

For every follow-up moment, the images were analyzed by one researcher using the Model-Based RSA software (version 4.2, RSAcore, Leiden University Medical Center, Leiden, the Netherlands) as shown in Figure 3.1 and according to the ISO standards (ISO 16087:2013).[17] The marker projections in the uniplanar radiographs were automatically detected by the software, and if needed the undetected marker projections were manually added by the researcher.

Figure 3.1: Example of RSA analyse of UKP study



Using the calibration box, the pixels have been converted to millimeters and roentgen foci were calculated. Afterwards, the intersection of the projection lines from roentgen focus to marker projection were used to match the markers of the right and left radiograph and reconstruct 3D markers. The reconstructed 3D markers were manually checked by the researcher and if the marker projections of the radiographs were not matched correctly this was amended. The stability of the markers was verified by the RSA software, which compares the inter-marker distances between the consecutive radiographs of a follow-up study. In case of marker instability (Mean Error > 0.35mm), the marker was excluded. When all included 3D markers were created and assessed for every follow-up scene, the 3D markers that are present in every scene are marked as 'Active' and used for the migration calculation of the PPK from the patient. An example of a list of the 3D markers is shown in the right column of Figure 3.1, where the active markers have a green checkmark.

3.2 Data Analysis

3.2.1. Preprocessing

The data from the RSA study is saved in an XML file per RSA follow-up scene directly from the RSA software. One RSA scene represents one follow-up moment of one patient. The XML files contain all information on the marker projections, the 3D marker models, and the implant models regarding location and status (e.g. active or non-active). A Python (Spyder IDE, version 3.6 [46, 47]) script was created to automatically obtain a list of all 3D markers and their corresponding locations from the tibia and femur marker models from the XML files as well as the femur an tibia implant positioning. The markers that were denoted as 'Active' were filtered and kept for analysis. If a 3D marker was deactivated for the migration calculation only because it was not present in all follow-up scenes of the patient, that 3D marker was denoted as 'Active' manually and included in the list of obtained 3D markers.

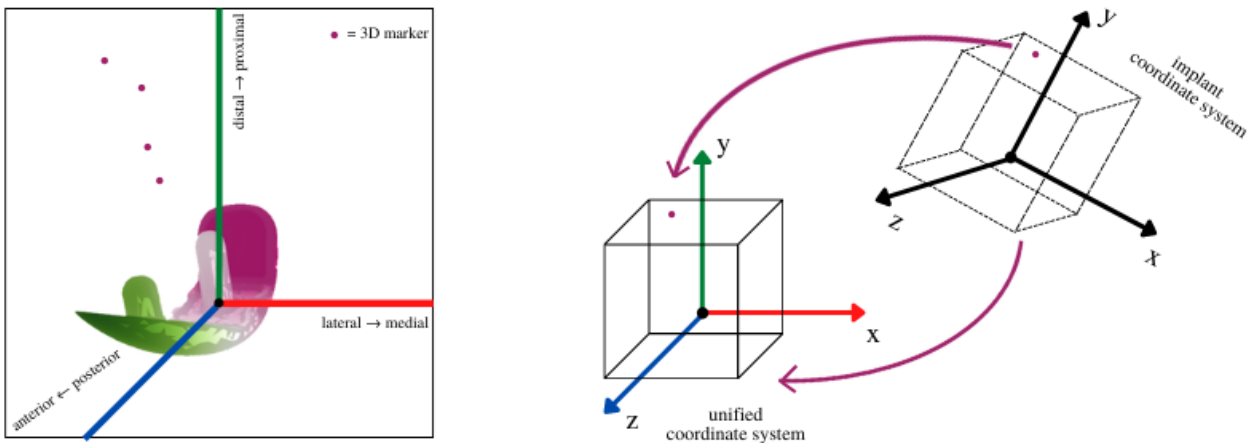
3.2.2. Marker Location Assessment

To assess the marker locations, all RSA scenes were plotted in the same 3D rendering as if all markers were placed in one virtual patient. To align all patients onto one patient representation, the following adjustments were made:

- Transformation to unified coordinate system;
  For the marker locations assessment the local coordinate system of the implant model was used to determine the transformation matrix to transform the 3D markers model to a unified coordinate system. In every RSA scene the position and orientation of the knee compared to the calibration box is different. This translates in a different position and orientation of the implant model and 3D markers model for every scene. The location of the 3D markers model is described with respect to the coordinate system of the implant. Hence, a transformation matrix to transform the data from the implant coordinate system to the unified coordinate system can be calculated based on the position and orientation of the implant center, using Equation 3.1. By determining the transformation matrix for every follow-up scene and applying the inverse transformation matrix to the 3D markers of that scene, all 3D markers were transformed to the unified coordinate system. A schematic drawing of this transformation is shown in Figure 3.2.

- Adjustment for surgical side;
  Medial UKAs in both the left and right knee were used in this data analysis. To make the 3D marker locations

Figure 3.2: Transformation of coordinate system



Equation 3.1

For the following input

$$\text{Implant Position} = \begin{bmatrix} T_x \\ T_y \\ T_z \end{bmatrix} \qquad \text{Implant Orientation} = \begin{bmatrix} \theta_x \\ \theta_y \\ \theta_z \end{bmatrix} \qquad \text{Marker Location} = \begin{bmatrix} m_x \\ m_y \\ m_z \end{bmatrix} \tag{3.1a}$$

the rotation matrices can be described as

$$R_x = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \cos\theta_x & -\sin\theta_x \\ 0 & \sin\theta_x & \cos\theta_x \end{bmatrix} \qquad R_y = \begin{bmatrix} \cos\theta_y & 0 & \sin\theta_y \\ 0 & 1 & 0 \\ -\sin\theta_y & 0 & \cos\theta_y \end{bmatrix} \qquad R_z = \begin{bmatrix} \cos\theta_z & -\sin\theta_z & 0 \\ \sin\theta_z & \cos\theta_z & 0 \\ 0 & 0 & 1 \end{bmatrix} \tag{3.1b}$$

this gives the following total rotation matrix

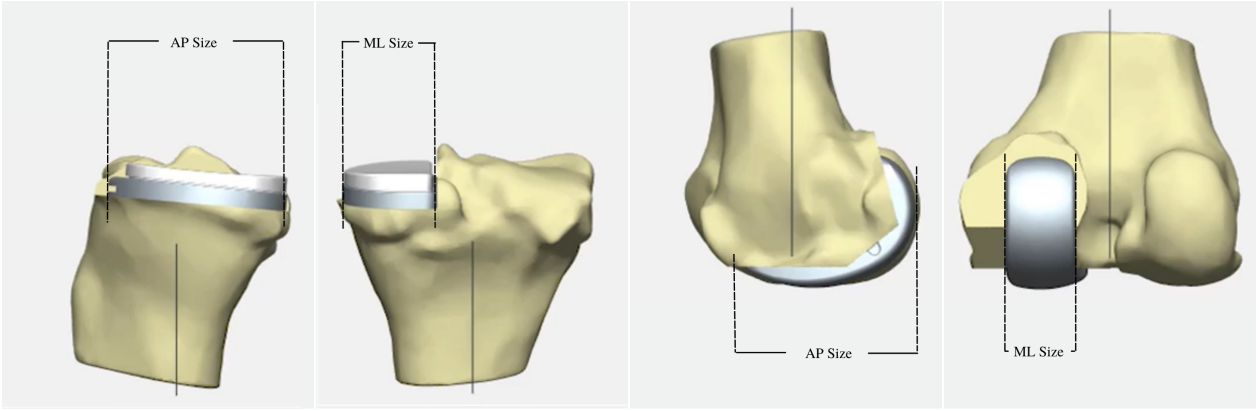
$$R = R_z \cdot R_x \cdot R_y = \begin{bmatrix} R_{11} & R_{12} & R_{13} \\ R_{21} & R_{22} & R_{23} \\ R_{31} & R_{32} & R_{33} \end{bmatrix} \tag{3.1c}$$

the transformed marker is calculated as follows

$$\begin{bmatrix} m'_x \\ m'_y \\ m'_z \\ 1 \end{bmatrix} = \begin{bmatrix} R_{11} & R_{12} & R_{13} & T_x \\ R_{21} & R_{22} & R_{23} & T_y \\ R_{31} & R_{32} & R_{33} & T_z \\ 0 & 0 & 0 & 1 \end{bmatrix}^{-1} \begin{bmatrix} m_x \\ m_y \\ m_z \\ 1 \end{bmatrix} \tag{3.1d}$$

comparable, the markers in left sided UKAs need to be transformed as if it was in a right sided UKA. Therefore, after transformation to the unified coordinate system the right sided UKAs were mirrored compared to the left sided UKAs. Since the orientation and rotation is already unified to the same origin, this can be performed by inverting the x-coordinates of the markers in left sided UKAs (Figure 3.2).

- Scaling based on implant size;
  The PPK has eight different sizes for both the tibial and femoral component. The component sizes are representative for the anatomical patient bone sizes. Therefore, the marker position will be scaled based on the component size in the medial-lateral (X-axis) and anterior-posterior (Z-axis) direction, as shown in Figure 3.3. The component sizes of the PPK implant were retrieved from the confidential product information. The length of the marker insertion device (14cm) is the same for every patient, hence there were no adjustments needed for the proximal-distal direction.



(a) Anterior-Posterior sizing of Tibial Component (b) Medial-Lateral sizing of Tibial Component (c) Anterior-Posterior sizing of Femoral Component (d) Medial-Lateral sizing of Femoral Component

Figure 3.3: Sizing of PPK Tibial and Femoral Component[45]

Once the adjustments were made, all marker locations can be shown in one 3D plot of a virtual patient. To make the visualization more comprehensible, the marker locations were shown together with a 3D rendering of the femur and tibia bone and of the PPK tibial and femoral component.

3.2.3. Marker Density Analysis

3.2.3.1. Voxelization

To analyze the marker density within the bone, the continuous geometric information of the 3D markers was converted into a rasterized volume with a discrete grid of bins by performing a voxelization operation. Here the tibial and femoral bone was divided into a raster of bins where every bin is a cube of 3mm x 3mm x 3mm. The marker density (N) for every bin was defined as the total number of markers that are located in the bin (Eq. 3.2). For example, a bin in which a marker of one patient from 6 follow-up scenes was located and a marker of another patient from 3 follow-up scenes, has a marker density of N=9. In addition, the scene prevalence is calculated which describes the percentage of scenes where a marker was located in a certain bin and therefore it shows how often a certain location of a bin is used and visible (Eq. 3.3). Afterwards a heat map was created to visualize the marker distribution based on the marker density per bin and its location.

$$\text{Marker Density:} \quad \rho\,(\text{N}) = \text{No. of markers in bin} \tag{3.2}$$

$$\text{Scene Prevalence:} \quad \text{P}\,(\%) = \frac{\text{Marker Density}}{\text{Total No. of RSA scenes}} \tag{3.3}$$

3.2.3.2. Spatial Smoothing

To capture important patterns of the marker density, an approximating function was created by smoothing the dataset. Hereby the marker density of the bins was modified so individual bins with a higher amount of markers than their neighboring bins were reduced, and bins with a lower amount of markers than their neighboring bins were increased leading to a smoother marker distribution. This was done by using a spatial smoothing filter with a weighted average, where the bins closer to the central bin (more vertices in common) are more important and have a higher weight. The averaging filter used, has kernel weights based on the Gaussian distribution for $\sigma = 2$.

Equation 3.4

For

$$\begin{bmatrix} b_1 & \cdots & b_{27} \end{bmatrix} = \text{the bins from the filter kernel} \tag{3.4a}$$

where

$$v_b = \text{number of common vertices with central bin} \tag{3.4b}$$

$$\rho_b = \text{number of markers in bin} \tag{3.4c}$$

the weight of the bin is defined as

$$w_b = \frac{v_b}{8} \tag{3.4d}$$

then the value of the central bin (N_{smooth}) is defined as

$$N_{smooth} = \sum_{b=1}^{8} \rho_b \cdot w_b \tag{3.4e}$$

after smoothing the **Marker Fraction** for each bin is calculated by

$$\text{F}\,(\%) = \frac{N_{smooth}}{\sum N_{smooth}} \tag{3.4f}$$

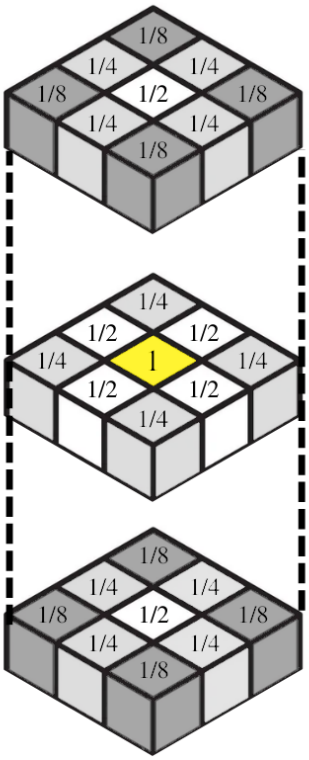


Figure 3.4: Smoothing filter weights [48]

To make sure specific marker density hotspots were still kept and not smoothed too much, a small bandwidth was chosen for the kernel that only contained the nearest neighbours of the bin (common vertex). This resulted in a a 3x3x3 kernel with corresponding weights as shown in Figure 3.4, where the yellow cube represents the central bin to which the new value will be assigned.[48, 49] The calculations to define the new value of the central bin are shown in Equation 3.4. The value used to define the smooth dataset is the marker fraction, which defines the percentage of the total marker amount that falls into the certain bin (Eq 3.4f). Therefore, the marker fraction represents the chance of a random marker being located in that bin. As an example, if the marker fraction of a bin is 1% this means that 1% of all markers are located in that bin and thus the chance of a random marker falling in the bin is also 1%.

3.2.4. Bin Selection

To detect favorable marker locations for the placement of eight tantalum markers, four bins were selected for both the femur and tibia separately where each bin represents the location to place two tantalum markers. After performing the spatial smoothing filter, all bins were ranked based on their marker density. To detect four separate hotspots with a high marker count, a condition was added that the selected bins may not be neighbours. Therefore, the four bins with the highest marker density that do not have a vertex in common were selected as the most favorable locations for marker placement in the femoral and tibial bone. The selected bins were visualized together with the PPK model and a mock-up femur/tibia to provide insight on the bin locations with respect to the implant and bone.

3.2.5. Distribution Analysis

To calculate the location distribution between the chosen bins, the condition number (CN) was calculated. This value describes the three dimensional spatial distribution of certain locations, which validates their dispersion on the locations on the x, y and z-axes. A higher condition number means lower marker distribution which, as described in Section 2.2, leads to a lower precision of the migration measurement. The formula to calculate the condition number is shown in Equation 3.5.[17]

To represent the clinical conditions, there were two markers placed in every selected bin. These markers have a random location within the 3x3x3 mm bin. Since there are infinite possible combinations of marker locations in the selected bins, the probable CN was approximated with sampling. Based on the central limit theorem, the distribution of sample means approximates a normal distribution as the sample size gets larger. This can be used to approximate the range of possible CN values from the four selected bins.[50] Therefore, 1000 samples with different marker locations within the selected bins were created and their CN values were calculated. Based on the sample values the mean CN and its standard deviation were calculated.

Equation 3.5

Given

$$\begin{bmatrix} a_1 & \cdots & a_n \end{bmatrix} = \text{the three-dimensional positions of } n \text{ markers} \tag{3.5a}$$

$$\underline{a} = \text{the geometrical centre of the markers} \tag{3.5b}$$

where the Matrix A is defined as

$$A = \begin{bmatrix} a_1 - \underline{a} & \cdots & a_n - \underline{a} \end{bmatrix} \tag{3.5c}$$

then after **singular value decomposition** of the Matrix A

$$\sigma_2 \text{ and } \sigma_3 = \text{the two smallest singular values [mm]} \tag{3.5d}$$

then the condition number (CN) is defined as

$$CN = \frac{1000}{\sqrt{\sigma_2^2 + \sigma_3^2}} \tag{3.5e}$$

4 Results

4.1 Study Population

Of the 26 patients included in the PPK study, one patient was excluded for the radiostereometric analysis because there were no tantalum markers placed and one patient was excluded for the RSA of the tibia because of movement of the implant model between the follow-up periods. Therefore, a total of 25 patients were included in the present study for marker location assessment of the femur and 24 patients for assessment of the tibia. The mean condition number of all RSA scenes was 61.7 for the femur with a minimum value of 34.3 and a maximum of 90.5 and 52.1 for the tibia with a minimum value of 32.9 and a maximum value of 99.9. More information on the inclusion numbers of the PPK study per follow-up period and the corresponding CN values, can be found in Table A.1 of the Appendix.

4.2 Marker Location Assessment

After preprocessing the data, all 3D markers that were denoted as 'Active' were included in the present study. A total of 5 markers were excluded because of instability of the marker. Table 4.1a and Table 4.1b show the number of patients and the total amount of 3D markers included per follow-up moment for the marker location assessment of respectively the femur and the tibia. The total amount of included RSA scenes for all follow-up moments of the femur was 139 scenes and these contained a total of 635 3D markers. This resulted in a mean number of 3D markers per RSA scene of 4.6. This means 51% of all tantalum markers that were placed in the patients femur (9 per patient) were visible in the RSA images. For the tibia, the total amount of included RSA scenes was 133 and these contained a total of 917 3D markers. This resulted in a mean number of 3D markers per scene of 6.9 which is 77% of all tantalum markers that were placed in the patients tibia.

After transforming the 3D markers to the unified coordinate system and scaling the marker locations based on the implant size, all 3D markers of each patient and every follow-up scene were combined in a 3D plot for both the femur and tibia. The results of the 3D plot for the marker location assessment of the femur are shown in Figure 4.1a in the anterior-posterior (AP) direction and in Figure 4.1b in the medial-lateral (ML) direction where the different colors each represent every follow-up scene of one patient. The results of the 3D plot of the tibia are shown in Figure 4.1c in the AP direction and 4.1d in the ML direction. There were no extreme outliers of 3D marker locations that were located outside the expected boundaries in or near the bone representations. The marker location assessment gives insight on the reach of the marker insertion tool with a length of 140mm during surgery. In the femoral bone the maximum distance of the 3D markers from the implant center was 46mm in the AP direction, 54mm in the ML direction and 87mm in the proximal direction. The maximum distances of the 3D markers in the tibial bone were 33mm in the AP direction, 44mm in the ML direction and 85mm distal direction.

Table 4.1: Marker information

(a) Femur

	Post-Op	6 wks	6 mo	1 yr	1 yr DE*	2 yr	**Total**
No. of patients / RSA scenes	25	25	24	24	18	23	**139**
No. of 3D markers	128	112	110	112	67	106	**635**
No. of 3D Markers per RSA scene	5.1	4.5	4.6	4.7	3.7	4.6	**4.6**

(b) Tibia

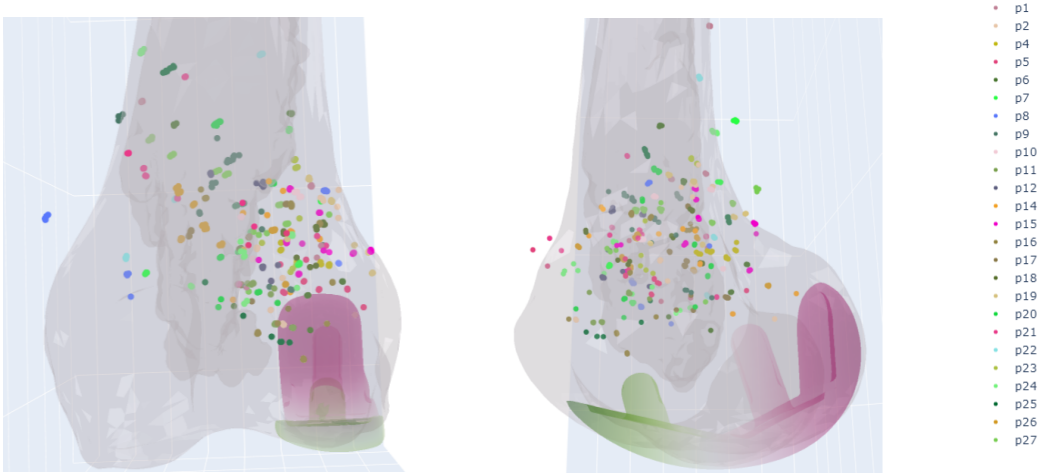
	Post-Op	6 wks	6 mo	1 yr	1 yr DE*	2 yr	**Total**
No. of patients / RSA scenes	24	24	23	23	17	22	**133**
No. of 3D markers	169	159	165	160	104	160	**917**
No. of 3D markers per RSA scene	7.0	6.6	7.2	7.0	6.1	7.3	**6.9**

* Double Examination (DE)

Figure 4.1: Location of all 3D markers

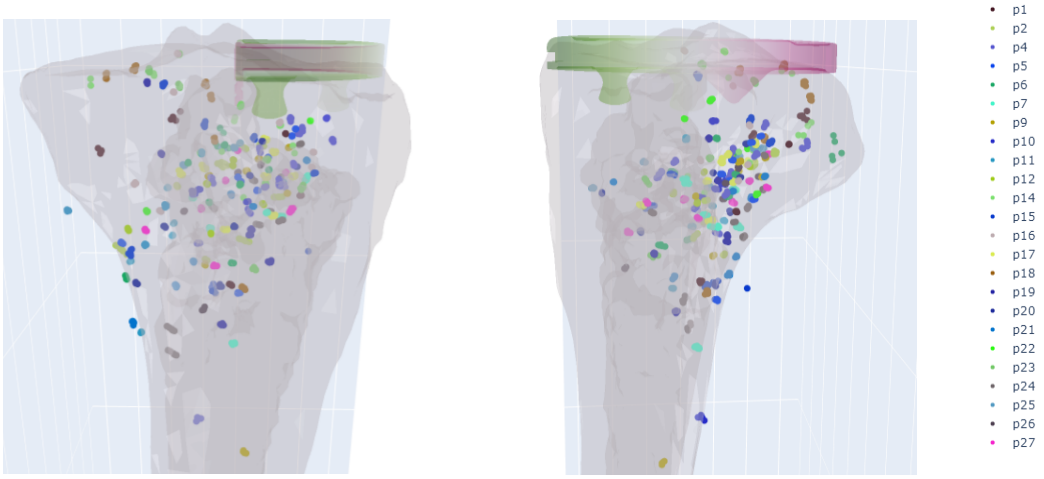
(a) Femur - 3D Markers - AP*

(b) Femur - 3D Markers - ML†



(c) Tibia - 3D Markers - AP*

(d) Tibia - 3D Markers - ML†



*Anterior-Posterior direction (AP)
† Medial-Lateral direction (ML)

4.3 Marker Density Analysis

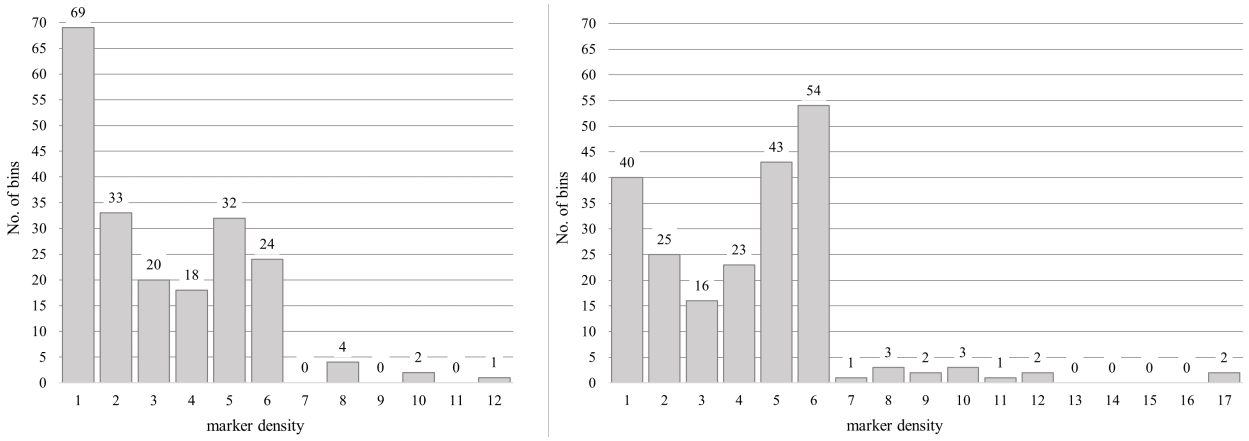
4.3.1. Voxelization

After the voxelization process 18,900 and 18,414 bins were created within the ranges of the 3D markers in respectively the femur and tibia to analyze the marker density. The distribution of marker density per bin in the femur is shown in the histogram of Figure 4.2a and the distribution in the tibia is shown in Figure 4.2b. The marker density analysis results for all bins, the non-empty bins and the bins with the highest marker count are shown in Table 4.2. Of all bins in the femur and tibia respectively 1.1% and 1.2% contained one or more 3D markers and were defined as non-empty bins. The average marker density of the non-empty bins in the femur was 3.1 markers, which means that all non-empty bins contained 3.1 3D markers on average. In the tibia the non-empty bins had an average marker density of 4.3 markers. The average scene prevalence of the non-empty bins shows that 2.3% and 3.2% of the scenes had a marker located in that specific bin for respectively the femur and tibia. Comparing the bin information of the femur and tibia in Table 4.2a and 4.2b, the total number of 3D markers is 31% less in the femur than the tibia and the number of bins is 6% less in the femur.

To determine whether there are locations that have a significantly better visibility and accessibility than other locations, the marker density and scene prevalence of the bins with the highest marker count are shown. The twelve fullest bins of both the femur and tibia represent 0.1% of all bins and both contained 15% of all 3D markers, which results in an average marker density that is respectively 233 times and 223 times higher than the average marker density of all bins combined. When comparing the twelve fullest bins to all non-empty bins, which are all proven

accessible locations, the average marker density is 2.5 times higher for the fullest bins of the femur and 2.6 times higher for the fullest bins of the tibia. To give insight on the distribution of the 3D markers, the locations of the non-empty bins and the twelve bins with the highest marker count are plotted and shown in Figure 4.4.

Figure 4.2: Marker density histogram of raw dataset



(a) Femur (b) Tibia

Table 4.2: Bin information of raw dataset

(a) Femur

		All bins	Non-empty bins	Fullest bins
No. of bins	N (%)	1,8900 (100)	203 (1.1)	12 (0.1)
No. of 3D markers	N (%)	635 (100)	635 (100)	94 (15)
Average marker density	N	0.03	3.1	7.8
Average scene prevalence	%	0.02	2.3	5.6

(b) Tibia

		All bins	Non-empy bins	Fullest bins
No. of bins	N (%)	18,414 (100)	215 (1.2)	12 (0.1)
No. of 3D markers	N (%)	917 (100)	917 (100)	133 (15)
Average marker density	N	0.05	4.3	11.1
Average scene prevalence	%	0.04	3.2	8.3

4.3.2. Spatial Smoothing

The effect of the spatial smoothing filter on the distribution of markers per bin is shown in the histograms of Figure 4.3. When comparing the marker distribution of the smoothed data to the distribution of the raw data (Figure 4.2, instead of a random distribution over the bins it is now and exponential distribution. This means the amount of bins that contain a certain marker fraction decreases exponentially as the marker fraction increases. This represents less pixelization of the data since the marker fraction of the bin is adjusted based on the amount of markers in the neighbouring bins, which makes it more representative of the actual marker distribution. In addition, the more spread amount of bins with high marker fractions makes the data more accessible to find high density hot-spots.

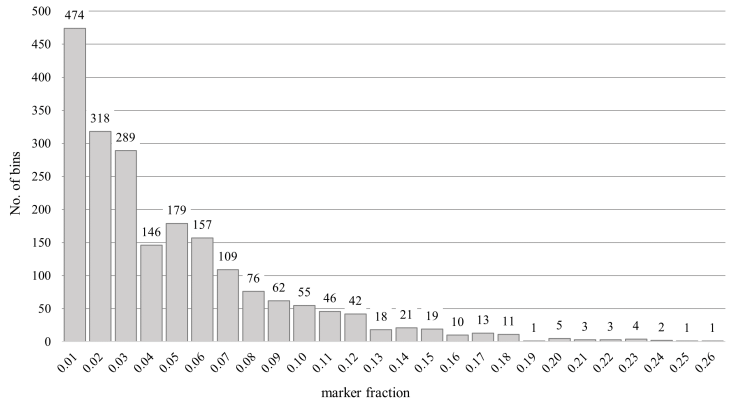
The density analysis after smoothing for all bins, the non-empty bins and the bins with the highest marker fraction are shown in Table 4.3. Corresponding to the histograms, there were 8.9 times more non-empty bins in the femur after smoothing and 8.0 times more in the tibia. The twelve fullest bins of the femur that represent 0.1% of al bins have a total marker fraction of 2.8%. This means that 2.8% of all markers are located in one of these twelve bins and their average marker fraction is 44 times higher than the average marker fraction of all bins which makes these locations more visible and accessible than the average location. For the tibia the total marker fraction of the twelve fullest bins is 3.9% and their average marker fraction is 60 times higher than the average marker fraction of all bins. When comparing the marker fraction distribution of the femur and the tibia, the bin with the highest

marker fraction in the femur is 1.6 times lower than the fullest bin in the tibia. In addition there are more bins with higher marker fractions in the tibia which makes the histogram in Figure 4.3b longer than the histogram of the femur in Figure 4.3a. This corresponds to a higher average marker fraction of the tibia compared to the femur for the fullest bins, while it is the same for all bins and the non-empty bins.

The heatmap of both the non-empty bins and the bins with the highest marker fraction are shown in Figure 4.5. Here the hot-spots with higher marker fraction are evidently more visible in the heatmap compared to the raw data shown in Figure 4.4. When comparing the heatmap of the fullest bins of the dataset after smoothing with the raw dataset, the bins are more centralized to one location for both the femur and the tibia. For the femur mostly the range in the distal direction is smaller. For the tibia the decrease of the range is mostly visible in both the AP and ML direction.

Figure 4.3: Marker fraction histogram of smooth dataset

(a) Femur



(b) Tibia

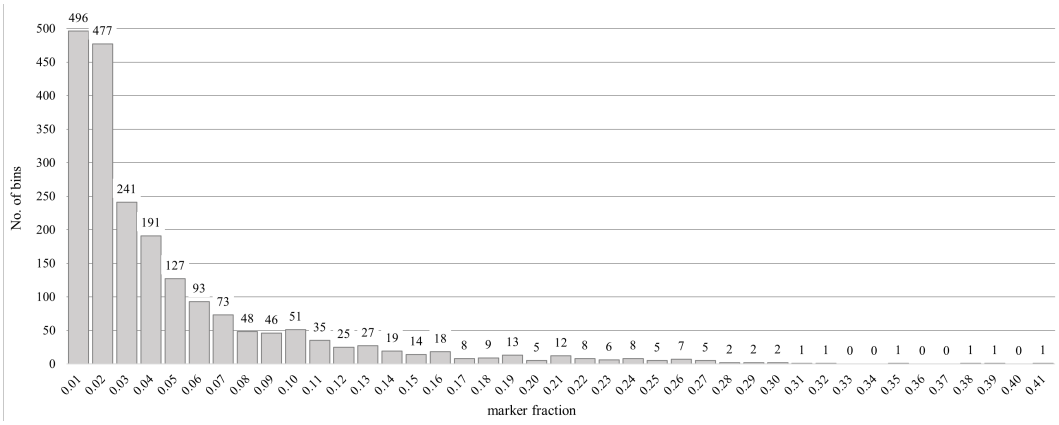


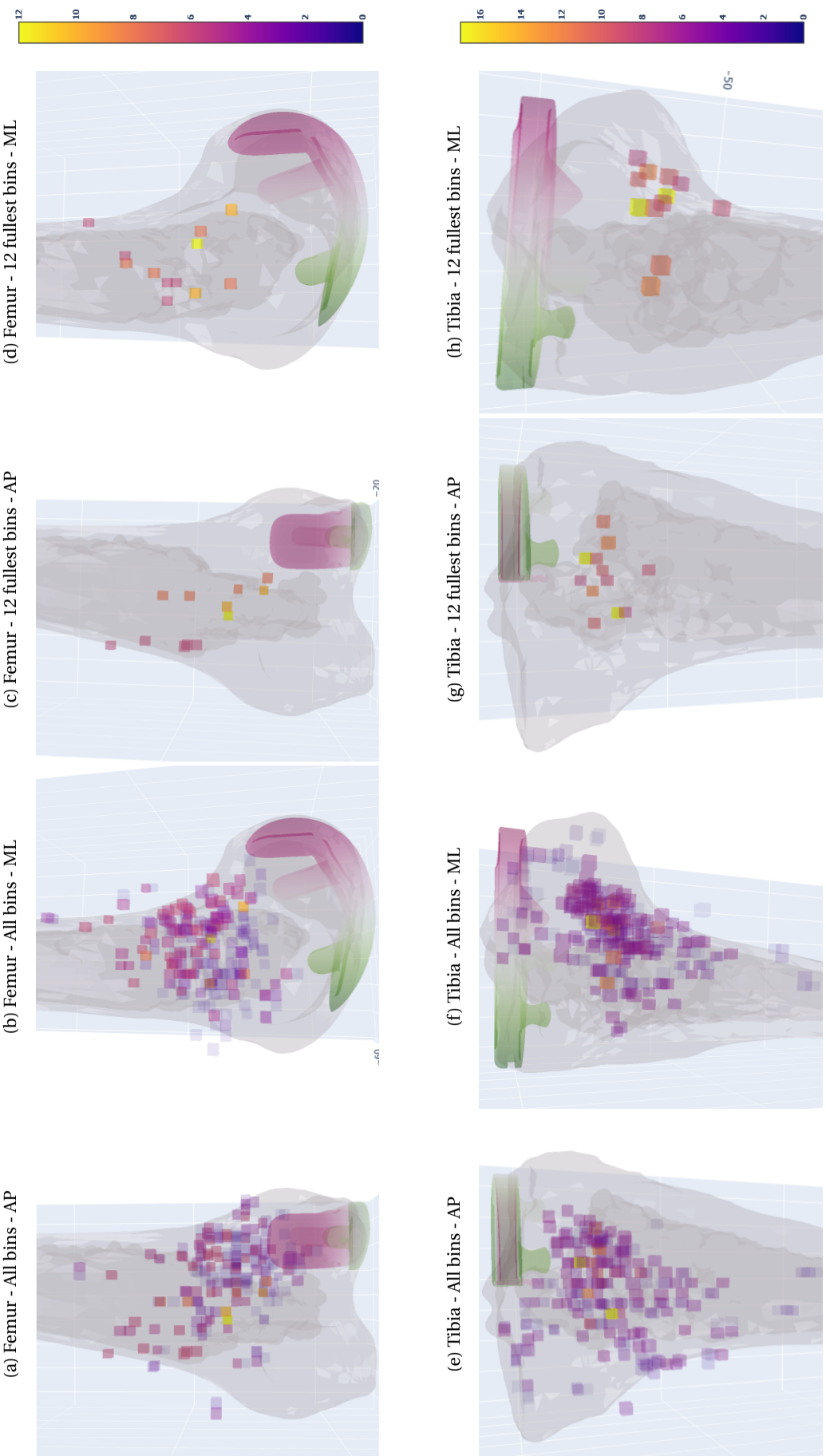
Table 4.3: Bin information of smooth dataset

(a) Femur

		All bins	Non-empty bins	Fullest bins
No. of bins	N (%)	18,900 (100)	2,065 (11)	12 (0.1)
Average marker fraction	%	0.005	0.048	0.233
Total marker fraction	%	100	100	2.8

(b) Tibia

		All bins	Non-empy bins	Fullest bins
No. of bins	N (%)	18,414 (100)	2,079 (11)	12 (0.1)
Average marker fraction	%	0.005	0.048	0.326
Total marker fraction	%	100	100	3.9



(a) Femur - All bins - AP (b) Femur - All bins - ML (c) Femur - 12 fullest bins - AP (d) Femur - 12 fullest bins - ML

(e) Tibia - All bins - AP (f) Tibia - All bins - ML (g) Tibia - 12 fullest bins - AP (h) Tibia - 12 fullest bins - ML

Figure 4.4: Density Analysis Results of raw dataset

Figure 4.5: Density Analysis Results after Gaussian smoothing

(a) Femur - All bins - AP

(b) Femur - All bins - ML

(c) Femur - 12 fullest bins - AP

(d) Femur - 12 fullest bins - ML

(e) Tibia - All bins - AP

(f) Tibia - All bins - ML

(g) Tibia - 12 fullest bins - AP

(h) Tibia - 12 fullest bins - ML

4.4 Bin Selection

In Table 4.4 the marker fraction and coordinates of the four selected bins for both the femur and tibia are shown. The selected bins in the femur represent 0.02% of all bins and they contain 1.0% of all markers. The average marker fraction of the four selected bins is 0.25% and therefore the chance that a marker is located in one of these four bins is 47 times higher than the chance that the marker is located in a random bin. The average marker fraction of the selected bins is 5 times higher than the average of the non-empty bins, which theoretically are all the accessible locations in this PPK study. The locations of the four selected bins of the femur can be seen in Figure 4.6. The distance of the center of the selected bins compared to the center of the implant range from 1.6mm to 28.6mm in the lateral direction, 31.9mm to 46.9mm in the proximal direction and 11.3mm to 23.3mm in the anterior direction.

The four selected bins in the tibia represent 0.02% of all bins in the tibia and they contain 1.4% of all markers. The average marker fraction of the four selected bins is 0.36% and therefore the chance that a marker is located in one of these four bins is 66 times higher than the chance that the marker is located in a random bin. The average marker fraction of the selected bins is 7 times higher than the average of the non-empty bins, which makes them more favourable for marker placement. The locations of the four selected bins of the tibia are shown in Figure 4.7. The distance of the center of the selected bins compared to the center of the implant range from 5.3mm to 20.3mm in the lateral direction, 17.5mm to 26.5 in the distal direction and 1.6mm to 13.6mm in the posterior direction.

When comparing the femur and the tibia, the selected bins of the femur have a smaller increase of marker fraction to the average bin than the tibia. Which makes the markers in the femur more distributed than in the tibia, with less centralized locations of high marker density. When looking at the coordinates of the selected bins, for

Table 4.4: Information of selected bins

(a) Femur

		Bin #1	Bin #2	Bin #3	Bin #4
Marker fraction	%	0.26	0.25	0.24	0.23
X-coordinate (ML)	mm	-28.6	-22.6	-19.6	-1.6
Y-coordinate (DP)	mm	34.9	46.9	31.9	40.9
Z-coordinate (AP)	mm	14.3	23.3	11.3	11.3

(b) Tibia

		Bin #1	Bin #2	Bin #3	Bin #4
Marker fraction	%	0.41	0.38	0.35	0.30
X-coordinate (ML)	mm	-5.3	-20.3	-14.3	-5.3
Y-coordinate (PD)	mm	17.5	26.5	20.5	26.5
Z-coordinate (AP)	mm	-7.6	-7.6	-13.6	-1.6

Figure 4.6: Selected bins in the femur

(a) Femur - Selected Bins - AP (b) Femur - Selected bins - ML (c) Femur - Selected bins - Vectors

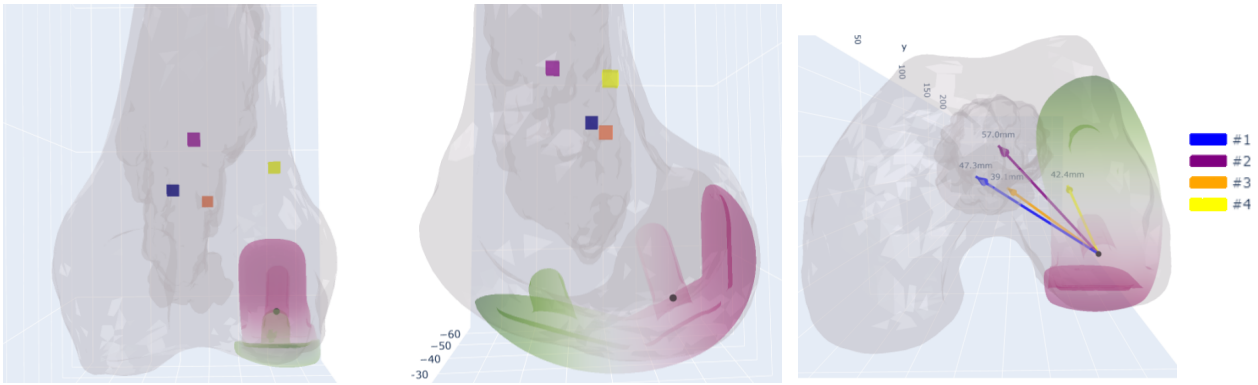
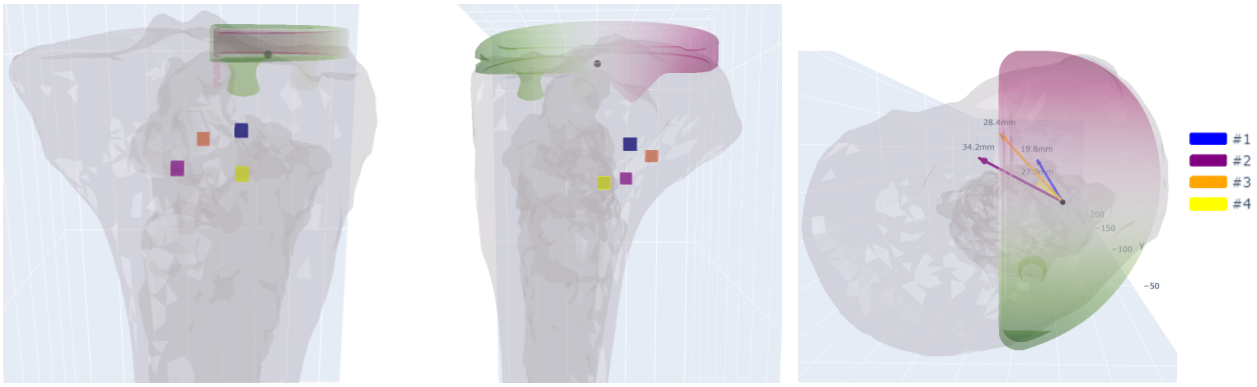


Figure 4.7: Selected bins in the tibia

(a) Tibia - Selected bins - AP (b) Tibia - Selected bins - ML (c) Tibia - Selected bins - Vectors



both the femur and tibia the lateral side from the implant center is favourable and for the femur the anterior side is favourable whilst the posterior side is favourable for the tibia. In addition, the range in each direction is smaller in the tibia which means the selected bins are less distributed over the tibia compared to the selected bins in the femur.

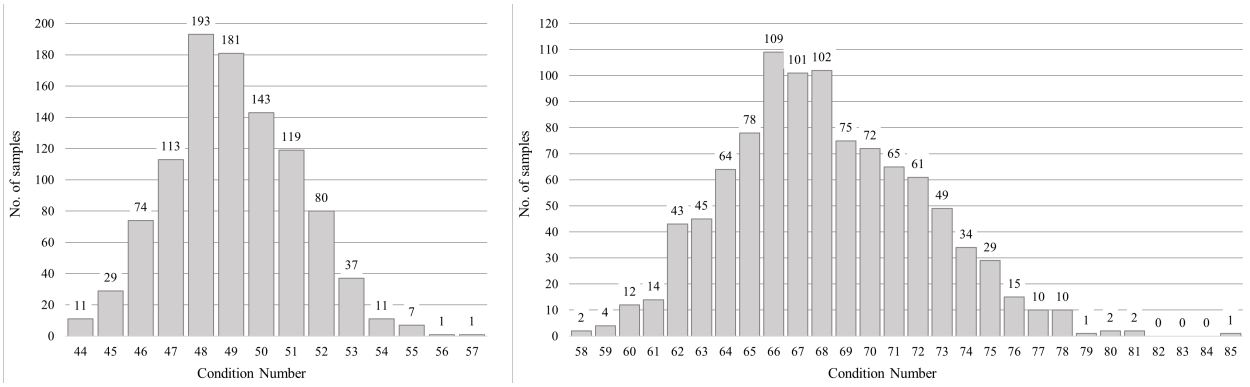
4.5 Distribution Analysis

After 1000 samples of possible marker position in the bins, the calculated CN value per sample are shown in Figure 4.8a for the femur and Figure 4.8b for the tibia. The range of the CN values for the selected bins in the femur was 44 to 57. The range in the tibia was 58 to 85. As expected by the central limit theorem, the distribution of the sample means approximates a normal distribution. The mean CN for the femur was 49.1 with a standard deviation of 2.1, which means there is a 95% chance when the markers are situated in the selected bins that the markers will have a distribution with a CN value between 44.9 and 53.3. The selected bins in the tibia had a distribution with a mean CN value of 68.2 and a standard deviation of 4.1. Therefore, 95% of markers placed in these bins will have a CN value between 60.0 and 76.4. The ranges of CN values for both the femur and tibia lie substantially underneath the ISO standard cut-off value of CN < 120.[17]

The mean CN values of the patients in the PPK study were respectively 61.7 (34.3-90.5) and 52.1 (32.9-98.9) for the femur and the tibia, as shown in Table A.1 of the Appendix. For the femur, the CN values of all samples were lower than the mean CN of the patients. For the tibia the mean CN of the selected bins is higher than the mean CN of the patients. However, the maximum CN values of the samples (Figure 4.8b) is lower than the maximum CN value of the patients.

Figure 4.8: Condition Number results

(a) CN value occurrences femur (b) CN value occurrences tibia



5 Discussion

In the present study, a method was developed to provide insights on favourable marker locations in RSA by analyzing marker placement in a previous study investigating the migration of UKA. Bins are created which represent locations in the femoral and tibial bone with a certain marker density. With density analysis it is shown that there are certain marker locations that have a significantly higher contribution to the total amount of markers than other locations, which makes them more desirable for marker placement. After smoothing there are noticeable hotspots where the marker density in multiple neighboring bins is higher than in other locations. The four selected bins have a significantly higher marker fraction than the average bin, which makes them more favourable for RSA analysis based on their accessibility and visibility. Up to this date, the present study is the first to develop a method for analysis of marker placement for UKA or any other implant.

5.1 Study Population

In the PPK study, fifteen of the twenty-five patients did not have a sufficient amount of markers visible in the femur with a condition number below the threshold to perform the migration calculations. A technique to overcome this issue is called the mean marker mode which is created based on all active markers in the loaded scenes. For ten patients the mean marker model was successfully created and the migration could be calculated. For the other five patients this was unsuccessful and therefore they were not included in the migration study.For the migration calculations of the tibia there were no patients with an insufficient amount of markers. However, one patient was excluded because of movement of the implant model between the follow-up scenes. Hence, the total amount of included patients for the migration study were 20 and 24 patients for the femur and tibia respectively, which is respectively 80% and 96% of all included patients. The number of included patients and the amount of mean marker models used per follow-up moment are shown in Table A.1 of the Appendix. It can therefore be concluded that correct marker placement to obtain a sufficient amount of visible markers is significantly more difficult in the femur than in the tibia. The percentage of excluded patients is also in line with other studies, as conducted in the systematic review of Gevers et al.[19] This shows the importance of having good marker placement to prevent exclusion of patients in RSA studies on UKA.

5.2 Marker Placement Analysis

5.2.1. Marker Location Assessment

Marker locations can be assessed by transforming the markers to a unified coordinate system based on the orientation of the implant model. The study population used to assess the marker locations, contained of 25 patients with a total of 139 RSA scenes of the femur and 133 of the tibia. The data after the transformation and scaling process gives an adequate resemblance of the real data in the RSA scenes. To account for the different bone sizes of the patients, a scaling method is used based on the implant size. Even though the scaling method does not take anatomical variation into account, it is believed that bone growth is an isometric process which means using a scale based on implant sizes is thought to be a realistic approximation.[51] In addition, numerous studies have proven the bilateral symmetry between the left and right lower limbs which indicates that it is appropriate to mirror the left sided PPK implants to fit into the location assessment.[52, 53] By using the implant model as a reference to transform the marker locations to the unified coordinate system, it is assumed that the implant is not moving. However, the actual RSA study does show implant migration in individual patients over the follow-up period.

The total amount of 'Active' 3D markers that were obtained from the RSA scenes of the PPK study was 635 markers in the femur and 917 markers in the tibia. Since it is assumed that that there is an equal amount of markers placed in both the femur and tibia, the difference is caused by the visibility of the markers during radiostereometric analysis. This is in line with the fact that more patients had to be excluded for the femur migration analysis because of a insufficient amount of markers. It therefore can be concluded that it is more difficult to place markers in the femur that are visible on both uniplanar radiographs.

By using the implant model center as a stagnant origin of the axes, the migration of the implant is displaced by the markers. This results in migration of a marker between different follow-up scenes. The systematic review of Hasan et al.[39] shows mean migration of unicompartmental knee implants at 2 year follow-up of 0.61mm. Since this is significantly smaller than the used bin size in this study, it can be assumed this has no impact on the performed analysis. Looking at Figure 4.1 all marker projections fit into a reasonably range from the implant in all directions after the transformation and scaling operation. For that reason, the present location assessment method shows to be a successful approach to combine marker locations of multiple patients and follow-up scenes.

5.2.2. Voxelization

Using voxelization, a grid of 3x3x3mm bins is created for the range in which the markers were located, which resulted in 18,900 bins for the femur and 18,414 for the tibia. This can be caused by either a larger amount of bone volume in which the markers can placed, or a larger range that can be reached with the insertion tool. Another explanation could be that the surgeons are aware of the difficulties of overprojection in the femur and are therefore trying to place the markers in more distance from the implant.
The bin size is determinative for the results. Hence, a larger bin size would give a higher amount of markers per bin which would represent a higher number of implanted tantalum markers but it would give less precise favourable marker locations. On the other hand, a smaller bin size would give a more precise location but will potentially only hold information of one or two markers per bin, which would not result in significantly higher marker density in favourable locations.

5.2.3. Marker Density Analysis

The marker density analysis contained 635 3D markers in the femur and 917 in the tibia. When assuming there were 9 tantalum markers implanted in both the femur and tibia of all patients, this is respectively 51% and 77% of the implanted markers which means that 49% and 23% of the markers of all patients in every follow-up image were not visible in both the left and right X-ray image and therefore not computed to a 3D marker. When comparing the femur and tibia, the average amount of active markers per follow-up scene were respectively 4.6 and 6.9 markers. Here the amount of active markers of the tibia is 1.5 times higher than that of the femur, which indicates it is more difficult to place markers in the femur that are not occluded by the implant or another markers in either the left or right X-ray image. The fact that marker placement is more difficult in the femur than in the tibia is confirmed by the substantial higher amount of excluded patients for the femur than for the tibia migration analysis in the PPK study.

The marker density per bin is a representative of the accessibility of a location and how often this location is used in combination with the visibility of the location in radiostereometric analysis. If all locations were equally accessible and visible, the marker density and fraction of the total amount of markers would be the same for every bin. Figure 4.4 clearly shows that there is great variation in marker density between bins, which implies there are more favourable locations compared to others. When looking at the 12 bins with the highest marker count, their mean marker density is 7.8 markers per bin in the femur and 11.1 markers per bin in the tibia. For the femur this is 233 times higher than the average marker density per bin of 0.03 markers and for the tibia this is 223 times higher than the average of 0.05 markers. Therefore, the marker density analysis shows that the markers are not evenly distributed over the reachable volume of the bone which proves there are favourable marker locations based on accessibility and visibility.

5.2.4. Spatial Smoothing

Spatial smoothing using a Gaussian weighted kernel, is a sufficient way to normalize the dataset as can be seen in Figure 4.3a and Figure 4.3b. After smoothing the marker density, the existing hot-spots in the bin locations becomes visible in the heatmap as shown in Figure 4.5. This is in line with literature stating a Gaussian kernel is sufficient for analyzing spatial distribution by creating a heatmap for density estimation.[54] The heatmap visualizes multiple bin locations with a significantly higher marker fraction that decreases when you move further from the center of the hotspot. The percentage of markers that are in the twelve bins with the highest marker density is specified by their total marker fraction, which is 2.8% in the femur and 3.9% in the tibia. If the data was equally distributed every bin would have the value of the average marker fraction which is 0.005%. However, the average marker fraction of the 12 fullest bins is respectively 0.23% and 0.33% for the femur and tibia which is significantly higher than the overall average marker fraction. This means it is respectively 44 and 60 times more likely that a marker is found in one of the twelve fullest bins compared to a random bin.

When comparing the amount of bins and there distribution of the femur and tibia, it can be seen that the bin locations of the tibia are more compact than of the femur. This is even more visible in the 12 fullest bins, which be-

came more centralized after smoothing compared to the raw data. Therefore, it can be concluded that the marker locations of the tibia are less distributed since there are more neighboring bins with high marker density which causes the marker fractions after smoothing to become more centralized.

Because of the shape of the Gaussian kernel the higher marker fractions in the heatmap are more centralized to locations with multiple bins with a higher amount of markers. Because of this smoothing technique, the bin locations of the twelve fullest bins are closer to each other compared to the twelve bins of the raw data as can be seen in Figure 4.4 and Figure 4.5. However, to give an approximation of the actual marker distribution the spatial smoothing filter is a sufficient method that accounts for the marker density of the closest neighbours to resemble the real marker distribution.

5.2.5. Bin Selection

The selected bins represent the locations with high marker visibility and accessibility without compromising the distribution of the marker locations. To compensate for the centralization of high density after spatial smoothing a requirement was needed to select bins with a sufficient amount of spacing between the locations of the bins. Using this method, it was attempted to identify the centers of different hotspots in the heatmap after smoothing. For both the femur and the tibia the selected bins are in the top ten of bins with the highest marker fractions. Therefore, not to much of a compromise was necessary to select bins with enough spatial distance. The combined marker fraction of the selected bins was 1.0% for the femur and 1.4% for the tibia, based on the marker fractions shown in Table 4.4. This means that the chance that a random marker in the femur would be located in one of these four bins instead of the other 18896 bins would be 1.0%. For the tibia it would be 1.4% that the marker would be located in these four bins instead of the other 18410 bins. In other words, the marker fraction of the selected bins in the femur is 47 times higher than their contribution to the total amount of bins and for the tibia this is 66 times higher. Therefore it can be concluded that the locations of the selected bins for both the femur and tibia have a significantly higher marker visibility and/or accessibility than a random location in the marker placement range which makes them more favorable for marker placement.

When comparing the twelve bins with highest marker density of the tibia in Figure 4.4 with the selected bins in Figure 4.6 and Figure 4.7, it shows that after smoothing and bin selection the spatial distance between the bins has decreased. This is a result of either higher visibility in these centralized locations or a potential surgeon preference to place markers in this location. The surgeon preference could be a result of easier accessibility but also a potential unawareness of sufficient marker locations and distributions. This results in a potential bias of the dataset, where the selected bins are not the only accessible locations with adequate visibility.

5.2.6. Distribution Analysis

The mean condition number of the selected bins in the femur is 49.1 and the mean condition number of the actual patient data is 59.1. Hence, it is believed that the selected locations have a better distribution than the marker locations used in clinical practice. For the tibia the mean condition number of the selected bins is 68.2 and the mean condition number of the actual patient data is 50.5. However, the maximum condition number of the actual patient data is higher than that of the selected bins, which are respectively 100 and 85. Therefore, it can be concluded that the distribution of the selected locations in the tibia is not evidently better than the marker locations used in clinical practice but it has the potential to prevent outliers. Since it is believed that a high condition number has more impact on the accuracy of the migration measurement, this can possibly prevent low accuracy measurements.[55]

The values of the distribution analysis are an approximation of the condition number if two markers were randomly placed in each bin. This includes the assumption that all markers are placed correctly within the boundaries of the bin, and are all visible. If in clinical practice not all markers are precisely placed within the selected bins, the range of marker distribution could differ. However, since the range of condition number values is significantly below the cut-off value of 120 it should not be a substantial disadvantage. In addition, the selected bins would most likely provide a sufficient amount of markers with good marker distribution and therefore decrease the amount of patients that need to be excluded.

5.3 Study Limitations

This method describes the marker placement of a real dataset. However, this dataset is relatively small compared to the range of locations with 635 markers divided over 18,900 bins and 917 markers divided over 18,414. In addition, all data is from one center and two surgeons which could lead to a bias for surgeon preferences in marker placement. There is a possibility that not all potential locations are being evaluated. There could be locations that are

surgically accessible and are not overprojected by the implant that do not occur in this dataset, which could possibly be assessed with a phantom study. Therefore, by using this method you can identify favourable locations of the locations where markers were placed but these are possibly not the optimal marker locations. To compensate for the limited amount of data a smoothing filter was used, however analyzing a greater dataset would potentially lead to a better approximation of the optimal marker locations and there actual visibility and accessibility. However, the objective of the present study was to develop a method to improve insight on favourable marker locations which is accomplished with the current density analysis.

Another limitation is the method of creating a grid of bins to assess the marker density. The size and range of the bins is determinative for the results of the density analysis. The bins have solid boundaries and this results in static values. It does not account if a marker is near the center of the bin or close to the edge and the method is also blind for markers that are closely outside of the boundary. Therefore, it could potentially be beneficial to optimize the bin sizes to give the best representation of the actual marker locations. However, by performing the spatial smoothing filter it is accounting for the potential close markers in neighboring bins which leads to a low computationally approach to determine marker density. In addition, an important factor to take into account when converting the results to clinical practice is that the two markers within the selected bin need to be sufficiently distributed to prevent overprojection of the markers. The four selected bins per bone are the locations for eight markers, which means two markers are placed in the same 3x3x3 mm cube. Since the volume of the tantalum markers is 9 times smaller than that of the bin, this is thought to be manageable.

A final limitation is the approach of the marker density, which is a value for the total amount of 3D markers in the bin. By just counting the markers, it does not give information on the origin of the marker. Hence, it is not possible to determine whether the markers in a bin are coming from several follow-up scenes of one and the same marker or from different markers from different patients. Even if the markers are coming from one patient, it is still not conceivable if it is the same bone marker or for example two closely placed markers. This factor makes it more difficult to interpret the marker density values. Since the main goal of the present study is to analyse marker locations based on visibility and accessibility the amount of markers is still an efficient method to evaluate that matter.

5.4 Clinical Implications

When comparing the contribution to the marker density of the selected bins versus the average bin, it is evident that there are certain locations that are more favourable for marker placement. This method results in actual locations in respect to the implant center, which makes it accessible to implement in clinical practice. The vectors represented in Figure 4.6c and Figure 4.7c give an insight on the approach to reach the favourable locations. This gives great potential to improve the marker visibility and distribution, especially in the femur which is more vulnerable for implant overprojection. It is believed that with proper education for the surgeons they can get relatively close to the actual bin locations and therefore improve the marker count and distribution for RSA in UKA. In addition, by showing the variations in the heatmap this could also enlighten surgeons on which marker locations to aim for or to avoid.

5.5 Future Perspectives

Additional research using data from multiple RSA studies in UKA is needed to further optimize the proposed method for analyzing marker density in UKA. Another way of optimizing the method is by simulating virtual marker locations to analyse their visibility and afterwards verify the accessibility with a phantom study. This could potentially give more insight on marker locations that are not commonly used but are a sufficient option for the future. For clinical implementation it could be beneficial to design an insertion mall for both the femur and tibia to assure that the markers are placed in the favourable locations. To find out if this is needed, further analysis can be performed to evaluate how close the surgeons come by hand and what effect this has on the marker visibility. Finally, a clinical study should be performed to evaluate the potential improvement. This should demonstrate the expected increase in marker visibility and distribution and result in lower exclusion rates which would potentially lead to more accurate migration calculation. When the method created in this thesis is optimized to determine the most optimal locations and the implementation strategy is improved, it's potential benefits for RSA studies in other implants should be evaluated to broaden the scope of the marker placement analysis method.

6 Conclusion

The proposed method in the present study has proven to be sufficient for marker placement analysis. Using this method, four bins of the femur and tibia could be selected who have a considerably higher contribution to the total amount of 3D markers than the average bin, which makes these locations more favourable for marker placement for radiostereometric analysis. Placing the markers in the selected bins would presumably increase the marker visibility during radiostereometric analysis and decrease patient exclusion. In particular it would give the most benefit for the analysis of the femur since the marker count and distribution show a substantial improvement in the selected bins. Further research is required to improve the method by using more data or simulating virtual markers and to fine-tune the optimal locations. In addition, a next step to implementation would be to design an insertion mall to accurately place the markers in the designated bins. That way the developed method has the potential to improve marker placement for future RSA studies in UKA and possibly also in other implants or joints.

7 References

[1] Chetan Gohal, Ajaykumar Shanmugaraj, Patrick Tate, Nolan S Horner, Asheesh Bedi, Anthony Adili, and Moin Khan. Effectiveness of valgus offloading knee braces in the treatment of medial compartment knee osteoarthritis: a systematic review. Sports health, 10(6):500–514, 2018.

[2] A Dell'Isola, R Allan, SL Smith, SSP Marreiros, and Martijn Steultjens. Identification of clinical phenotypes in knee osteoarthritis: a systematic review of the literature. BMC musculoskeletal disorders, 17(1):1–12, 2016.

[3] Methodology for trend scenario for dutch public health (vtv). Foresight report, National Institute for Public Health and the Environment, P.O. Box 1, 3720 BA Bilthoven, The Netherlands, 2018.

[4] Tabatha Griffin, Neville Rowden, David Morgan, Robert Atkinson, Peter Woodruff, and Guy Maddern. Unicompartmental knee arthroplasty for the treatment of unicompartmental osteoarthritis: a systematic study. ANZ journal of surgery, 77(4):214–221, 2007.

[5] Samuel W Carlson and Rafael J Sierra. Unicompartmental knee arthroplasty over total knee arthroplasty: a more cost-effective strategy for treating medial compartment arthritis. Annals of Translational Medicine, 8(7), 2020.

[6] Matthew C Lyons, Steven J MacDonald, Lyndsay E Somerville, Douglas D Naudie, and Richard W McCalden. Unicompartmental versus total knee arthroplasty database analysis: is there a winner? Clinical Orthopaedics and Related Research®, 470(1):84–90, 2012.

[7] AJ Price, J Webb, H Topf, CAF Dodd, JW Goodfellow, DW Murray, et al. Rapid recovery after oxford unicompartmental arthroplasty through a short incision. The Journal of arthroplasty, 16(8):970–976, 2001.

[8] Nederlandse Orthopaedische Vereniging Nederland. Geïsoleerde mediale en laterale artrose van de knie. Guideline, NOV, 2021. Accessed on 02-04-2022: `https://richtlijnendatabase.nl/richtlijn/geisoleerde_mediale_en_laterale_artrose_van_de_knie/startpagina_geisoleerde_mediale_en_laterale_artrose_van_de_knie.html`.

[9] Johan Kärrholm, Peter Herberts, Peter Hultmark, Henrik Malchau, Bo Nivbrant, and Jonas Thanner. Radiostereometry of hip prostheses. review of methodology and clinical results. Clinical orthopaedics and related research, (344):94–110, 1997.

[10] Dutch Arthroplasty Register (LROI). Annual report 2020. Online annual report, Netherlands Orthopaedic Association (NOV), Bruistensingel 230, 5232 AD 's-Hertogenbosch, The Netherlands, 2020. Accessed on 25-04-2022: `https://www.lroi-report.nl/`.

[11] J Newman, RV Pydisetty, and C Ackroyd. Unicompartmental or total knee replacement: the 15-year results of a prospective randomised controlled trial. The Journal of bone and joint surgery. British volume, 91(1):52–57, 2009.

[12] Musa Zaid, Michael Kaplan, H. John Cooper, and Shaun Patel. Unicompartmental knee replacement. Medical report, Orthobullets, feb 2022. Accessed on 31-03-2022: `https://www.orthobullets.com/recon/5020/unicompartmental-knee-replacement`.

[13] Todd Borus and Thomas Thornhill. Unicompartmental knee arthroplasty. JAAOS-Journal of the American Academy of Orthopaedic Surgeons, 16(1):9–18, 2008.

[14] G Rebecca Aspinall and Michael J Dunbar. Assessing clinical results and outcome measures. In Surgical Treatment of Hip Arthritis, pages 30–36. Elsevier, 2009.

[15] Bart Ten Brinke, Annechien Beumer, Koen LM Koenraadt, Denise Eygendaal, Gerald A Kraan, and Nina MC Mathijssen. The accuracy and precision of radiostereometric analysis in upper limb arthroplasty: a systematic review of 23 rsa studies. Acta orthopaedica, 88(3):320–325, 2017.

[16] Xunhua Yuan, Kimberley Lam Tin Cheung, James L Howard, Brent A Lanting, and Matthew G Teeter. Radiostereometric analysis using clinical radiographic views: validation measuring total hip replacement wear. Journal of Orthopaedic Research, 34(9):1521–1528, 2016.

[17] International Organization for Standardization. Implants for surgery: Roentgen stereophotogrammetric analysis for the assessment of migration of orthopaedic implants. Technical Report ISO 16087:2013, Case postale 56, CH-1211 Geneva 20, 2013.

[18] Koen T Van Hamersveld, Perla J Marang-van de Mheen, Lennard A Koster, Rob GHH Nelissen, Sören Toksvig-Larsen, and Bart L Kaptein. Marker-based versus model-based radiostereometric analysis of total knee arthroplasty migration: a reanalysis with comparable mean outcomes despite distinct types of measurement error. Acta orthopaedica, 90(4):366–372, 2019.

[19] Imke AM Gevers, Jantsje H Pasma, Bart L Kaptein, and Hennie Verburg. Migration of unicompartmental knee replacements; a systematic review. Master's thesis, Technical University of Delft, Erasmus University Rotterdam and Leiden University, 2022.

[20] David J Hunter, Jason J McDougall, and Francis J Keefe. The symptoms of osteoarthritis and the genesis of pain. Rheumatic Disease Clinics of North America, 34(3):623–643, 2008.

[21] Roger H Thomas, Donald Resnick, Naomi P Alazraki, Dale Daniel, and Richard Greenfield. Compartmental evaluation of osteoarthritis of the knee: a comparative study of available diagnostic modalities. Radiology, 116 (3):585–594, 1975.

[22] Keith Sinusas. Osteoarthritis: diagnosis and treatment. American family physician, 85(1):49–56, 2012.

[23] Gregory M Martin, TS Thornhill, and JN Katz. Total knee arthroplasty. UpToDate, 2014.

[24] Tae Kyun Kim, Anurag Mittal, Prashant Meshram, Woo Hyun Kim, and Sang Min Choi. Evidence-based surgical technique for medial unicompartmental knee arthroplasty. Knee Surgery & Related Research, 33(1):1–14, 2021.

[25] Kyung Tae Kim. Unicompartmental knee arthroplasty. Knee surgery & related research, 30(1):1, 2018.

[26] Orthopaedic Associates of Muskagon. Unicompartmental (partial) knee replacement. Accessed on 14-04-2022: `https://www.oamkg.com/specialties/knee/partial-knee-replacement.html`.

[27] Alfredo Schiavone Panni, Michele Vasso, Simone Cerciello, and Alessandro Felici. Unicompartmental knee replacement provides early clinical and functional improvement stabilizing over time. Knee Surgery, Sports Traumatology, Arthroscopy, 20(3):579–585, 2012.

[28] Bernardino Saccomanni. Retracted article: Unicompartmental knee arthroplasty: a review of literature. Clinical rheumatology, 29(4):339–346, 2010.

[29] Amir A Jamali, Richard D Scott, Harry E Rubash, and Andrew A Freiberg. Unicompartmental knee arthroplasty: past, present, and future. Am J Orthop (Belle Mead NJ), 38(1):17–23, 2009.

[30] DW Murray and RW Parkinson. Usage of unicompartmental knee arthroplasty. Bone Joint J, 100(4):432–435, 2018.

[31] Emmanuel Thienpont. Conversion of a unicompartmental knee arthroplasty to a total knee arthroplasty: can we achieve a primary result? The Bone & Joint Journal, 99(1_Supple_A):65–69, 2017.

[32] Alexander D Liddle, Hemant Pandit, Andrew Judge, and David W Murray. Effect of surgical caseload on revision rate following total and unicompartmental knee replacement. Jbjs, 98(1):1–8, 2016.

[33] Cyrus Brodén, Henrik Olivecrona, Gerald Q Maguire, Marilyn E Noz, Michael P Zeleznik, and Olof Sköldenberg. Accuracy and precision of three-dimensional low dose ct compared to standard rsa in acetabular cups: an experimental study. BioMed Research International, 2016, 2016.

[34] Marie Christina Keller, Christof Hurschler, and Michael Schwarze. Experimental evaluation of precision and accuracy of rsa in the lumbar spine. European Spine Journal, 30(7):2060–2068, 2021.

[35] Stefano Campi, BJL Kendrick, BL Kaptein, ER Valstar, WFM Jackson, CAF Dodd, AJ Price, and DW Murray. Five-year results of a randomised controlled trial comparing cemented and cementless oxford unicompartmental knee replacement using radiostereometric analysis. The Knee, 28:383–390, 2021.

[36] Bart G Pijls, Edward R Valstar, Klaas-Auke Nouta, Josepha WM Plevier, Marta Fiocco, Saskia Middeldorp, and Rob GHH Nelissen. Early migration of tibial components is associated with late revision: a systematic review and meta-analysis of 21,000 knee arthroplasties. Acta orthopaedica, 83(6):614–624, 2012.

[37] L Ryd, BE Albrektsson, L Carlsson, F Dansgard, P Herberts, A Lindstrand, L Regner, and S Toksvig-Larsen. Roentgen stereophotogrammetric analysis as a predictor of mechanical loosening of knee prostheses. The Journal of bone and joint surgery. British volume, 77(3):377–383, 1995.

[38] Bart G Pijls, José WM Plevier, and Rob GHH Nelissen. Rsa migration of total knee replacements: a systematic review and meta-analysis. Acta orthopaedica, 89(3):320–328, 2018.

[39] Shaho Hasan, Lode A van Dijk, Rob GHH Nelissen, José WM Plevier, Leendert Blankevoort, and Bart G Pijls. Rsa migration of unicondylar knee arthroplasties is comparable to migration of total knee arthroplasties: A meta-analysis. Journal of ISAKOS, 2021.

[40] Edward R Valstar, Richie Gill, Leif Ryd, Gunnar Flivik, Niclas Börlin, and Johan Kärrholm. Guidelines for standardization of radiostereometry (rsa) of implants. Acta orthopaedica, 76(4):563–572, 2005.

[41] Trygve Holm-Glad, Ole Reigstad, Masako Tsukanaka, Magne Røkkum, and Stephan M Röhrl. High precision and accuracy of model-based rsa for analysis of wrist arthroplasty. Journal of Orthopaedic Research®, 36(11): 3053–3063, 2018.

[42] J Ranstam, L Ryd, and I Onsten. Accurate accuracy assessment: review of basic principles. Acta Orthopaedica Scandinavica, 71(1):106–108, 2000.

[43] Sim Johal, Naoki Nakano, Mark Baxter, Ihab Hujazi, Hemant Pandit, and Vikas Khanduja. Unicompartmental knee arthroplasty: the past, current controversies, and future perspectives. The Journal of Knee Surgery, 31 (10):992–998, 2018.

[44] David J Beard, Loretta J Davies, Jonathan A Cook, Graeme MacLennan, Andrew Price, Seamus Kent, Jemma Hudson, Andrew Carr, Jose Leal, Helen Campbell, et al. Total versus partial knee replacement in patients with medial compartment knee osteoarthritis: the topkat rct. Health Technology Assessment (Winchester, England), 24(20):1, 2020.

[45] Zimmer Biomet. Persona ® partial knee. Accessed on 22-04-2022: `https://www.zimmerbiomet.com/en/products-and-solutions/specialties/knee/persona-partial-knee.html`. Version 1.6.0.

[46] Guido Van Rossum and Fred L. Drake. Python 3 Reference Manual. CreateSpace, Scotts Valley, CA, 2009. ISBN 1441412697.

[47] Pierre Raybaut. Spyder-documentation. Available online at: pythonhosted. org, 2009.

[48] MingLei Shu, HuanQing Cui, YingLong Wang, and Cheng-Xiang Wang. Planning the obstacle-avoidance trajectory of mobile anchor in 3d sensor networks. Science China Information Sciences, 58(10):1–10, 2015.

[49] Mehmet Celenk, Mike L Farrell, Haluk Eren, K Kumar, G Dave Singh, and Scott Lozanoff. Upper airway detection and visualization from cone beam image slices. Journal of X-ray science and technology, 18(2):121–135, 2010.

[50] Sang Gyu Kwak and Jong Hae Kim. Central limit theorem: the cornerstone of modern statistics. Korean journal of anesthesiology, 70(2):144, 2017.

[51] Tomer Stern, Rona Aviram, Chagai Rot, Tal Galili, Amnon Sharir, Noga Kalish Achrai, Yosi Keller, Ron Shahar, and Elazar Zelzer. Isometric scaling in developing long bones is achieved by an optimal epiphyseal growth balance. PLoS biology, 13(8):e1002212, 2015.

[52] Melissa A Pierre, David Zurakowski, Ara Nazarian, Diana A Hauser-Kara, and Brian D Snyder. Assessment of the bilateral asymmetry of human femurs based on physical, densitometric, and structural rigidity characteristics. Journal of biomechanics, 43(11):2228–2236, 2010.

[53] Christof Seiler, Stefan Weber, Walter Schmidt, Felix Fischer, Nils Reimers, and Mauricio Reyes. Automatic landmark propagation for left and right symmetry assessment of tibia and femur: a computational anatomy based approach. In Annual Meeting of the International Society for Computer Assisted Surgery. Citeseer, 2009.

[54] Kunxiaojia Yuan, Xiaoqiang Cheng, Zhipeng Gui, Fa Li, and Huayi Wu. A quad-tree-based fast and adaptive kernel density estimation algorithm for heat-map generation. International Journal of Geographical Information Science, 33(12):2455–2476, 2019.

[55] Leif Ryd, Xunhua Yuan, and Håkan Löfgren. Methods for determining the accuracy of radiostereometric analysis (rsa). Acta Orthopaedica Scandinavica, 71(4):403–408, 2000.

A Appendix

A.1 Population of the PPK Study

Table A.1: Study Demographics

(a) Femur

	Post-Op	6 wks	6 mo	1 yr	1 yr DE*	2 yr
No. of included patients	20	19	18	19	10	17
No. of mean marker models	10 (50%)	10 (53%)	10 (56%)	10 (53%)	4 (40%)	10 (59%)
Mean Condition Number	53.6	60.1	58.3	57.2	51.7	61.7
Min. Condition Number	27.9	34.3	34.3	34.3	34.3	34.3
Max. Condition Number	105.9	90.5	90.5	90.5	69.8	90.5

(b) Tibia

	Post-Op	6 wks	6 mo	1 yr	1 yr DE*	2 yr
No. of included patients	24	24	23	23	16	22
No. of mean marker models	0	0	0	0	0	0
Mean Condition Number	51.3	51.3	51.4	51.4	45.2	52.1
Min. Condition Number	32.9	32.9	32.9	32.9	27.9	32.9
Max. Condition Number	98.9	98.9	98.9	98.9	99.9	98.9

* Double Examination (DE)