Preoperative Magnetic Resonance as an Alternative to Computed Tomography Three-Dimensional Imaging for Characterizing Bone Loss in Shoulder Arthroplasty Candidates with Glenohumeral Osteoarthritis

A prospective, blinded, and controlled clinical-trial.

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Study Device (Non-Interventional)	Magnetic Resonance Imaging
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Study Summary

Title	Preoperative Magnetic Resonance as an Alternative to Computed Tomography Three-Dimensional Imaging for Characterizing Bone Loss in Shoulder Arthroplasty Candidates with Glenohumeral Osteoarthritis: A prospective, blinded, and controlled clinical trial.
Short Title	3D MR versus 3D CT in Glenohumeral Osteoarthritis
Protocol Number	S17-00500
Methodology	A prospective, unrandomized, single-blinded, self-controlled, and single-armed diagnostic radiological evaluation study.
Study Duration	12-Months
Study Center(s)	Single-Center
Purpose	To examine the non-inferiority of three-dimensional (3D) magnetic resonance (MR) versus the gold-standard, 3D computed tomography (CT) imaging, in the analysis of bone loss in shoulder arthroplasty (SA) candidates with glenohumeral osteoarthritis (OA). This study does not assess the safety and efficacy of MR imaging for musculoskeletal disorders.
Number of Subjects	50 subjects
Diagnosis and Main Inclusion Criteria	Patients with glenohumeral OA who are candidates for SA based on clinical examination with radiographic evidence of significant glenoid wear; males and females age 18 and above.
Study Intervention and Planned Use	3D MR imaging of the shoulder for evaluation of glenoid bone loss.
Reference Intervention	3D CT imaging of the shoulder for evaluation of glenoid bone loss.
Statistical Methodology	Paired sample t-test to compare measurements by model and ANOVA to assess differences among modalities.

I. PURPOSE OF THE STUDY AND BACKGROUND

Purpose

The purpose of this study is to examine the noninferiority of 3-dimensional (3D) magnetic resonance (MR) as an alternative to 3D computed tomography (CT) imaging to characterize glenoid bone loss in shoulder arthroplasty (SA) candidates with glenohumeral osteoarthritis and radiographic evidence of severe glenoid erosion. MR has been routinely used in musculoskeletal imaging with and without contrast. This study employs no non-FDA approved investigational MRI hardware or software.

Background & Study Rationale

There has been over a five-fold growth in incidence of shoulder arthroplasty (SA) for glenohumeral osteoarthritis (OA) since 2000 (1) (2) (3) (4). Asymmetric glenoid erosion may occur in glenohumeral OA (5). Patient-specific variations in magnitude and retroversion of glenoid bone loss in glenohumeral osteoarthritis pose a challenge for orthopaedic surgeons in joint reconstruction (6). Eccentric loading of the glenohumeral joint may lead to glenoid loosening which potentially requires revision surgery (7). Moreover, posterior glenoid erosion is a risk factor for poorer outcomes in function and pain (8) (9) (10). The management of glenoid erosion in shoulder arthroplasty demands individualized surgical techniques as well as implants to optimize outcomes and maximize implant longevity. Surgical techniques to address glenoid retroversion include eccentric reaming, glenoid bone grafts, augmented glenoid components, total shoulder arthroplasty, or specialized implants (7) (11) . The “gold-standard” modality for assessment of complex glenoid anatomy to assist with surgical planning is 3D CT imaging (9) (12) (13). However, CT imaging exposes patients to radiation. Recently, 3D MR has been developed to characterize glenoid bone loss (14).

There is significant variation in glenoid morphology among patients with glenohumeral OA. Prior studies have discussed higher distributions of patients with glenoids who had posterior erosion and/or retroversion (15-18) . To better guide treatment approaches, Walch et al. described glenoid morphology using CT scans in 113 shoulders between 1988 and 1995 (19) . Specifically, the authors developed three broad classification types based on humeral head position, glenoid retroversion, and erosion pattern: Type A, Type B, and Type C. Types A and B have subgroups based on severity.

Three-dimensional reconstruction of CT images at the glenohumeral joint have reliably assisted surgeons with preoperative planning whereas two-dimensional (2-D) radiographs and CT scans may misrepresent important anatomical characteristics of the shoulder leading to insufficient evaluation of erosion (12) (13).

To mitigate radiation exposure from 3D CT, 3D MR could serve as an alternative for patients with end-stage glenohumeral OA indicated for shoulder reconstruction.

Study Design

Prospective, unrandomized, double blinded, self-controlled clinical trial

Objective

1. The primary objective is to evaluate the noninferiority of 3D MR when compared to 3D CT for characterizing bone morphology in patients with glenohumeral osteoarthritis.

Hypothesis

3D MR imaging provides the same information as 3D CT in characterizing glenoid morphology.

Primary Endpoints

- Differences and/or similarities in glenoid erosion and version measurements between of 3D CT and 3D MR.

Outcome Measure Evaluation Criteria

- Degree of concordance/discordance between interpretation from 3D CT and 3D MR

II. CHARACTERISTICS OF THE RESEARCH POPULATION

Number of Subjects
A total of fifty (50) patients will be enrolled in this study.

Gender of Subjects
Men and women will be included in this study.

Age of Subjects
Subjects will be at least 18 years of age.

Racial and Ethnic Origin
There are no enrollment restrictions based on race or ethnic origin.

Inclusion Criteria
- Males and females ages 18 or more;
- Patients suffering from glenohumeral OA;
- Radiographic evidence of severe glenoid erosion;
- Indication for TSA based on clinical exam;
- Patient is willing and able to review and sign a study informed consent form.

Exclusion Criteria
- Prior arthroplasty at the affected shoulder;
- Patients with inflammatory arthritis;
- Patients with post-capsulorrhaphy arthritis;
- Patients with post-traumatic arthritis;
- Patients with rotator cuff tear arthropathy;
- Patients exhibiting a lack of physical or mental ability to perform or comply with the study procedures;
- Patients who are pregnant;
- Patients with implanted medical devices that are contraindicated to exposure up to a 3.0-tesla magnetic field.

Vulnerable Subjects
Vulnerable subjects will not be enrolled.

Subject Withdrawal
Patients are free to withdraw at any time from the study.

III. METHODS AND PROCEDURES

Sample Size Analysis
Using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA) based on paired t-test analysis, for alpha = .05 and power = .80, ten pairs are required, at minimum, for the study.

Methods and Procedures

Visit 1 -- Recruitment and Enrollment:
The study will employ convenience sampling of surgical candidates with glenohumeral osteoarthritis from the practice of the primary investigator, who is the treating surgeon. Immediately following his or her clinical visit with the primary investigator, each patient who is a candidate for shoulder arthroplasty will receive information on the study, including benefits and harms of participating in the study from the co-investigator at primary investigator's clinical office (NYU Langone Orthopedic Center). Written consent will be obtained from subjects based upon their medical condition (as determined by their physician). The consent process will take place during an office visit at which time the investigator has determined subject's voluntary participation has been upheld. Subjects will be informed about the study and the intended purpose. They will be given the opportunity to ask questions and receive thorough explanations. They will be made aware of the possible risks and anticipated benefits. They will also be informed of alternative procedures. Subjects will then be given another opportunity to ask questions and agree or disagree to consent. Potential subjects may enroll by providing informed consent with the co-investigator. The study will not exclude potential participants based on sex, race, and/or ethnicity. Subsequently, the study co-investigator will determine subject eligibility to participate in the study by obtaining information on potential contraindications of MR imaging, such as having prior history of injury involving metal or metallic particles as well as presence of medical implants, such as cardiac pacemakers.

This recruitment and enrollment visit should take no more than thirty (30) minutes.

Visit 2 -- Preoperative Imaging:
Subjects will have both 3D CT and 3D non-contrast MR scheduled on the same day. The CT scan, which is standard of care, will be scheduled at NYU Langone Orthopedic Hospital followed by the MR, the investigational procedure, at NYU Langone Orthopedic Center. Before imaging, the subjects will be screened for potential contraindications to each imaging modality in accordance with institutional standard of care routine procedures. The standard of care CT imaging will take no more than 30 minutes while the investigational MR imaging will take no more than 60 minutes in duration. Each enrolled subject will receive a standard of care CT scan along with an investigational MRI scan of the shoulder girdle while supine. Each enrolled subject's CT imaging is not dependent on receiving prior MR imaging; he/she will not experience delays in receiving standard of care CT imaging as a result of study participation.

The CT protocol consists of 3-mm axial images of the glenoid reconstructed into 1-mm sagittal and coronal 2D reconstructions using the following parameters: 120 kV, 280 mA, and pitch of 0.9. The CT data were also used to produce a 3D reconstruction of each glenoid.

The 2D glenoid version is measured by 2 musculoskeletal-trained radiologists on 2 occasions, at a minimum of 2 weeks apart, with the observers blinded to each other's results. The 2 observers meet before obtaining data to review the appropriate technique for measuring glenoid version. The 2D glenoid version is determined using the method of Friedman et al (17) with the mid glenoid cut being determined by dividing the total number of axial cuts through the glenoid by 2 (20).

The 2D CT images are imported in Vitrea software. The 3D volume rendering model will be produced. The 3D glenoid version is measured by the same 2 observers on 2 occasions, at a minimum of 2 weeks apart, with the observers blinded to each other's results. Three points which were previously validated were first interactively placed on the Mimics 3D model by the observer: the inferior tip of the scapula body, the center of the glenoid surface, and the medial pole of the scapula, as described by Kwon et al. (12) As described in detail below, these points were used to define the transverse scapular plane, based

on which a new 2D CT image is generated. Each observer then manually selected the anterior and posterior aspect of the glenoid on this 3D-corrected image, and version was determined according to the Friedman et al. (17) The new CT image along the transverse scapular plane is generated according to the following procedure. The true coronal scapular plane passed through the 3 points. The scapular axis was defined as the line passing through the center of the glenoid and the medial pole of the scapula. The transverse scapular plane was perpendicular to the coronal scapular plane and passed through the scapular axis. A new CT image along the transverse scapular plane is generated from the original CT data set using the Vitrea workstation.

MRI is performed using 3T scanners with a dedicated 16-channel shoulder array coils. The MRI sequences include 3-mm slice thickness and 0.5-mm gap width with a field of view of 14 or 15 cm. There were 6 diagnostic sequences with axial, coronal, and sagittal proton density weighting as well as coronal T2 with frequency selective fat suppression and sagittal T1 images. The protocol also included an axial 3D dual echo-time T1-weighted FLASH sequence with Dixon-based water–fat separation with the following parameters: TR 10, TE 2.45/3.7, field of view of 200 mm, acquired voxel size 1.0×1.0×1.4 mm, reconstructed voxel size 1.0×1.0×1.0 mm, flip angle 9 deg, matrix 192×192, bandwidth of 400 Hz/pixel, number of partitions=120 and a slice thickness of 1mm.

MRI 3D Post-processing: The water-only source images from the Dixon sequence were post-processed using standard subtraction software on a syngo MMWP workstation (VB 3oE, Siemens). The lowest mean signal intensity (water min) from multiple ROIs placed on the soft tissues surrounding the osseous structures was used as a constant to calculate a subtraction image where the pixel values are subtracted from this constant (water_min – SI (i) with negative values being set to zero). This resulted in images with increased signal in the osseous structures, surrounded by signal poor/void soft tissue structures. These subtracted Dixon images then underwent manual segmentation, generating 3D reconstructions of each shoulder (Tera Recon software (4.4.5.36.2068)).

The 3D MRI glenoid version is measured by the two observers with the same method used for CT 3D glenoid version measurement following generating a new 2D axial MR images form the 3D MRI model using the three-point method as described above.

Data Analysis

Using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA) Paired sample t-test to compare measurements by model and ANOVA to assess differences among modalities.

DATA SAFETY MONITORING PLAN (DSMP)

I. Study Monitoring
The co-investigator, Soterios Gyftopoulos, MD will be the data safety monitor for this project. After a three (3) months follow-up period, Dr. Gyftopoulos will review the data for SAE's, protocol deviations and other issues. If it is determined that certain events occur above an expected rate (i.e. increased shoulder pain), then enrollment will be stopped.

II. Types of Data
Under this DSMP, the following data/events will be captured and documented:

- Radiologic images;
- Diagnostic radiology interpretations;
- Reportable and/or adverse events; and
- Protocol Deviations.

III. Responsibilities and roles for gathering, evaluating and monitoring the data:
Principal Investigator

After six months following study initiation, the PI will meet with any co-investigators and the Research Coordinator to discuss the current findings and analysis. During these meetings, the PI will also be responsible for verifying data accuracy, and compliance with the study protocol.

Research Coordinator
The Research Coordinator will be responsible for providing data management support to the PI by collecting and documenting the required study data. This information will be documented in a secure Microsoft Excel spreadsheet with appropriate headings to distinguish the various types of data/events. The Research Coordinator will meet with the PI and any co-investigators to discuss the current findings/analysis, concerns/issues (unanticipated problems and adverse events), and the overall study in general.

IV. Reporting Adverse Events and Unanticipated Problems to the Monitoring Entity

All reportable events will be sent to the IRB in accordance with the timeframes specified by NYU SoM reporting guidelines. The Principal Investigator will have the responsibility of completing and submitting a Reportable New Information (RNI) form to the IRB through Research Navigator.

V. Assessments

After 6 months and 1 year following study initiation, the Principal Investigator, Co-Investigator(s) and Research Coordinator will review and assess the data and/or events captured under the DSMP.

VI. Criteria for Action

Should there be an event or series of events that occur that increases the risks to the participants, the "following steps" will be taken:

1. An investigation into the event will be conducted;
2. If required, a Reportable New Information (RNI) form will be submitted to the IRB;
3. All primary study staff (PI, Co-I, Research Coordinator) will be notified;
4. After a review,
    a. The protocol may be modified;
    b. The study may be suspended; or
    c. A decision may be made to close out the study

VII. Procedures for Communicating – dissemination of safety information

Outcomes of monitoring reviews will be communicated to the IRB through a yearly summary that will include a narrative on all adverse and reportable events (previously reported or not, serious or not), as well as any proposed changes to the protocol and/or study analysis.

Data Storage and Confidentiality

All patient health information will be de-identified and assigned a code. Information linking participants' names, medical record numbers or other PHI will be stored in securely on NYU Langone Health's digital server via RedCap. Participant medical information will be stored electronically within a password protected database available only to the principal investigator, co-investigators, and research staff as necessary for data analysis. The names, medical record numbers, and other PHI of the study participants will be deleted from their stored medical information and replaced with a linkage code. Access to participant medical information contained within this project will be restricted to approved study personnel.

IV. RISK/BENEFIT ASSESSMENT

The following are risks and discomforts that patients may experience during their participation in this research study.

Exposure to Magnetic Field
is an increased risk of burns from devices that conduct electrical energy. These devices can include metallic objects, pulse oximeters, EKG leads, or skin tattoos. These devices can be either in or on the patient in order for a skin burn to occur. The FDA has found that 70% of all reported injuries from MRIs were burns to the skin. To reduce this risk, all patients who are scanned in this study must complete thorough screening to ensure that no conductive materials are present in or on the patient's body. Additionally, the power limits of the magnet will be adjusted as necessary.

Another possible risk is that a metal object could be pulled into the scanner and hit the patient. The patient could be physically injured as a result. To reduce this risk, everyone near the magnet will remove all metal from their clothing or pockets when in the scanning environment. The door to the scan room will remain closed during the exam.

There are no known risks or adverse effects resulting directly from exposure to MRI. However, subjects who have a pacemaker or metal objects in their body such as shrapnel or metal in the eye should not have the scan performed.

Exposure to Magnetic Resonance Scanner
The magnetic resonance scanner may exacerbate a fear of closed spaces, expose patients to loud noises

Loss of Confidentiality
While every effort will be made to keep participant information confidential, there is the potential risk of loss of confidentiality. In order to minimize this risk, any information that can identify a subject will be removed and replaced with a unique study ID that only the study coordinator/investigators will know.

Psychological Risks
When completing the radiologic imaging, patients may find testing conditions unpleasant, such as space constrictions in medical imaging devices.

Protection Against Risks
The Principal Investigator is responsible for the collection, management and retention of research data and all study related regulatory files. The Principal Investigator shall adopt an orderly system of data organization, which includes a complete regulatory binder that dates the records being retained. The PI will be responsible for communicating all study methods and systems to all research personnel, and for their compliance with the study protocol and all NYU and Federal regulations. Patient PHI, such as MRNs can only be used within NYULMC's administrative records, thus ensuring minimal research risks and protecting patient identity from public utilization. As the owner of the research data, the medical center will assert its rights with respect to research data in order to assure compliance with regulatory and contractual requirements.

Potential Benefits to the Subjects
Study participants will not directly benefit from this study.

V. INVESTIGATOR'S QUALIFICATIONS AND EXPERIENCE

The CV, human subjects' tutorial completion report, and medical license (if applicable) are available for all investigators who are participating in this study. All research personnel have medical research experience and are qualified to participate in this quality study. Most importantly, staff have been properly educated and certified with CITI training to conduct research in a matter that will maintain full patient confidentiality.

VI. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT/ASSENT

Subject Capacity
All subjects enrolled in this study will have capacity to provide informed consent.

Debriefing Procedures
No information will be withheld from the subject.

Consent Forms
Informed consent will be obtained from all subjects and documented with a signed, written consent form using the NYU SoM's English standard consent form.

Documentation of Consent
In addition to following the consent process, it is understood by the study staff that retrieving informed consent is an ongoing process that continues after the actual informed consent has been signed. There is a "Documentation of Consent" checklist that will be used as additional documentation. This form will serve as secondary proof that the informed consent process has been executed.

Costs to the Subject
Subjects will not incur any additional financial costs as a participant in this study beyond those normally associated with this type of condition. The 3D CT imaging is billed to the patient/patient's insurance provider, hospital insurance, or third-party payer as per standard of care. The investigational 3D MR imaging is provided to enrolled participants at no cost – the patient/patient's insurance provider, hospital insurance, or third-party payer is not responsible for the cost of the investigational MR imaging.

Payment for Participation
No payments/reimbursements will be provided to subjects for their participation in this study.

VII. References

1. Day JS, Lau E, Ong KL, Williams GR, Ramsey ML, Kurtz SM. Prevalence and projections of total shoulder and elbow arthroplasty in the United States to 2015. Journal of Shoulder and Elbow Surgery. 2010;19(8):1115-20.
2. Kim SH, Wise BL, Zhang Y, Szabo RM. Increasing Incidence of Shoulder Arthroplasty in the United States. The Journal of Bone & Joint Surgery. 2011 Dec 21,;93(24):2249-54.
3. Trofa D, Rajaee SS, Smith EL. Nationwide trends in total shoulder arthroplasty and hemiarthroplasty for osteoarthritis. American journal of orthopedics (Belle Mead, N.J.). 2014 Apr;43(4):166.
4. Schwartz B, Savin D, Youderian A, Mossad D, Goldberg B. National trends and perioperative outcomes in primary and revision total shoulder arthroplasty. International Orthopaedics (SICOT). 2015 Feb;39(2):271-6.
5. Bell RH, Noble JS. The management of significant glenoid deficiency in total shoulder arthroplasty. Journal of Shoulder and Elbow Surgery. 2000 May;9(3):248-56.
6. Knowles NK, Keener JD, Ferreira LM, Athwal GS. Quantification of the position, orientation, and surface area of bone loss in type B2 glenoids. Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.]. 2015 Apr;24(4):503-10.
7. Stephens SP, Paisley KC, Jeng J, Dutta AK, Wirth MA. Shoulder arthroplasty in the presence of posterior glenoid bone loss. The Journal of bone and joint surgery. American volume. 2015 Feb 4,;97(3):251-9.
8. Iannotti JP, Norris TR. Influence of Preoperative Factors on Outcome of Shoulder Arthroplasty for Glenohumeral Osteoarthritis. The Journal of Bone & Joint Surgery. 2003 Feb 1,;85(2):251-8.
9. Nyffeler RW, Sheikh R, Atkinson TS, Jacob HAC, Favre P, Gerber C. Effects of glenoid component version on humeral head displacement and joint reaction forces: An experimental study. Journal of Shoulder and Elbow Surgery. 2006;15(5):625-9.
10. Walch G, Moraga C, Young A, Castellanos-Rosas J. Results of anatomic nonconstrained prosthesis in primary osteoarthritis with biconcave glenoid. Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.]. 2012 Nov;21(11):1526.
11. Hsu JE, Ricchetti ET, Huffman GR, Iannotti JP, Glaser DL. Addressing glenoid bone deficiency and asymmetric posterior erosion in shoulder arthroplasty. Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.]. 2013 Sep;22(9):1298-308.
12. Kwon YW, Powell KA, Yum JK, Brems JJ, Iannotti JP. Use of three-dimensional computed tomography for the analysis of the glenoid anatomy. Journal of Shoulder and Elbow Surgery. 2005 Jan;14(1):85-90.
13. Beuckelaers E, Jacxsens M, Van Tongel A, De Wilde LF. Three-dimensional computed tomography scan evaluation of the pattern of erosion in type B glenoids. Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.]. 2014 Jan;23(1):109-16.
14. Gyftopoulos S, Beltran L, Yemin A, Strauss E, Meislin R, Jazrawi L, et al. Use of 3D MR reconstructions in the evaluation of glenoid bone loss: a clinical study. Skeletal Radiol. 2014 Feb;43(2):213-8.
15. Neer CSI. Replacement Arthroplasty for Glenohumeral Osteoarthritis. The Journal of Bone & Joint Surgery. 1974 Jan 1,;56(1):1-13.
16. Neer CS, Morrison DS. Glenoid bone-grafting in total shoulder arthroplasty. The Journal of Bone & Joint Surgery. 1988 Sep 1,;70(8):1154-62.
17. Friedman RJ, Hawthorne KB, Genez BM. The use of computerized tomography in the measurement of glenoid version. The Journal of Bone & Joint Surgery. 1992 Aug 1,;74(7):1032-7.
18. Mullaji AB, Beddow FH, Lamb GH. CT measurement of glenoid erosion in arthritis. The Journal of bone and joint surgery. British volume. 1994 May;76(3):384.
19. Walch G, Badet R, Boulahia A, Khoury A. Morphologic study of the Glenoid in primary glenohumeral osteoarthritis. The Journal of Arthroplasty. 1999;14(6):756-60.
20. De Wilde LF, Verstraeten T, Speeckaert W, Karelse A. Reliability of the glenoid plane. Journal of Shoulder and Elbow Surgery. 2010;19(3):414-22.