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# Projected Cartilage Area Ratio Determined by 3-Dimensional MRI Analysis

## Validation of a Novel Technique to Evaluate Articular Cartilage

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**Background:** We have developed 3-dimensional (3D) magnetic resonance imaging (MRI) analysis software that allows measurement of the *projected cartilage area ratio* with a particular thickness intended to allow quantitation of the cartilage in the knee. Our aims in this study were to validate the projected cartilage area ratio in both pig and human knees and to examine the ratio in patients reporting knee pain.

**Methods:** After 3D MRI reconstruction, the femoral cartilage was projected onto a flat surface. The projected cartilage area was determined in pig knees using our 3D MRI analysis software, and was compared with the area obtained with other software. The projected cartilage area ratio (for cartilage thickness ≥1.5 mm) at 4 segments was also validated in human knees. Finally, changes in the projected cartilage area ratio were examined in 8 patients with knee pain who had undergone 2 MR images at 3 to 21-month intervals.

**Results:** The projected cartilage areas determined with our 3D MRI analysis software were validated in pig knees. The projected cartilage area ratio at each segment in human knees had an intraclass correlation coefficient (ICC) of 0.87 to 0.99 (n = 16) between readers and 0.76 to 0.99 (n = 20) between measurements on repeat MR images. The projected cartilage area ratio (for cartilage thickness ≥1.5 mm) at the most affected segment in 8 human patients significantly decreased between the pairs of MR images obtained at intervals of 3 to 21 months.

**Conclusions:** We proposed a novel evaluation method using 3D MRI to quantify the amount of cartilage in the knee. This method had a low measurement error in both pig and human knees.

**Clinical Relevance:** The projected cartilage area ratio based on a particular thickness may serve as a sensitive method for assessing changes in cartilage over time.

Osteoarthritis is one of the most common degenerative joint diseases and has become a major socioeconomic problem in today's aging society[1]. Preventing the progression of osteoarthritis is an urgent task, but no disease-modifying drugs are currently available because of the lack of comprehensive knowledge of the pathophysiological factors that contribute to the disease process and its progression[2]. Methods for evaluating the decrease in the amount of cartilage over a short time interval, such as a year, would help in assessing the efficacy of drug treatments.

Knee osteoarthritis is typically diagnosed from radiographs; however, these images do not depict the cartilage directly—rather, they provide joint widths[3]. Magnetic resonance imaging (MRI) provides another noninvasive and useful method for evaluation of each compartment of the knee joint[4,5], and several software programs can now show 3-dimensional (3D) reconstructed images of the knee joints derived from planar MR images[6]. Furthermore, 3D MRI provides the morphology of the entire knee joint and enables a quantitative evaluation of the cartilage[7].

We developed 3D MRI analysis software that enables a semi-automatic reconstruction of 3D images of the cartilage in the knee joint. This software allows measurement of what we term the *projected cartilage area ratio,* which provides a

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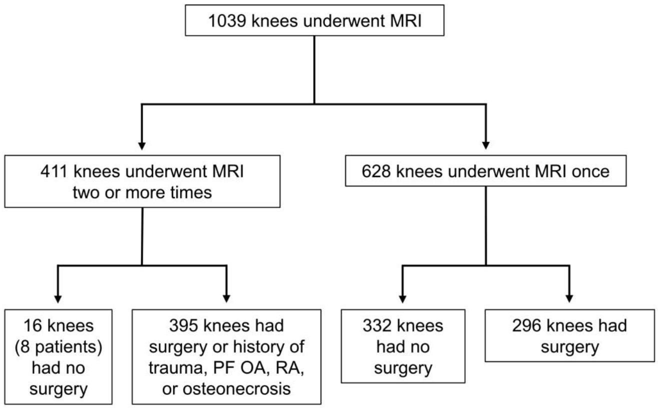


Fig. 1
Enrollment of patients with knee pain and data from 2 MR images. PF OA = patellofemoral joint osteoarthritis, and RA = rheumatoid arthritis.

particular thickness intended for quantitation of the amount of cartilage. The purposes of the present study were (1) to validate the cartilage thickness and the projected cartilage area ratio in pig knees, (2) to validate the internal consistency of the ratio in human knees, and (3) to evaluate the temporal alterations in the ratio in the knees of patients reporting knee pain. We hypothesized that this software would have a low measurement error and could measure cartilage loss over time.

## Materials and Methods

### *Enrollment of Patients with Knee Pain and Data from 2 MR Images*

This study was approved by the Medical Research Ethics Committee of the Tokyo Medical and Dental University. From September 2011 to March 2017, 1,039 knees were examined by MRI; 628 knees (including 332 without surgery and 296 with surgery) were excluded because MRI was performed only once (Fig. 1). MRI was performed ≥2 times on the remaining 411 knees; 395 of those knees were excluded because of surgery, history of trauma, patellofemoral osteoarthritis, rheumatoid arthritis, or osteonecrosis. The remaining 16 knees, representing 8 patients (5 male and 3 female) with knee pain who had undergone at least 2 MRI examinations, constituted the study group. The patients ranged in age from 22 to 68 years and had Kellgren-Lawrence grades between 1 and 3; the interval between the first and second MR images was between 3 and 21 months (Table I). In all 8 patients, the second MRI examination was performed relatively soon after the first examination because the patient continued to report knee pain even after administration of conservative treatments based on the first MRI examination. We confirmed the symptom of all 8 patients by examining the electronic medical records.

### *MR Image Scanning*

Human and pig knees underwent 3.0-T MRI (Achieva 3.0T TX; Philips) using 16-channel coils. The sagittal plane of the knee joint was imaged using both a fat-suppressed spoiled gradient-echo sequence (scan duration, 7 minutes 30 seconds) and a proton-weighted sequence (scan duration, 7 minutes 10 seconds). For both sequences, sagittal imaging was performed at an in-plane resolution of 0.31 × 0.31 mm, a partition thickness of 0.36 mm (320 slices), and a field of view (cephalad to caudad × anterior to posterior) of 150 × 150 mm.

### *Extraction of Cartilage Area from MR Images*

MRI DICOM (Digital Imaging and Communications in Medicine) data were analyzed using our software. Approximately 4 minutes after reading the MRI data, the cartilage area was automatically displayed. The software was completely deterministic. The software at that time often misjudged the water-cartilage boundary (see Appendix Supplementary Figure 1); therefore, the cartilage area underwent a precise manual correction that required approximately 30 minutes (Fig. 2-A). Two authors (A.H. and S.S.) who had both trained as orthopaedic surgeons for 6 years and had experience in manual correction of over 200 knees performed the manual corrections.

### *The Projected Cartilage Area Ratio Determined by 3D MRI Analysis*

Our software provided a 3D reconstruction of the femoral cartilage (Fig. 2-B). We use the term *projected cartilage area* to describe the projection of the femoral cartilage onto a flat surface for evaluation (Fig. 2-B). The 3D-reconstructed femoral cartilage was projected directly onto the 2D plane, so the area perpendicular to the plane was evaluated as having cartilage present if even 1 cartilage voxel existed in the aligned voxels (Fig. 2-C).

**TABLE I Characteristics of the Enrolled Patients**

| Variable | Patient 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| Sex | Male | Female | Male | Male | Female | Male | Female | Male |
| Age *(yr)* | 56 | 54 | 46 | 22 | 68 | 58 | 49 | 64 |
| Affected side | Left | Right | Left | Right | Right | Left | Right | Left |
| Kellgren-Lawrence grade | 3 | 2 | 2 | 1 | 2 | 2 | 2 | 2 |
| Time between 1st and 2nd MR image *(mo)* | 21 | 8 | 16 | 9 | 13 | 12 | 14 | 3 |

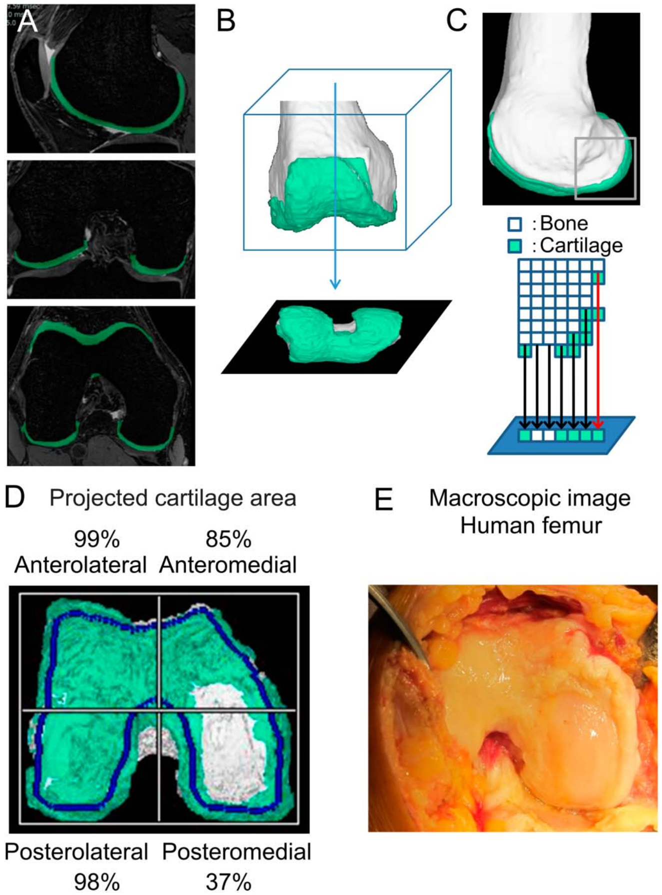


Fig. 2

**Figs. 2-A through 2-E** Determination of the femoral projected cartilage area from the reconstructed 3D MRI. **Fig. 2-A** Cartilage area obtained semi-automatically. **Fig. 2-B** Reconstructed 3D image and the projected cartilage area. **Fig. 2-C** Scheme for determining the projected cartilage area. **Fig. 2-D** Example of the projected cartilage area and projected cartilage area ratio (for cartilage thickness ≥0 mm) for the 4 segments. **Fig. 2-E** Macroscopic image of the femoral cartilage for the case on the left in the other panels.

The projected cartilage area was then quantified using the projected cartilage area ratio, which was the ratio of the projected cartilage area to the total area of the region of interest (ROI). Our software determined the long axis of the femur from the MRI data. The cartilage area was then projected onto a flat surface that included the long axis, the femur was rotated so that the posterior condylar line of the femur was horizontal, and the software drew lines that split the projected femur equally in the longitudinal and transverse directions, resulting in 4 segments. The software automatically drew a closed curve 2 mm inside of the projected bone contour and finally set up 4 ROIs (anteromedial, anterolateral, posteromedial, and posterolateral) that were enclosed by the closed curve and the 2 orthogonal lines, as shown in Figure 2-D. A macroscopic image of the femoral cartilage in the same knee is shown in Figure 2-E.

The 2 posterior segments almost completely cover the region from the anterior portion to the posterior portion of each meniscus with the knee in a slightly flexed position. The 2 anterior segments cover approximately half of the lower part of the patellofemoral joint.

We performed this evaluation of projected cartilage areas and area ratios for cartilage thicknesses of ≥0, ≥0.5, ≥1.0, and ≥1.5 mm (Fig. 3).

### *Validation with Pig Knees*

Six fresh-frozen pig knee joints (Tokyo Shibaura Zouki) were used for these experiments. The cartilage thickness measurement by the software was validated in 1 of these knees by creating 10 osteochondral defects in the femoral condyle using a biopsy punch before the MRI evaluation of the femoral cartilage. The cartilage thickness at the 10 holes was manually measured after exposure of the cross-sections of the defects. A 3D image was reconstructed automatically with our software; the regions with cartilage thicknesses of ≥0.5, ≥1.0, ≥1.5, and ≥2.0 mm were projected in 2 dimensions; and the areas of these regions were evaluated. The correlation between

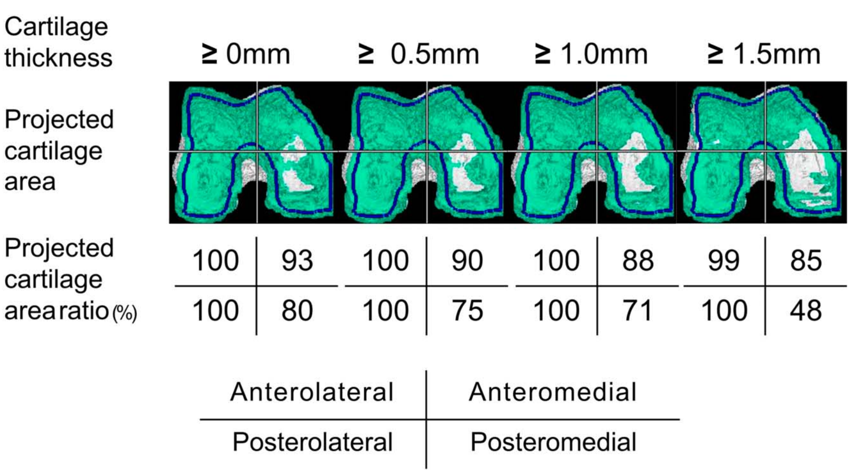


Fig. 3

Projected femoral cartilage area (for cartilage thicknesses of ≥0, ≥0.5, ≥1.0, and ≥1.5 mm) and projected cartilage area ratio.

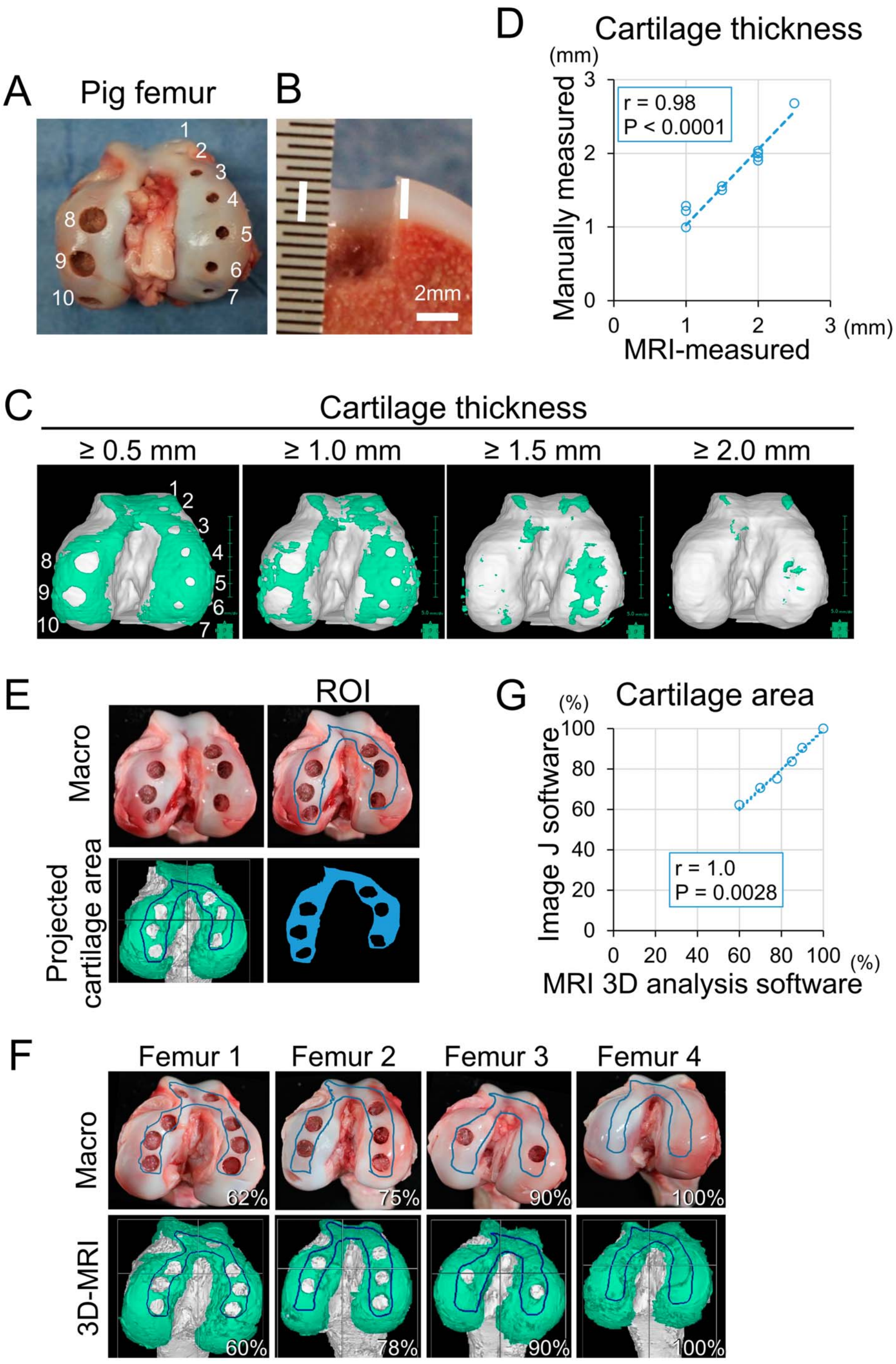


Fig. 4

**Figs. 4-A through 4-G** Validation of the cartilage thickness and projected cartilage area ratio obtained in pig knees using 3D MRI analysis software. **Fig. 4-A** Osteochondral defects (numbered 1 to 10) were created in the femoral condyle to validate the cartilage thickness. **Fig. 4-B** Manual measurement of cartilage thickness with a ruler. **Fig. 4-C** Projected cartilage areas (for cartilage thicknesses of ≥0.5, 1.0, 1.5, and 2.0 mm) for measurement of the cartilage thickness. **Fig. 4-D** Correlation between MRI-measured and manually measured cartilage thicknesses. **Fig. 4-E** Macroscopic images and projected cartilage areas of the femoral condyle for validation of the cartilage area. The region of interest (ROI) for the projected cartilage area in pig knees was set manually (lower left), and the projected cartilage area was obtained using the 3D MRI analysis software. The ROI was also pasted onto the macroscopic image (upper right) and the cartilage area was obtained using ImageJ software (lower right). **Fig. 4-F** Representative macroscopic images and projected cartilage areas of the femoral condyle along with the projected cartilage area ratios. **Fig. 4-G** Correlation between the projected cartilage area ratio (for cartilage thickness ≥1.5 mm) obtained with the 3D MRI analysis software and with ImageJ software.

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| Segment | Intra-reader (n=16) | | Inter-reader (n=16) | |
|---|---|---|---|---|
| | ICC | CoV | ICC | CoV |
| Anteromedial | 0.99 | 1.4 | 0.99 | 2.0 |
| Anterolateral | 0.99 | 1.2 | 0.87 | 1.0 |
| Posteromedial | 0.99 | 1.0 | 0.99 | 1.1 |
| Posterolateral | 0.99 | 1.1 | 0.95 | 1.0 |


| Segment | Intra-measurement (n=10) | |
|---|---|---|
| | ICC | CoV |
| Anteromedial | 0.96 | 1.1 |
| Anterolateral | 0.92 | 1.1 |
| Posteromedial | 0.99 | 0.8 |
| Posterolateral | 0.76 | 1.7 |

Fig. 5

Intra-reader, inter-reader, and intra-measurement reliabilities of the projected cartilage area ratio (for cartilage thickness ≥1.5 mm). ICC = intraclass correlation coefficient, and CoV = coefficient of variation.

the MRI-measured and manually measured cartilage areas was then determined.

Measurement of the projected cartilage area ratio was validated by creating several osteochondral defects in the femoral condyle of each of the 6 pig knees before scanning by MRI. The 3D image was reconstructed, the ROI for the projected cartilage area was set manually in the pig knees, and the projected cartilage area was obtained using the 3D MRI analysis software. The ROI was also pasted onto the macroscopic image, and the cartilage area was measured using ImageJ software (National Institutes of Health). The correlation between the projected cartilage area ratios obtained with the 3D MRI analysis software and with the ImageJ software was then determined.

### *Validation of the Projected Cartilage Area Ratio in Human Knees*

The intra-reader intraclass correlation coefficient (ICC) and the coefficient of variation (CoV) for the projected cartilage area (for cartilage thickness ≥1.5 mm) of the 4 femoral segments were determined using measurements performed 1 day apart by a single examiner on the first and second MR images of the 8 enrolled patients (16 knees).

The inter-reader ICC and CoV for the projected cartilage area (for cartilage thickness ≥ 1.5 mm) of the 4 femoral segments were determined using measurements performed independently by 2 examiners on the first MR image of each enrolled patient.

In addition, the ICC and CoV for measurements from repeat MRI scans were determined using knee MR images conducted on 10 volunteers aged 32 to 52 years. After the first MR image, the volunteers stepped off the MRI platform for a moment, then back on, and the knee MRI scans were repeated. The projected cartilage area (for cartilage thickness ≥1.5 mm) was obtained from the first and the second MR image by a single examiner, and the projected cartilage area ratio (for cartilage thickness ≥1.5 mm) was obtained at the 4 segments (see Appendix Supplementary Table I). The mean measurement error and standard deviation (SD) were obtained using the absolute value of the difference in the projected cartilage area ratio (for cartilage thickness ≥1.5 mm)

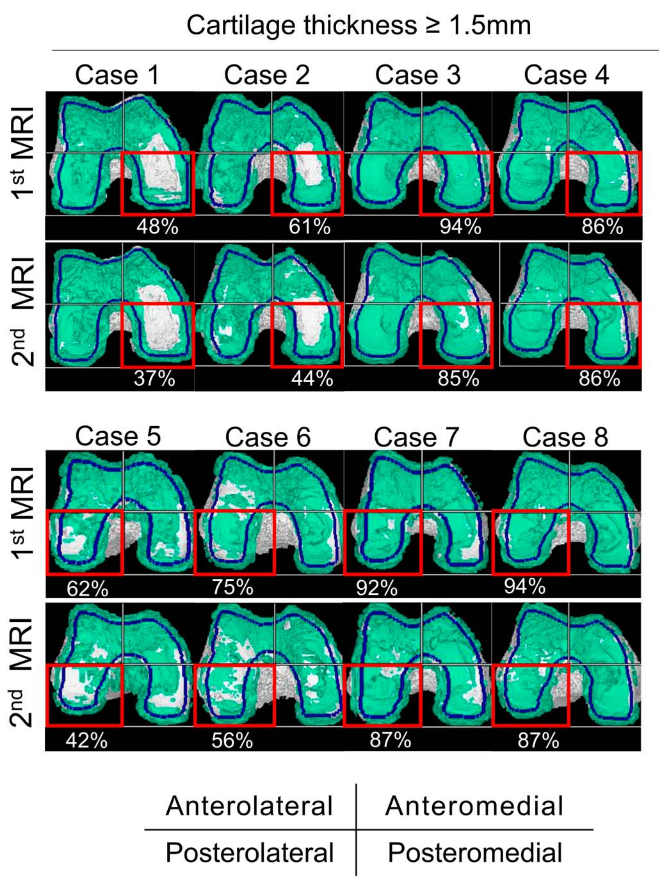


Fig. 6

Femoral projected cartilage area (for cartilage thickness ≥1.5 mm) in patients with knee pain and data from 2 MR images. The selected segment is surrounded with a red square, and the projected cartilage area ratio at the selected segment is shown. The left knees were reversed horizontally to facilitate visualization.

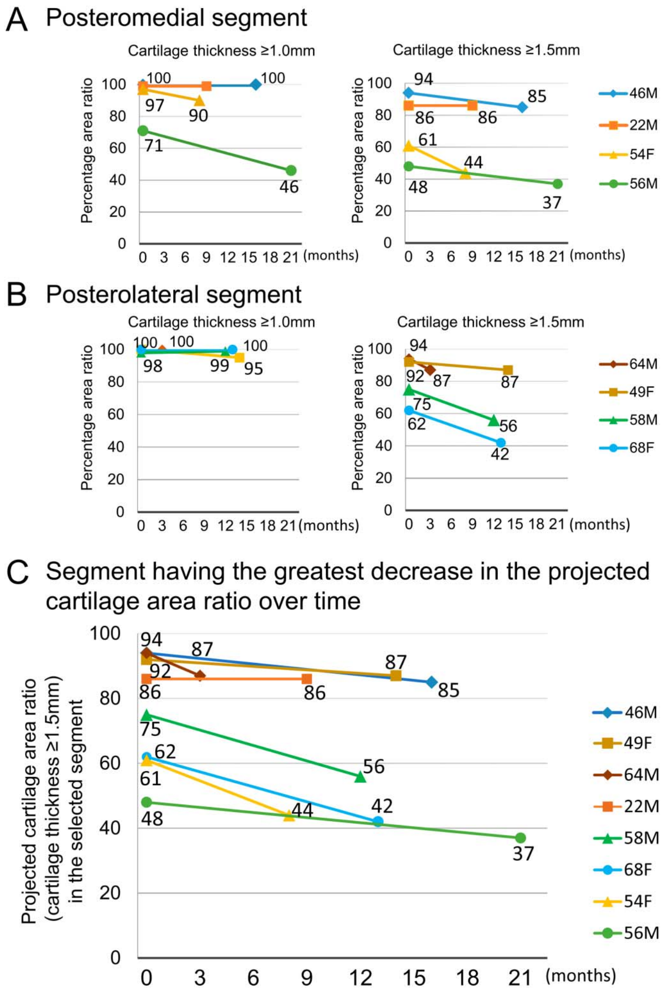


Fig. 7

**Figs. 7-A, 7-B, and 7-C** Temporal alteration of the femoral projected cartilage area ratio at the selected segment. **Fig. 7-A** Posteromedial segment. **Fig. 7-B** Posterolateral segment. **Fig. 7-C** Segment in which the greatest decrease in the projected cartilage area ratio over time was shown.

between the first and the second MR image (see Appendix Supplementary Table II).

Alteration of the projected cartilage area ratio in the knees of patients with knee pain and data from 2 MR images was assessed using the segment (anteromedial, anterolateral, posteromedial, or posterolateral) that showed the greatest decrease in the projected cartilage area ratio over time (for cartilage thickness ≥1.5 mm). The resulting data were graphed by plotting the projected cartilage area ratio at the selected segment in the first MR image and in the second MR image. The 2 points for each patient were then connected. The projected cartilage area ratio for an alternate cartilage thickness (≥1.0 mm) was also examined.

### *Statistical Analysis*

Data for correlation analyses were statistically evaluated with the Spearman correlation coefficient (GraphPad Prism, version 6). The ICCs and CoVs were calculated in R (version 3.2.3, The R Foundation for Statistical Computing). Temporal alterations in the projected cartilage area ratio were analyzed using the Wilcoxon signed-rank test. Two-tailed p values of <0.05 were considered significant. Post hoc power analyses for the correlation test and paired t test were performed by using G*Power 3.1 (Heinrich Heine Universität Düsseldorf)[8,9].

## Results

### *Validation of the Cartilage Thickness and Projected Cartilage Area Ratio in Pig Knees*

The manually measured cartilage thicknesses (Figs. 4-A and 4-B) and the cartilage thicknesses measured using the projected cartilage areas (for cartilage thicknesses of ≥0.5, ≥1.0, ≥1.5, and ≥2.0 mm) in MRI scans (Fig. 4-C) were correlated (Fig. 4-D). The post hoc power analysis indicated high power (effect size [dz] = 0.97, power [1 − β] = 1.00, alpha error = 0.05). The projected cartilage area obtained using ImageJ software (Fig. 4-E) and the projected cartilage area obtained using the 3D MRI analysis software (Fig. 4-F) were also correlated (Fig. 4-G). The post hoc power analysis indicated high power (dz = 0.99, power = 1.00, alpha error = 0.05).

### *Validation of the Projected Cartilage Area Ratio in Human Knees*

The intra-reader ICC for the projected cartilage area ratio (for cartilage thickness ≥1.5 mm) was 0.99 and the intra-reader CoV was 1.0 to 1.4 at each segment (Fig. 5). The inter-reader ICC was 0.87 to 0.99 and the inter-reader CoV was 1.0 to 2.2 at each segment. The intra-measurement ICC was 0.76 to 0.99 and the intra-measurement CoV was 0.8 to 1.7.

The difference in the projected cartilage area ratio (for cartilage thickness ≥1.5 mm) between the first and the second MR image on the same day (the measurement error; see Appendix Supplementary Table I) was 0.7% ± 0.8% (n = 10) at the anteromedial, 0.8% ± 0.9% (n = 10) at the anterolateral, 1.0% ± 0.8% (n = 10) at the posteromedial, 0.4% ± 0.7% at the posteromedial, and 0.7% ± 0.5% (n = 40) at all segments (see Appendix Supplementary Table II).

### *Alterations in the Projected Cartilage Area Ratio in Patients with Knee Pain*

Among the 8 patients who reported knee pain and had undergone 2 knee MRI scans, the segment with the greatest decrease in the projected cartilage area ratio (for cartilage thickness ≥1.5 mm) was the posteromedial segment in 4 patients and the posterolateral segment in 4 patients (Fig. 6).

The projected cartilage area ratio (for cartilage thickness ≥1.5 mm) decreased during the time interval from the first to the second MR image in 3 of the 4 patients whose posteromedial segment was the most affected (Fig. 7-A). The projected cartilage area ratio (for cartilage thickness ≥1.5 mm) decreased during this time interval in all 4 patients whose posterolateral segment was the most affected (Fig. 7-B). The projected cartilage area ratio (for cartilage thickness

≥1.5 mm) at the most affected segment decreased in 7 patients and decreased significantly overall during this time interval in all 8 patients (Fig. 7-C). The post hoc power analysis using the mean and standard deviation of the 8 first MR images (76.5% ± 17.7 %) and 8 second MR images (65.5% ± 22.8%) indicated high power (dz = 1.54, power = 0.95, alpha error = 0.05).

## Discussion

Several advances have been made in the past decade in the use of quantitative MRI techniques for evaluating cartilage[10]. The most common approach for computing cartilage thickness uses 2D or 3D minimum Euclidean distances for which a vector is drawn perpendicular to each point on the surface[11]. Another 3D approach uses normal vectors computed on 1 surface (articular or bone-cartilage interface) and determines where the vectors on the first surface intersect the second surface[12]. A measure of the spatial distribution of change in cartilage volume and thickness between time points can be obtained from the bone-cartilage interface[13] and the total bone shape[14]. Once the shapes are aligned, the cartilage thickness patterns can be matched at a local level. Our system is novel in that it allows measurement of the projected cartilage area ratio, representing the proportion of the surface covered by cartilage of at least a specified thickness.

The manual correction portion of our processing is a potential source of variability. We accounted for this by examining the intra-reader and inter-reader reliabilities of the projected cartilage area ratio. We imported the MRI data into our software, automatically extracted the cartilage area, and then conducted 2 independent manual corrections. Since our software indicated the fixed cartilage area before manual correction, the intra-reader and inter-reader reliabilities of the resulting projected cartilage area ratios reflect the repeatability of the manual correction.

The projected cartilage area ratio in human knees had an intra-reader ICC, inter-reader ICC, and intra-measurement ICC of 0.76 to 1.0 for each segment. ICC values of <0.5, 0.5 to <0.75, 0.75 to <0.9, and ≥0.9 are indicative of poor, moderate, good, and excellent reliability, respectively[15]. These results suggest that the projected cartilage area ratio is a reliable method for quantitatively measuring the femoral cartilage. The projected cartilage area can also provide anatomical information regarding where the cartilage is thin.

The cartilage thickness used in assessing the projected cartilage area ratio can be adjusted according to disease conditions so that even slight changes can be revealed in a relatively short period of time. For patients who reported knee pain, the alteration in the projected cartilage area ratio was greater when we set the limit at 1.5 mm than at 1.0 mm (Figs. 7-A and 7-B) or 2.0 mm (data not shown).

Patients 6 and 7 showed an apparent improvement in the articular cartilage coverage over time, although this is an uncommon occurrence. One factor leading to such imprecision may be inaccuracies in determining the long axis of the femur (due to the limited field of view of the MRI) that resulted in differences in its calculated position between the first and second MR images. We need to improve the software so that these 2 axes coincide more precisely.

In this study, we analyzed only the femoral cartilage and did not assess the tibial or patellar cartilage. The automatic determination of the ROI was technically difficult for these other locations; therefore, we were unable to analyze the tibial and patellar cartilage concomitantly with the femoral cartilage. However, we are resolving this problem. For the tibial cartilage, the cartilage area is projected onto a flat surface and 2 ROIs are set as follows: For the medial segment, a closed curve is drawn along the foot of the medial intercondylar eminence and 2 mm inside of the projected tibial bone contour. Similarly, for the lateral segment, a closed curve is drawn along the foot of the lateral intercondylar eminence and 2 mm inside of the projected tibial bone contour. For the patellar cartilage, the cartilage area is projected onto a flat surface, a closed curve is drawn 2 mm inside of the projected patellar bone contour, and a single ROI is set.

Our study had several limitations. The cartilage area was automatically selected with our software, but manual correction was required and the manual correctors were not blinded to the previous results for the repeated measurements because MRI scan dates were systematically displayed in our software. The 3D-reconstructed femoral cartilage was also projected directly onto the 2D plane, so the apparent thickness in the 2D projection was greater than the actual thickness because of the slope of the cartilage. The examination of the alterations in the projected cartilage area ratio in patients over a time interval required retrospective selection of the patients, so the 8 enrolled patients may not be representative of a general population reporting knee pain. Our system can detect cartilage thickness but it cannot differentiate between healthy and unhealthy cartilage. Finally, the analyses in pigs do not necessarily reflect human results.

Our method had a low measurement error in both pig and human knees. This method may be useful for measuring cartilage 1loss over time in patients with osteoarthritis of the knee. Prospective studies with more patients and including clinical scores and radiographs are needed to confirm this possibility.

## Appendix

eA Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJSOA/A122). ■

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