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1 Title Page

2 Quantitative Knee Cartilage Measurement at MR Imaging of Patients with Anterior
3 Cruciate Ligament Tear

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32 Quantitative Knee Cartilage Measurement at MR Imaging of Patients with Anterior

33 Cruciate Ligament Tear

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43 Abstract

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46 In previous studies, numerous approaches were proposed that assess knee cartilage
47 volume quantitatively by using 3D magnetic resonance (MR) imaging. However,
48 clinical use of these approaches is limited because it is prone to metal artifact in
49 postoperative cases. Our purpose in this study was to validate a method for knee
50 cartilage volume quantification by using conventional MR imaging in patients who
51 underwent anterior cruciate ligament (ACL) reconstruction surgery. The study included
52 16 patients who underwent MR imaging before and 1 year after ACL reconstruction
53 surgery. Knee cartilage volumes were measured by our computer-based method with
54 use of T1-weighted sagittal images. We classified the cartilage into 8 regions and made
55 comparisons between preoperative and postoperative cartilage volumes in each region.
56 There was a significant difference between preoperative and postoperative cartilage
57 volumes with regard to medial posterior weight-bearing, medial posterior, lateral
58 posterior weight-bearing, and lateral posterior portions ($p=0.006$, $p=0.023$, $p=0.017$ and
59 $p=0.002$, respectively). These results were consistent with the previous studies showing
60 that knee cartilage loss occurs frequently in these portions due to an anterior subluxation

61 of the tibia accompanied by ACL tear. With our method, knee cartilage volumes could
62 be quantitatively measured with conventional MR imaging in patients who underwent
63 ACL reconstruction surgery.

64 Key Words

65 knee cartilage: anterior cruciate ligament: magnetic resonance imaging

66

67

68 Introduction

69 Hyaline cartilage covering the surface of the diarthrodial joint is important for normal
70 joint function and can transmit and distribute pressure without sustaining substantial
71 wear [1,2]. In addition, because articular cartilage provides a nearly frictionless gliding
72 surface, these forces can be transmitted during dynamic joint activity [3–8]. In order to
73 satisfy these complex functional requirements, articular cartilage shows unique
74 morphologic features and biomechanical properties that are unmatched by artificial
75 material [1,2,9,10]. Observing cartilage destruction and loss is important for evaluating
76 osteoarthritis (OA) [11,12].

77 Magnetic resonance (MR) imaging has been in use for cartilage evaluation for
78 many years because it provides high soft-tissue contrast and spatial resolution. MR
79 imaging enables direct qualitative and quantitative visualization and evaluation of the
80 cartilage [13]. In recent years, some investigators have developed computer-based
81 methods to create 3D cartilage reconstruction from magnetic resonance images [12,14–
82 17]. These methods can be used for assessment of cartilage degeneration and cartilage
83 loss quantitatively by evaluation of cartilage volume, while the methods have high
84 susceptibility to metal artifacts due to their sequence design depending on the gradient
85 echo technique, which is not recommended for quantitative analysis of cartilage in

86 post-operative status.

87 Anterior cruciate ligament (ACL) tear leads to anterior subluxation of the tibia
88 with engagement of the anterior femoral condyle against the posterior tibial plateau [18–
89 23]. As a result, cartilage loss occurs in the anterior femoral condyle and posterior tibial
90 plateau [19,21]. In addition, 74% of patients who underwent ACL reconstruction
91 surgery displayed some signs of radiographic OA within 7 years post-surgery. Thus, OA
92 is common in ACL-reconstructed knees [24]. Therefore, our purpose in this study was
93 to verify a quantification method for knee cartilage volumes by using conventional MR
94 imaging in patients who had undergone ACL reconstruction surgery.

95

96 Materials and methods

97 Patients

98 The study included 16 patients who underwent MR imaging before and 1 year after
99 ACL reconstruction surgery (Tables 1,2). This study was conducted in accordance with
100 the Declaration of Helsinki and its updates and was approved by the local ethics
101 committee. Informed consent was obtained from all of the patients.

102

103 MR imaging

104 All patients in this study group underwent MR imaging, with T1-weighted images
105 obtained before (baseline) and 1 year after (follow-up) ACL reconstruction surgery. MR
106 images were performed with the Achieva 1.5T A-series (Philips) and the Achieva 3.0T
107 TX (Philips). Imaging parameters are summarized in Table 3. In follow-up studies,
108 special care was taken so that the slice position was identical to that of the baseline
109 study.

110

111 Image analysis

112 In this study, we used an original software in which cartilage is manually segmented
113 from MR images taken at baseline and at follow-up, and the interval difference in
114 cartilage volume between baseline and follow-up is displayed with Microsoft Excel and
115 a color map.

116 The original software was developed with Microsoft Visual C# 2013. The MR images
117 taken at baseline and at follow-up were imported into the software. Then, 3 steps for
118 cartilage segmentation and volumetry were followed.

119

120 Step-1: semi-automated bone segmentation for bone area elimination at bone/cartilage
121 interface

122 The interface between the subchondral bone and its cartilage is a sharp curvilinear line
123 in most cases. Therefore, to eliminate bone pixels from volumetry of the cartilage, all
124 the slices in each MR study were binarized automatically by Otsu's method [25], and
125 fused images of the binary images and the original images were created (Fig.1). Here,
126 the threshold was selected to separate bony structures from the soft tissues including
127 cartilage, a pixel value larger than the threshold was displayed in green, and a pixel
128 value less than the threshold was displayed with that of the original images. The green
129 pixels containing bone area were then automatically extracted from the display. When
130 the bone was not completely displayed in green, we manually eliminated the signal
131 from the bone by mouse dragging operation. Extracting the bone using automatic
132 binarization facilitated easier segmentation of the cartilage boundary for the subsequent
133 processing, thus reducing the time for segmentation without affecting the accuracy of
134 cartilage quantification.

135

136 Step-2: manual segmentation of the knee cartilage at its interface to joint space

137 We manually segmented the articular side of the knee cartilage which we deemed
138 cartilage by mouse dragging operation. The segmented part was displayed in red (Fig.2).

139 During cartilage segmentation, the pixels formally displayed in green were never

140 repainted as red, so that the bony areas were not added to the knee cartilage volumes. In
141 baseline and follow-up images, we carefully performed this operation only on a slice
142 judged to be the same section by observing between baseline and follow-up slices where
143 articular cartilage is visible. The number of slices used for image analysis therefore
144 resulted in the same for baseline as for follow-up. The total of the measured areas was
145 calculated as volume.

146

147 Step-3: automated sub-region (8-regions) segmentation and volume calculation

148 We divided the segmented cartilage into quarters from the pixel where the cartilage
149 exists at the most anterior position to the pixel at the most posterior position in the slices
150 with the cartilage, and divided these into medial and lateral portions. We defined the 8
151 regions as lateral anterior, lateral anterior weight-bearing, lateral posterior
152 weight-bearing, lateral posterior, medial anterior, medial anterior weight-bearing,
153 medial posterior weight-bearing, and medial posterior portions (Fig.3.). The way we
154 segmented the cartilage came from the findings of previous studies; ACL tear leads to
155 anterior subluxation of the tibia with impaction of the anterior femoral condyle against
156 the posterior tibial plateau along with cartilage loss in the anterior femoral condyle and
157 posterior tibial plateau [19,21]. The amount of cartilage volume change was obtained by

158 subtraction of the volume of the baseline from that of the follow-up, and color mapping
159 was performed based on the value of these changes (Fig.4.).

160 One radiological technologist with three months of experience and enough
161 prior knowledge about the position of the cartilage performed computer-based analysis
162 twice with a half of year interval. In order to examine the validity of the original
163 software, pre- and post-operative knee cartilage was quantified using our software
164 (which includes semi-automatic and manual segmentation) and an image analysis
165 software called ImageJ (National Institutes of Health, Bethesda, MD) in one case
166 (20-year-old, male). In ImageJ, we manually segmented cartilage utilizing the “Polygon
167 selection” tool.

168

169 Statistical analysis

170 SPSS version 22.0 (IBM Corp, New York, NY) for Windows was used for statistical
171 analysis. When we compared the paired samples, normality was tested by the
172 Shapiro-Wilk test and did not find normality; we therefore performed the Wilcoxon
173 signed-rank test, which is a nonparametric test.

174 Intra-observer agreement was estimated using intra-class correlation
175 coefficients (ICC) employing a one-way random effects model for intra-observer

176 agreement. ICC values were interpreted as poor agreement for values between 0 and
177 0.20, fair agreement for values between 0.21 and 0.40, moderate agreement for values
178 between 0.41 and 0.60, substantial agreement for values between 0.61 and 0.80, and
179 almost perfect for values between 0.81 and 1.00 [25]. We compared the time taken per
180 slice between the original software and ImageJ in a Wilcoxon signed-rank test.
181

182 Results

183 There was a significant difference between baseline and follow-up cartilage volumes in
184 the medial posterior weight-bearing, medial posterior, lateral posterior weight-bearing,
185 and lateral posterior portions ($p=0.006$, $p=0.023$, $p=0.017$, and $p=0.002$, respectively).
186 However, there was no significant difference between baseline and follow-up cartilage
187 volumes in the medial anterior, medial anterior weight-bearing, lateral anterior, and
188 lateral anterior weight-bearing portions ($p=0.352$, $p=0.098$, $p=0.642$, and $p=0.602$,
189 respectively), as shown in Table 4. A representative case is shown in Fig.5.

190 Intra-observer agreement of knee cartilage volume in 8 regions was almost
191 perfect (ICC = 0.955; 95% confidence interval [95% CI], 0.943-0.965). Intra-observer
192 agreement for delta values (difference between the baseline and follow-up) was
193 substantial (ICC = 0.803; 95% CI, 0.732-0.857). The knee cartilage volume in the
194 original software/ImageJ was 2108/2038 mm³ (0.094% difference) and 2108/2110 mm³
195 (3.4% difference) at the baseline and follow-up, respectively. The mean time (\pm
196 standardized deviation) taken with the original software and ImageJ was 50.9 (\pm 10.1)
197 and 131 (\pm 0.000788) seconds, respectively ($p = 0.00004$).

198

199 Discussion

200 In this study, we evaluated cartilage volumes in 16 patients before and 1 year after ACL
201 reconstruction surgery. There was a significant difference between baseline and
202 follow-up cartilage volumes in each of 4 regions (medial posterior weight-bearing,
203 medial posterior, lateral weight-bearing posterior, and lateral posterior portions). In
204 previous studies, quantitative knee cartilage evaluation was conducted using 3D-MR
205 images [12,14–17], but to the best of our knowledge, there were no studies in which
206 there was a quantitative evaluation of postoperative cartilage volume as in this study.
207 T1-weighted images are used routinely for the analysis of anatomic structures.
208 Moreover, they have an advantage over gradient echo sequences and fat suppression
209 images, being free from postoperative metal artifacts. Therefore, this method could be
210 applied immediately to clinical practice.

211 Previous investigations reported that ACL tear leads to anterior subluxation of
212 the tibia with impaction of the anterior femoral condyle against the posterior tibial
213 plateau along with cartilage loss in the anterior femoral condyle and posterior tibial
214 plateau [19,21]. Also, previous studies showed that ACL-reconstructed knees had
215 greater contact along the medial ridge of the medial plateau and the posterior aspect of
216 the lateral plateau, compared to healthy contralateral knees and to the knees of healthy
217 persons during exercise [15]. Furthermore, in another study, 74% of the patients who

218 had undergone ACL reconstruction surgery showed several signs of radiographic OA
219 within 7 years after surgery, indicating that early-onset OA is common in
220 ACL-reconstructed knees [24]. For these reasons, cartilage loss may occur in the
221 anterior femoral condyle and posterior tibial condyle at the time of ACL tear. In this
222 study, the results that there was a significant difference between baseline and follow-up
223 cartilage volumes in the medial posterior weight-bearing, medial posterior, lateral
224 weight-bearing posterior, and lateral posterior portions were consistent with this
225 hypothesis. That may suggest that our newly proposed method could successfully
226 quantify knee cartilage volume.

227 In this study, we showed that there is significant reduction in the reasonable
228 anatomical location of the knee cartilage in patients who underwent ACL reconstruction
229 surgery. Moreover, the knee cartilage volumes can be evaluated by using the
230 conventional MR images with our software. We consider this is due to careful scan
231 planning in terms of stable slice selection and imaging parameter, including slice
232 thickness and slice gap. Together with compatible results from the data using the free
233 software of ImageJ, we considered our cartilage volumetry was to be valid.

234 In our study results, the knee cartilage volumes did not show any significant
235 difference in the anterior and anterior weight-bearing portions of both medial and lateral

236 sides. This may be attributed to the fact that we could not divide segmented cartilage
237 into the femoral side and the tibial side. In our study population, as ACL tears were
238 caused by trauma, cartilage wear was considered to be localized. For more sensitive
239 detection of the localized cartilage loss, measurement of cartilage volume should be
240 performed on the femoral side and the tibial side separately. However, in this study, it
241 was difficult to separate the cartilage into the femoral side and the tibial side on the
242 T1-weighted sagittal images.

243 We believe that as the original software used in this study is accurate,
244 reproducible, and less time-consuming, it can be applied to the comparison among the
245 procedures of ACL reconstruction. In a previous study, the comparison among the
246 procedures of ACL reconstruction was performed, but the investigations evaluated ACL
247 by arthroscopy, whereas a cartilage evaluation was not done [26]. We considered that
248 adding cartilage evaluation to one of the prognostic evaluations might reveal signs of
249 OA, which is considered to occur frequently in ACL-reconstructed knees.

250 Our study had several limitations. First, the devices used for MR images differ
251 between inter- and intra- patients due to the retrospective design of this study. However,
252 the MR parameters used in this study did not differ greatly between the devices, and the
253 results of this research implied that cartilage volume may be quantified by use of

254 routine images, independent of the device. The second limitation was the small number
255 of patients included in this study. Further study on more patients is needed for
256 confirmation of the results. Thirdly, although the cartilage region is clearly depicted
257 using 3D imaging methods such as the 3D-FISP sequence, we have no 3D imaging
258 methods available for comparison. However, we believe that it is meaningful to
259 quantitatively evaluate cartilage using 2D-T1w MR images although accuracy for
260 cartilage volumetry may be inferior to 3D sequences due to the slice gap. Finally,
261 because our original software was not free from manual segmentation for the most part,
262 cartilage evaluation could be subjective and time-consuming. Moreover, when
263 conducting similar research in other institutes, there is a possibility that some variation
264 may occur depending on the analyst's skill. Therefore, in order fundamentally to solve
265 these problems, we need to build a new algorithm for automating our original software.

266

267 Conclusion

268 Knee cartilage volumes could be measured quantitatively with conventional MR
269 imaging in patients who underwent ACL reconstruction surgery.

270

271 Compliance with ethical standards

272

273 Conflict of interest

274 All authors have no conflicts of interest to disclose.

275

276 Ethical approval

277 All procedures in studies involving human participants were performed in accordance

278 with the ethical standards of the Faculty of Health Sciences, Hokkaido University, and

279 with the 1964 Helsinki Declaration and its later amendments or comparable ethical

280 standards.

281

282 Informed consent

283 Informed consent was waived by the ethical committee of Faculty of Health Sciences,

284 Hokkaido University as this was a retrospective study.

285

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359

360

361

Table 1. Characteristics of patients

| | Value |
|--------------------------------|--------------|
| Total no. of subjects included | 16 |
| Age. mean (range) in years | 30.1 (13-58) |
| Sex. female/male | 7/9 |
| Knee. right/left | 5/11 |

362

363

Table 2. Athletic activity or situation associated with the injury, and period from injury to surgery

| Case number | Situation | Days | Sex | Age [years] |
|-------------|------------|-------|-----|-------------|
| 1 | tumble | 756 | M | 36 |
| 2 | rugby | 92 | M | 19 |
| 3 | ski | 85 | M | 55 |
| 4 | soccer | 3626 | M | 32 |
| 5 | basketball | 136 | F | 13 |
| 6 | badminton | 0 | M | 19 |
| 7 | tumble | 139 | F | 45 |
| 8 | gym vault | 111 | M | 18 |
| 9 | gym vault | 15706 | F | 58 |
| 10 | volleyball | 57 | F | 15 |
| 11 | volleyball | 1461 | F | 51 |
| 12 | volleyball | 100 | M | 49 |
| 13 | volleyball | 85 | F | 16 |
| 14 | triathlon | 110 | M | 20 |
| 15 | rugby | 93 | M | 19 |
| 16 | soccer | 24 | F | 17 |

365

366

Table 3. Acquisition parameters of MR imaging

| Magnetic Field Strength [T] | 1.5 | 3 |
|--------------------------------|--|--|
| Sequence | | SE T1WI |
| Section | | sagittal |
| Slice Thickness [mm] | | 3 |
| FA [degree] | | 90 |
| NEX | | 2 |
| Slice Gap [mm] | | 0.3 |
| TR [msec] | 500 or 579 | 700 or 800 |
| TE [msec] | 15 | 10 or 12 |
| ETL | 3 or 4 | 3 |
| BW [Hz] | 230 - 259 | 242 - 255 |
| Pixel Size [mm] | $0.222 \times 0.222 - 0.390 \times$ 0.390 | $0.273 \times 0.273 - 0.3125 \times$ 0.3125 |
| No. of Slices | 23 or 24 | 23 or 25 |

Table 4. Comparison between baseline and follow-up cartilage volume in each region

| Regions | n | Baseline | | Follow-up | | P value (<0.05) | |
|---------|-----------------------------|----------------------------|-----------------------|----------------------------|-----------------------|------------------------|-------|
| | | Mean [mm ³] | SD [mm ³] | Mean [mm ³] | SD [mm ³] | | |
| Medial | Anterior | 16 | 31.8 | 29.0 | 31.2 | 43.1 | 0.352 |
| | Anterior weight-bearing | 16 | 203 | 54.6 | 171 | 65.4 | 0.098 |
| | Posterior weight-bearing | 16 | 309 | 69.2 | 252 | 82.4 | 0.006 |
| | Posterior | 16 | 321 | 105 | 310 | 86.2 | 0.023 |
| | Anterior | 16 | 115 | 96.4 | 89.8 | 50.3 | 0.642 |
| Lateral | Anterior weight-bearing | 16 | 164 | 74.5 | 153 | 84.6 | 0.605 |
| | Posterior weight-bearing | 16 | 376 | 96.8 | 320 | 113 | 0.017 |
| | Posterior | 16 | 351 | 107 | 278 | 71.7 | 0.002 |

371 SD = standard deviation



Fig.1. Original image (A) and fused image (B)



Fig.2. Segmentation of cartilage at fused image

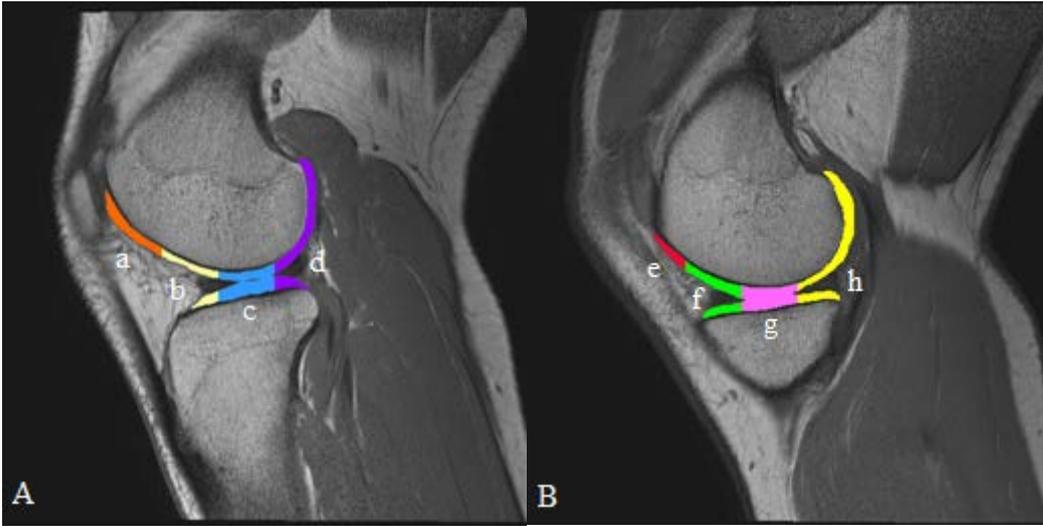


Fig.3. Cartilage classification into 8 regions.

(A) Sagittal MR image of the lateral side of the knee (B) Sagittal MR image of the medial side of the knee. (a) Lateral anterior portion (b) Lateral anterior weight-bearing portion (c) Lateral posterior weight-bearing portion (d) Lateral posterior portion (e) Medial anterior portion (f) Medial anterior weight-bearing portion (g) Medial posterior weight-bearing portion (h) Medial posterior portion

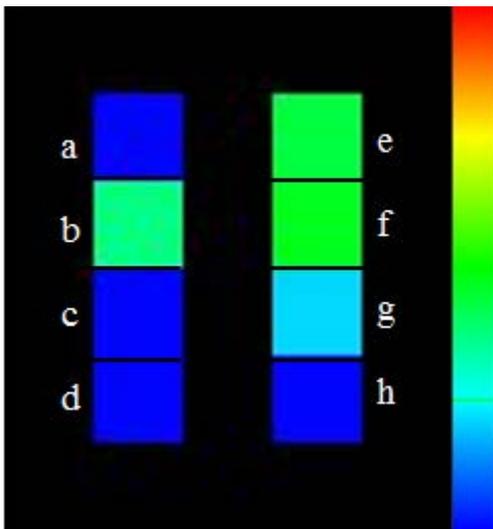
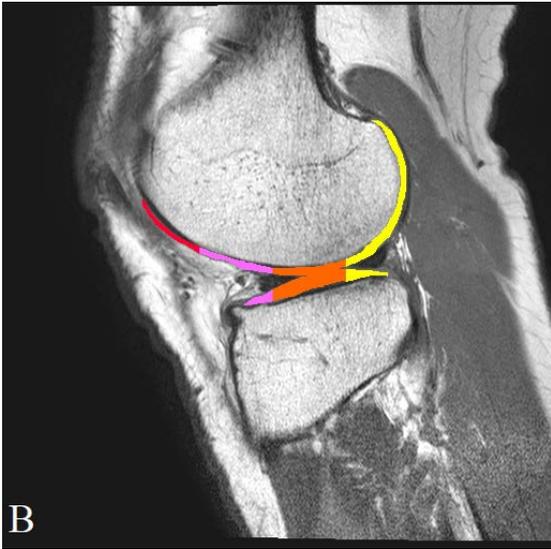


Fig.4. Cartilage volume map in a 36-year-old man's right knee

The closer to red, the larger the difference between the follow-up and baseline is to the positive value. The closer to blue, the larger the difference between the follow-up and baseline is to the negative value. Green indicates almost unchanged.

- (a) Lateral anterior portion (b) Lateral anterior weight-bearing portion (c) Lateral posterior weight-bearing portion (d) Lateral posterior portion (e) Medial anterior portion (f) Medial anterior weight-bearing portion (g) Medial posterior weight-bearing portion (h) Medial posterior portion



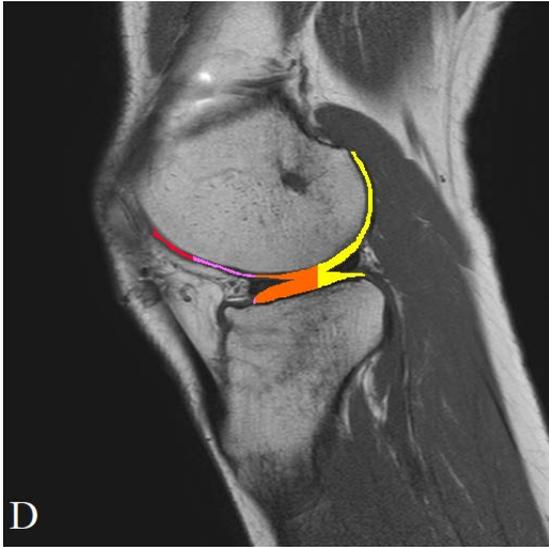


Fig.5. Example of a case with significant cartilage volume loss at multiple cartilage regions.

Sagittal T1-w MR images of knee in 36-year-old man before and 1 year after ACL reconstruction surgery. (A) baseline image. (B) is colored cartilage of (A). (c) is followup image. (D) is colored cartilage of (C). The cartilage volume at baseline (followup) was 70.9 (37.6), 131.3 (43.8), 484.9 (314.0) and 458.0 (313.0) mm³ in anterior, anterior weight-bearing, posterior weight-bearing and posterior at baseline, respectively. These interval changes are difficult to recognize using conventional visual assessment.