



HOKKAIDO UNIVERSITY

Title	Computer-Based Radiographic Quantification of Joint Space Narrowing Progression Using Sequential Hand Radiographs : Validation Study in Rheumatoid Arthritis Patients from Multiple Institutions
Author(s)	Ichikawa, Shota; Kamishima, Tamotsu; Sutherland, Kenneth et al.
Citation	Journal of digital imaging, 30(5), 648-656 https://doi.org/10.1007/s10278-017-9970-9
Issue Date	2017-10
Doc URL	https://hdl.handle.net/2115/71769
Rights	This is a post-peer-review, pre-copyedit version of an article published in Journal of digital imaging. The final authenticated version is available online at: http://dx.doi.org/10.1007/s10278-017-9970-9 .
Type	journal article
File Information	J digit imaging_30(5)_648-656.pdf



Blind title page

Title; Computer-based radiographic quantification of joint space narrowing progression using sequential hand radiographs: Validation study in rheumatoid arthritis patients from multiple institutions

Short title; Computer-based quantification of joint space narrowing progression using sequential hand radiographs

Type of paper; Hypothesis Driven Research

Abstract

Purpose: We have developed a refined computer-based method to detect joint space narrowing (JSN) progression with the joint space narrowing progression index (JSNPI) by superimposing sequential hand radiographs. The purpose of this study is to assess the validity of a computer-based method using images obtained from multiple institutions in rheumatoid arthritis (RA) patients.

Materials and Methods: Sequential hand radiographs of 42 patients (37 females and 5 males) with RA from two institutions were analyzed by a computer-based method and visual scoring systems as a standard of reference. The JSNPI above the smallest detectable difference (SDD) defined JSN progression on the joint level. The sensitivity and specificity of the computer-based method for JSN progression was calculated using the SDD and a receiver operating characteristic (ROC) curve.

Results: Out of 314 metacarpophalangeal joints, 34 joints progressed based on the SDD, while 11 joints widened. 21 joints progressed in the computer-based method, 11 joints in the scoring systems and 13 joints in both methods. Based on the SDD, we found lower sensitivity and higher specificity with 54.2% and 92.8%, respectively. At the most discriminant cut-off point according to the ROC curve, the sensitivity and specificity was 70.8% and 81.7%, respectively.

Conclusion: The proposed computer-based method provides quantitative measurement of JSN progression using sequential hand radiographs and may be a useful tool in follow-up assessment of joint damage in RA patients.

Keywords

Radiography, Computer Assisted Detection, Hand

Introduction

Plain radiography is used to monitor the long term progression of joint space narrowing (JSN) and bone erosion as well as single time point damage in patients with rheumatoid arthritis (RA) [1, 2]. Published scoring systems [3, 4], consisting of assessment of JSN and erosion in hands/wrists and feet, are currently the gold standard for assessment of radiographic progression in clinical trials. However, these methods are time consuming, and their use requires specialized training that results in a lack of qualified readers [5, 6]. The more quantitative and reproducible tools are needed to detect small changes over the time in clinical trials.

Computer-based methods of radiographic assessment are expected to address the issues of scoring systems. Various computer-based methods based on identifying joint contours have been introduced to measure joint space width (JSW) cross-sectionally [7-13], although their algorithms and the degree of user interaction is somewhat different. Peloschek et al. used a model-based approach based on prior knowledge of bone shapes to automatically locate the joints and measure JSW [7]. On the other hand, Pfeil et al. used an edge-based approach to detect the edges of the two specified bones by filtering within a region of interest (ROI), and measuring JSW [8]. Since a radiograph is a two-dimensional projection of a three-dimensional structure, the

definition of the joint margin is ambiguous, especially in distal contours in metacarpophalangeal (MCP) joints [14]. Thus, the definition of the bony edge for JSW measurement is up to the designer of the computer-based method and longitudinal accuracy for the detection of the bony margin may be limited.

Our group has recently developed and validated a computer-based method, which can detect JSW changes as the joint space difference index (JSDI) by superimposing sequential hand radiographs [15, 16]. The JSDI was defined as the difference of the pixel values between baseline and follow-up images; but the pixel values are susceptible to imaging conditions and bone density may also change chronologically which results in reducing quantitativity for the assessment of JSN progression. Furthermore, the JSDI is dependent on the digital image acquisition systems and radiographic protocol, and shared use of the software among multiple centers is limited. To overcome these issues, we developed a refined method that can extract the topological difference of proximal contours relative to the distal contours of the joints between baseline and follow-up images and detect JSN progression with the joint space narrowing progression index (JSNPI) by superimposing the two images. We hypothesize that defining the distal contours of MCP joints, which tend to be a broad bright band, making its definition ambiguous on radiographs, is not needed for assessment of JSN progression. Thus, the

purpose of this study is to investigate the performance of a refined computer-based method for JSN progression in MCP joints using superimposed sequential hand radiographs from two institutions.

Materials and methods

Study subjects

A total of 42 rheumatoid patients (37 females and 5 males), who were available for sequential hand radiographs with a 1-year average (mean $\pm$ standard deviation, 1.16 ± 0.48 years) follow-up interval, were enrolled in this study from a rheumatological hospital (Group 1) and a rheumatological clinic (Group 2). Demographic and baseline characteristics of the subjects are shown in Table 1. All subjects satisfied the American Rheumatism Association 1987 revised criteria for the classification of RA [17]. The first group consisted of 15 patients with long-term sustained clinical low disease activity, who had been treated with non-biologic disease-modifying antirheumatic drugs (DMARDs) with or without biologics. The second group consisted of 27 patients of active disease treated with Tocilizumab and/or DMARDs. Details of our patient population have been previously reported [15, 18].

This retrospective study was approved by the local ethics committee and was

performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients.

Radiographic acquisition and visual scoring assessment

The radiographs of 15 patients in Group 1 were acquired using Radnext 32 (Hitachi, Tokyo, Japan) under the following standard conditions: X-ray aluminum filter thickness 0.5 mm, film-focus distance 100 cm, tube voltage 50 kV, tube current 100 mA, exposure 0.025 sec, and the X-ray beam centered on the MCP joint of the second finger. Each radiograph from Group 1 was scored for JSN by an experienced rheumatologist (J.F.) according to the Genant-modified Sharp score (GSS) as follows: 0 = normal; 0.5 = subtle or equivocal narrowing; 1.0 = focal or mild narrowing; 1.5 = mild-to-moderate narrowing; 2.0 = moderate narrowing or dislocation in the absence of erosion; 2.5 = moderate-to-severe narrowing; 3.0 = complete loss of joint space or dislocation in the presence of erosion; 3.5 = partial or equivocal ankyloses; and 4.0 = definite ankyloses [4, 19].

Bilateral hand radiographs of 27 patients in Group 2 were acquired using UD150L-40E (Shimadzu, Kyoto, Japan) under the following standard conditions: X-ray aluminum filter thickness 1.5 mm, film-focus distance 100 cm, tube voltage 40 kV, tube

current 200 mA, exposure 0.025 sec, and the X-ray beam centered on the midpoint between both hands at the level of the third metacarpophalangeal head. Each radiograph from Group 2 was scored for JSN by an experienced rheumatologist (K.K.) according to the Sharp van der Heijde score (SHS) as follows: 0 = normal; 1 = focal or doubtful; 2 = >50% of the original joint space; 3 = <50% of the original joint space or subluxation; and 4 = ankyloses or complete luxation [3, 19]. All radiographs were obtained as digital imaging and communications in medicine (DICOM) images with 1024×1024 pixels and a 0.15mm×0.15mm pixel size at 10-bit grayscale. All radiographs were read and scored with images chronologically displayed side by side. Readers were blind to other clinical information. Reproducibility of the scoring for each reader has been guaranteed by previous articles with radiographic scoring assessment by the same experienced readers [16, 18, 20].

Image processing for radiographic image

We utilized an in-house software application programmed with Microsoft Visual C# 2013. Figure 1 shows a schematic overview of the image processing. The x and y axes were defined by the horizontal and vertical directions, respectively, and the origin was located in the upper left-hand corner of the image.

Initially, the proximal contours of MCP joints were semi-automatically extracted in both baseline and follow-up radiographs by an operator as following procedures. After reading a baseline image into the software, the image was rotated until the analyzed joint space was approximately horizontal on the display. Next, a rectangular ROI with size fixed at 50×25 pixels was manually located in the center of joint space and the radiograph underwent filtering with a 3×3 square neighborhood median filter to reduce image noise. A Sobel filter for y direction was then applied to extract the joint margin inside the ROI. To determine the proximal contours of the joints, the pixels showing the highest pixel value at each column inside the bottom half of the ROI were marked as reported previously [21]. To eliminate isolated pixels, the number of connected pixels was counted for the marked pixels and any pixels that belonged to a group whose number less than 3 pixels were excluded. The operator made corrections in the process of contouring the joint margin whenever necessary. After extracting the rough joint margin, the missing points were complemented by connecting adjacent pixels of each marked group and the final joint margin was determined. The same procedure was performed for the follow-up image.

A fused image was then created by copying each pixel value in the baseline image to the blue and green channels, and each pixel value in the follow-up image to the red

channel of the fused image [15]. At this point, the ROI rectangle from the baseline image was also copied to the fused image. The follow-up image can be shifted or rotated relative to the baseline image and the distal contours of MCP joints were aligned between two images. A new fused image was created based on the shifted values. We assumed the topological difference of proximal contours relative to the distal contours of the MCP joints between the two images as JSN progression when proximal phalanxes in the two images were aligned accurately.

The joint was finally divided into columns on the fused image, and the number of pixels between the extracted margins was summed along 40 pixels inside the ROI. If the extracted margin of the follow-up image showed lower y location than that of the baseline image on a column, the difference of extracted margins was calculated as a positive integer. On the other hand, the difference of extracted margins was calculated as a negative integer when the extracted margin of the follow-up image showed higher y location than that of the baseline image. We calculated the difference of extracted margins by multiplying the summation of the difference between the extracted margins by the area per pixel ($0.15\text{mm} \times 0.15\text{mm}$). We refer to this value as the JSNPI.

Computer-based analysis for quantifying joint space narrowing progression

The JSN progression of the second to fifth MCP joints was measured using the in-house software application by a non-specialist (S.I.) for RA assessment, who was blind to other clinical information. Severely damaged (subluxation, ankylosed and complete luxation) joints were excluded in the computer-based method analysis on each reader's score. Computer-based analysis was repeated twice to assess the intra-observer reliability and to calculate the smallest detectable difference (SDD) with a 1-month interval.

Statistical analyses

Statistical analyses were performed using SPSS version 22.0 (IBM Corp., New York, NY). All statistical analyses were performed for two groups together and each group separately.

Intra-observer reliability for the JSNPI was estimated using calculations of intra-class correlation coefficients (ICC) (one-way random). The ICC values are interpreted as follows: <0.40, poor to fair agreement; 0.41 to 0.60, moderate agreement; 0.61 to 0.80, substantial agreement; 0.81 to 1.00, almost perfect agreement [22].

The performance of the computer-based method was assessed by setting the visual scoring assessment as the gold standard for JSN progression. We compared the JSNPI

of joints with JSN progression in the follow-up period (increase in GSS or SHS) to those without JSN progression (no change in GSS or SHS) using the Mann-Whitney U test. A value of $p < 0.05$ was deemed as statistically significant. Data from the first time measurement was used for this analysis and three widened joints according to the visual scoring systems were excluded.

The sensitivity and specificity of the computer-based method were evaluated by setting the cut-off point for JSNPI using the SDD and a receiver operating characteristics (ROC) curve. Data from the first time measurement was used for calculating the sensitivity and specificity for JSN progression. We considered progression on a joint level as the JSNPI above the measurement error and therefore the SDD was used as a cut-off level for progression [23, 24]. We assumed that there would be almost no difference in JSW in the joints showing no change in scoring systems between the baseline and follow-up images and the JSNPI of these joints were used for calculating the SDD. The SDD was calculated as $1.96 \times SD$, where SD is the standard deviation of the change in the JSNPI of the joints showing no change in visual scoring assessment between two measurements [23, 25]. Progression was defined as an increase in JSNPI more than the SDD. Widening was defined using a cut-off level in the opposite direction. ROC curve was also used for setting the optimal cut-off point on the JSNPI [15]. We

chose the point for balancing the sensitivity and specificity as the optimal cut-off point, which is the point on the curve closest to the upper left-hand corner. This cut-off point was defined as that yielding the minimal value for $(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$ [26].

Results

Out of 336 MCP joints, 314 MCP joints in 42 patients were targeted by the computer-based method after excluding 22 severely damaged joints. If there were no changes in scoring systems between the baseline and follow-up images, the joint space in the fused image was visualized as grey shadow and the difference of proximal contours between two images cannot be seen (Figure 2). In contrast, the computer-based method visualized JSN progression as the topological difference of proximal contours relative to the distal contours of the joints between two images (Figure 3). In Group 1, 38 joints (33.0%) needed manual adjustment for extracting joint margins in at least one sequential radiograph, while 102 joints (51.3%) needed manual adjustment in Group 2. Intra-observer reliability for the JSNPI was in almost perfect agreement in Group 1 (ICC=0.91; 95% CI, 0.88-0.94) and in substantial agreement in Group 2 (ICC=0.71; 95% CI, 0.63-0.77). The overall intra-observer reliability for the JSNPI was in almost

perfect agreement (ICC=0.82; 95% CI, 0.78-0.86).

Table 2 shows the JSNPI for joints with and without JSN progression. There were 24 MCP joints with JSN progression (increase in GSS or SHS), while 287 MCP joints without JSN progression (no change in GSS or SHS) according to the visual scoring systems. The joints with JSN progression showed a higher value in JSNPI. This increase in JSNPI was significantly higher than for joints without JSN progression for two groups together, and each group separately (Table 2).

Table 3 shows the concordance between the visual scoring systems and the computer-based analysis base on the SDD. Progression was defined as an increase in JSNPI more than the SDD, resulting in a cut-off of 0.707 mm² for Group 1, 0.805 mm² for Group 2 and 0.773 mm² for Group 1/Group 2. Although we expected the computer-based method would be more sensitive, only half (n=13) of the joints (n=24) that progressed according to the visual scoring systems were classified as progression joints based on the SDD. In joints with no change (n=287) according to the visual scoring systems, most of the joints (n=258) were also classified as no change joints, while 21 joints progressed and 8 joints widened. Three widened joints in the visual scoring systems were also classified as widening joints.

Table 4 shows the sensitivity and specificity of the computer-based method for JSN

progression based on the SDD and the ROC curve. Group 1 revealed a lower sensitivity and higher specificity with 35.7% and 93.1% based on the SDD. On the other hand, Group 2 revealed a higher sensitivity and specificity with 80.0% and 92.1%. The sensitivity and specificity for Group 1/Group 2 were 54.2% and 92.8% based on the SDD. Based on the optimal cut-off point by ROC curve analysis, higher sensitivity for JSN progression was found than for those based on the SDD with 64.3%, 100.0%, and 70.8% for Group 1, Group 2 and Group 1/Group 2, respectively. While lower specificity was found than for those based on the SDD with 65.3%, 81.5% and 81.7% for Group 1, Group 2 and Group 1/Group 2, respectively. The area under the curve was 0.736 (95% confidence interval [95% CI] 0.599 - 0.874, $p = 0.004$), 0.960 (95%CI 0.918-1.000, $p < 0.001$) and 0.820 (95%CI 0.727 - 0.914, $p < 0.001$) for Group 1, Group 2 and Group 1/Group 2, respectively (Figure 4).

Discussion

Accurate estimate of JSN is important in clinical trials and daily clinical routine because cartilage degradation, which can be visualized radiographically as JSN, is a surrogate parameter for outcome in RA [27]. Although various software applications have been introduced to measure JSW quantitatively with high reproducibility, the definition of the

bony margin for JSW measurement depends on the designer of the computer-based method [14]. To address these issues, we established a computer-based method that can quantify JSN progression using superimposed sequential radiographs while eliminating the process of contouring the distal edge of MCP joints that is ambiguous on radiographs.

Until now, many of the presented methods have been tested on datasets from one institute, in which hand radiographs were acquired via the same radiographic protocol [7, 28]. Pfeil et al. reported that computer-aided analysis for joint space measurements is affected by alternation of tube voltage to a lesser extent [29]. Therefore, we used datasets from two institutions with different digital image acquisition systems to demonstrate that our computer-based method can allow shared use by several users in different locations. In the present study, the JSNPI of progressive joints showed significantly higher value than that of stable joints in two groups together and each group separately. Furthermore, the sensitivity and specificity of the computer-based method are acceptable using ROC curve to define cut-off. However, the JSNPI of Group 2 showed inferior intra-observer reproducibility than that of Group 1, although showing substantial agreement. This may be explained by the influence of higher disease activity of Group 2, which resulted in severe joint destruction and required more human

interaction for extracting joint margins. Pfeil et al. also reported that the joints with higher score in SHS for JSN reduced detection of joint margins resulting in a lower quality of reproducibility in their computer-aided analysis [30]. In addition, bilateral hands were simultaneously radiographed in Group 2 and the influence of oblique incidence of the X-ray beam may have been significant. These results revealed that the computer-based method was useful to quantify JSN progression with relatively good reproducibility and allowed shared use of the software in multiple centers.

We chose to use the SDD as a cut-off for JSN progression to account for measurement error as previously reported [23]. The SDD reflects variation of hand positioning during imaging, radiographic protocol execution and ROI positions. When progression was considered based on the SDD, some conflicting results were found between the scoring systems and the computer-based method. Only half of the joints that progressed according to the scoring systems were also classified as progression joints. Damman et al. also showed discordant results in classification of progression with the scoring system and their computer-based method in osteoarthritis patients, in which only half (n=37) of the 76 progressed joints according to the scoring system were also classified as progressed based on the SDD [23]. When using the SDD as the cut-off point, our study found a low sensitivity with 54.2%. These conflicting results may be caused by

the fact that the SDD does not account for real disease progression, although we chose joints that exhibited no change in scoring systems to expect almost no disease progression. In addition, variations of registration between the baseline and follow-up images could have been an influence on the SDD.

In contrast, when setting the optimal cut-off point using the ROC curve, the computer-based method had a relatively high sensitivity and specificity with 70.8% and 81.7%, respectively. In our previous computer-based method, we found the sensitivity and specificity with 78.6% and 85.3% in MCP joints, respectively [15], supporting the validity of the proposed computer-based method. However, lower sensitivity was seen in Group 1 when setting the cut-off point using both the SDD and ROC curve. This was due to low disease activity and the fine scale scoring system of Group 1, which might have caused small radiographic progression. Also in another approach to quantitative measurement of JSW, the sensitivity and specificity for JSN were evaluated. Finckh et al. reported the sensitivity and the specificity of their computer-based method with 87.6% and 88.4% in MCP and proximal interphalangeal (PIP) joints [28]. Pfeil et al. documented the sensitivity and specificity of their computer-based method with 88.1% and 77.8% in MCP joints [31]. Although head to head comparison of these computer-based programs have been performed [32, 33], we cannot directly compare

the performance of our computer-based method with these software applications because our software focuses on detecting chronological change rather than measuring JSW cross-sectionally.

There were several limitations to our study. First, the performance of the computer-based method was validated only in MCP joints. The accuracy of automatic edge detection might be decreased and more user interaction might be needed in PIP joints due to their small and rounded structures. Thus, we will refine the edge detection algorithm and develop an automated computer-based method that automatically extracts joint contours and aligns sequential hand radiographs with only minimal human intervention for practical application. The second limitation was that the number of joints, especially the joints with JSN progression according to visual scoring, was small. Further study, with a larger number of joints with JSN progression from a multicenter database, is needed to confirm that the computer-based method can quantify JSN progression with high sensitivity and specificity. The third limitation was that there was no gold standard for JSN progression when comparing the performance of the scoring systems and the computer-based method. Hence, comparison with different computer-aided techniques and imaging modalities will be the subject of future work to show advantage of the computer-based method compared to conventional scoring

systems.

In conclusion, the results of the computer-based method were consistent with reference standards and showed relatively high sensitivity and specificity for JSN progression. In addition, our computer-based method enables objective measurement of JSN progression without the definition of ambiguous distal margins of MCP joints and can be shared in multiple centers. These results suggest that quantitative measurement of JSN progression could be achieved with our computer-based method using sequential hand radiographs and our proposed method may become a useful tool in follow-up assessment of joint damage in RA patients.

References

1. Fouque-Aubert A, Chapurlat R, Miossec P, Delmas PD: A comparative review of the different techniques to assess hand bone damage in rheumatoid arthritis. *Joint Bone Spine* 77:212-217, 2010
2. van der Heijde DM: Radiographic imaging: the 'gold standard' for assessment of disease progression in rheumatoid arthritis. *Rheumatology (Oxford)* 39 Suppl 1:9-16, 2000
3. van der Heijde D: How to read radiographs according to the Sharp/van der Heijde method. *J Rheumatol* 27:261-263, 2000
4. Genant HK, Jiang Y, Peterfy C, Lu Y, Redei J, Countryman PJ: Assessment of rheumatoid arthritis using a modified scoring method on digitized and original radiographs. *Arthritis Rheum* 41:1583-1590, 1998
5. Boini S, Guillemin F: Radiographic scoring methods as outcome measures in rheumatoid arthritis: properties and advantages. *Ann Rheum Dis* 60:817-827, 2001
6. van Der Heijde D, Boonen A, Boers M, Kostense P, van Der Linden S: Reading radiographs in chronological order, in pairs or as single films has important implications for the discriminative power of rheumatoid arthritis clinical trials. *Rheumatology (Oxford)* 38:1213-1220, 1999

7. Peloschek P, et al.: An automatic model-based system for joint space measurements on hand radiographs: initial experience. *Radiology* 245:855-862, 2007
8. Pfeil A, et al.: Computer-aided joint space analysis of the metacarpal-phalangeal and proximal-interphalangeal finger joint: normative age-related and gender-specific data. *Skeletal Radiol* 36:853-864, 2007
9. Duryea J, Jiang Y, Zakharevich M, Genant HK: Neural network based algorithm to quantify joint space width in joints of the hand for arthritis assessment. *Med Phys* 27:1185-1194, 2000
10. Angwin J, Lloyd A, Heald G, Nepom G, Binks M, James MF: Radiographic hand joint space width assessed by computer is a sensitive measure of change in early rheumatoid arthritis. *J Rheumatol* 31:1050-1061, 2004
11. Sharp JT, Gardner JC, Bennett EM: Computer-based methods for measuring joint space and estimating erosion volume in the finger and wrist joints of patients with rheumatoid arthritis. *Arthritis Rheum* 43:1378-1386, 2000
12. Pfeil A, et al.: Normative reference values of joint space width estimated by computer-aided joint space analysis (CAJSA): the distal interphalangeal joint. *J Digit Imaging* 21 Suppl 1:104-112, 2008
13. Bottcher J, et al.: Computerized digital imaging techniques provided by digital

X-ray radiogrammetry as new diagnostic tool in rheumatoid arthritis. *J Digit Imaging* 19:279-288, 2006

14. Huo Y, Vincken KL, van der Heijde D, De Hair MJ, Lafeber FP, Viergever MA: Automatic Quantification of Radiographic Finger Joint Space Width of Patients With Early Rheumatoid Arthritis. *IEEE Trans Biomed Eng* 63:2177-2186, 2016

15. Ichikawa S, Kamishima T, Sutherland K, Okubo T, Katayama K: Performance of computer-based analysis using temporal subtraction to assess joint space narrowing progression in rheumatoid patients. *Rheumatol Int* 36:101-108, 2016

16. Ichikawa S, Kamishima T, Sutherland K, Okubo T, Katayama K: Radiographic quantifications of joint space narrowing progression by computer-based approach using temporal subtraction in rheumatoid wrist. *Br J Radiol* 89:20150403, 2016

17. Arnett FC, et al.: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 31:315-324, 1988

18. Fukae J, et al.: Structural deterioration of finger joints with ultrasonographic synovitis in rheumatoid arthritis patients with clinical low disease activity.

Rheumatology (Oxford) 53:1608-1612, 2014

19. Peterfy CG WC, Szechinski J, DiCarlo JC, Lu Y, Genovese M, et al. :

Comparison of the Genant-modified Sharp and van der Heijde-modified Sharp scoring

methods for radiographic assessment in rheumatoid arthritis. . Int J Clin Rheumtol
6:15–24., 2011

20. Katayama K, et al.: One-year maintenance with routine assessment of patient
index data 3-based remission may inhibit radiographic progression in patients with
rheumatoid arthritis treated with routine clinical therapy: A retrospective comparison of
radiographic outcome and its prognostic factors between maintained remissions with
patient-reported outcome index and physician-oriented disease activity indices. Mod
Rheumatol:1-11, 2016

21. Duryea J, Li J, Peterfy CG, Gordon C, Genant HK: Trainable rule-based
algorithm for the measurement of joint space width in digital radiographic images of the
knee. Med Phys 27:580-591, 2000

22. Landis JR, Koch GG: The measurement of observer agreement for categorical
data. Biometrics 33:159-174, 1977

23. Damman W, et al.: Sensitivity-to-change and validity of semi-automatic joint
space width measurements in hand osteoarthritis: a follow-up study. Osteoarthritis
Cartilage 24:1172-1179, 2016

24. Bruynesteyn K, Boers M, Kostense P, van der Linden S, van der Heijde D:
Deciding on progression of joint damage in paired films of individual patients: smallest

detectable difference or change. *Ann Rheum Dis* 64:179-182, 2005

25. Studenic P, Stamm T, Smolen JS, Aletaha D: Reliability of patient-reported outcomes in rheumatoid arthritis patients: an observational prospective study.

Rheumatology (Oxford) 55:41-48, 2016

26. Akobeng AK: Understanding diagnostic tests 3: Receiver operating characteristic curves. *Acta Paediatr* 96:644-647, 2007

27. Aletaha D, Funovits J, Smolen JS: Physical disability in rheumatoid arthritis is associated with cartilage damage rather than bone destruction. *Ann Rheum Dis*

70:733-739, 2011

28. Finckh A, et al.: Performance of an automated computer-based scoring method to assess joint space narrowing in rheumatoid arthritis: a longitudinal study. *Arthritis*

Rheum 54:1444-1450, 2006

29. Pfeil A, et al.: Feasibility study of semi-automated measurements of finger joint space widths. *Rheumatol Int* 31:1349-1354, 2011

30. Pfeil A, et al.: Reproducibility and influence of hand rotation on computer-aided joint space analysis. *Joint Bone Spine* 79:384-388, 2012

31. Pfeil A, et al.: The usefulness of computer-aided joint space analysis in the assessment of rheumatoid arthritis. *Joint Bone Spine* 80:380-385, 2013

32. Sharp JT, et al.: Computer based methods for measurement of joint space width: update of an ongoing OMERACT project. J Rheumatol 34:874-883, 2007

33. Sharp JT, et al.: Multiple computer-based methods of measuring joint space width can discriminate between treatment arms in the COBRA trial -- Update of an ongoing OMERACT project. J Rheumatol 36:1825-1828, 2009

Figure Legends

Figure 1

Schematic overview of image processing.

Initially, the proximal contours of metacarpophalangeal (MCP) joints were extracted in both baseline and follow-up radiographs. A fused image was then created by copying each pixel value in the baseline image to the blue and green channels, and each pixel value in the follow-up image to the red channel of the fused image. The topological difference of proximal contours relative to the distal contours of the MCP joints between the two images were deemed as joint space narrowing (JSN) progression when proximal phalanxes in the two images were aligned accurately. The JSN progression was eventually measured as the joint space narrowing progression index (JSNPI).

Figure 2

The fourth metacarpophalangeal (MCP) joint for right hand of a 57-year-old female with rheumatoid arthritis. There was no joint space narrowing (JSN) progression, corresponding to a Sharp/van der Heijde score of 0 at both baseline (a) and follow-up (b).

In the fused image (c), the joint space was visualized as grey shadow and the difference of proximal contours between the baseline and follow-up cannot be seen.

Figure 3

The fourth metacarpophalangeal (MCP) joint for right hand of a 55-year-old male with rheumatoid arthritis. There was joint space narrowing (JSN) progression, corresponding to a Sharp/van der Heijde score of 0 at baseline (a) and 1 at follow-up (b). In the fused image (c), the computer-based method visualized JSN progression as the topological difference of proximal contours relative to the distal contours of the joints between the baseline and follow-up images.

Figure 4

Receiver operating characteristic (ROC) curve for joint space narrowing progression index (JSNPI).
ROC curves for JSNPI in Group 1 (a), Group 2 (b) and Group 1/Group 2 (c) are shown.

Table 1. Demographic and baseline characteristics of patients with rheumatoid arthritis

Characteristic	Group 1	Group 2
Total no. of subjects included	15	27
Age, mean (range) years	54 (32-69)	60 (31-83)
Sex, no. female/male	13/2	24/3
Duration of symptoms, median (range) months	50 (26-196)	69 (18-253)
Swollen joint count, range	0-2	2-30
Tender joint count, range	0-2	2-39
DAS28-ESR, mean (SD)	2.03 (0.55)	5.99 (1.27)

DAS28, disease activity score with 28 joints; ESR, erythrocyte sedimentation rate; SD, standard deviation.

Table 2. Comparison of the joint space narrowing progression index (JSNPI) between joints with and without joint space narrowing (JSN) progression

Group	JSNP(-)			JSNP(+)			p-value
	n	mean (mm ²)	SD (mm ²)	n	mean (mm ²)	SD (mm ²)	
Group 1	99	0.151	0.448	14	1.152	1.892	0.005
Group 2	188	0.136	0.565	10	1.766	0.788	<0.001
Group 1/Group 2	287	0.141	0.527	24	1.408	1.562	<0.001

JSNP(-), non-joint space narrowing progression; JSNP(+), joint space narrowing progression; SD, standard deviation.

Table 3. Concordance between visual scoring systems and the computer-based analysis base on the smallest detectable difference (SDD)

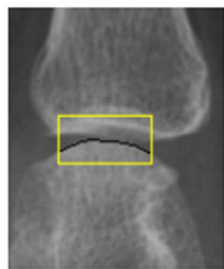
JSNPI	Visual scoring assessment			Total
	Widening	No change	Progression	
Group 1				
Widening	2	1	0	3
No change	0	91	9	100
Progression	0	7	5	12
Total	2	99	14	115
Group 2				
Widening	1	8	0	9
No change	0	165	2	167
Progression	0	15	8	23
Total	1	188	10	199
Group 1/ Group 2				
Widening	3	8	0	11
No change	0	258	11	269
Progression	0	21	13	34
Total	3	287	24	314

JSNPI, joint space narrowing progression index.

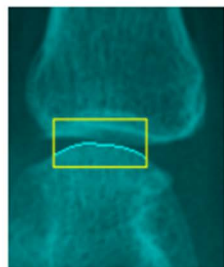
Table 4. Sensitivity and specificity of the computer-based method for joint space narrowing progression

Method	Group	Cut-off value (mm ²)	Sensitivity (%)	Specificity (%)
SDD	Group 1	0.707	35.7	93.1
	Group 2	0.805	80.0	92.1
	Group 1/Group 2	0.773	54.2	92.8
ROC	Group 1	0.225	64.3	65.3
	Group 2	0.551	100.0	81.5
	Group 1/Group 2	0.529	70.8	81.7

SDD, smallest detectable difference; ROC, receiver operating characteristic.



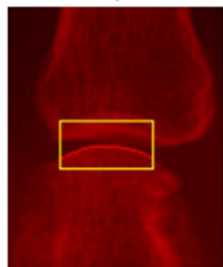
proximal contour delineation
in baseline radiograph



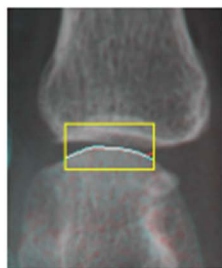
copying pixel value to the blue and
green channels of the fused image



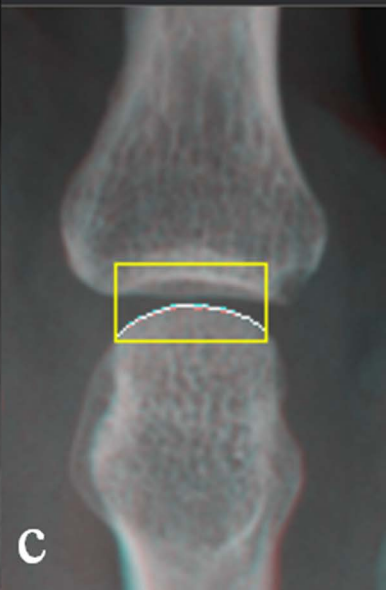
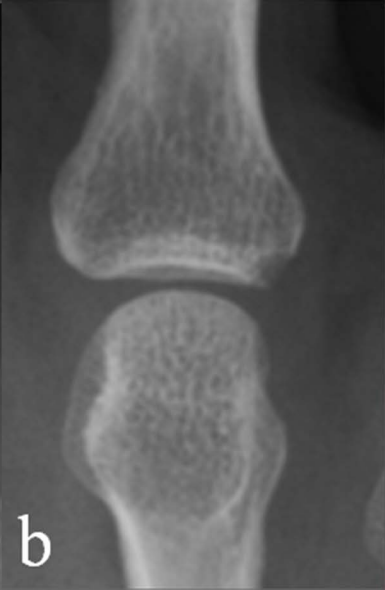
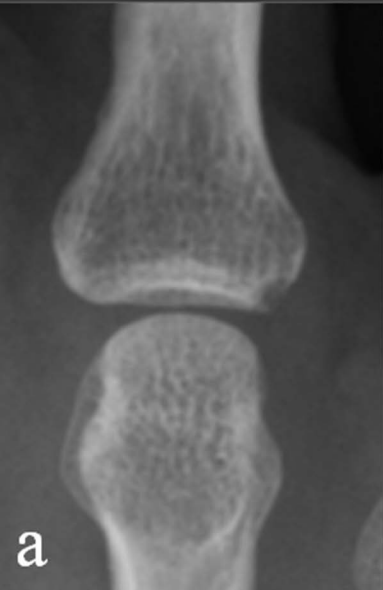
proximal contour delineation
in follow-up radiograph

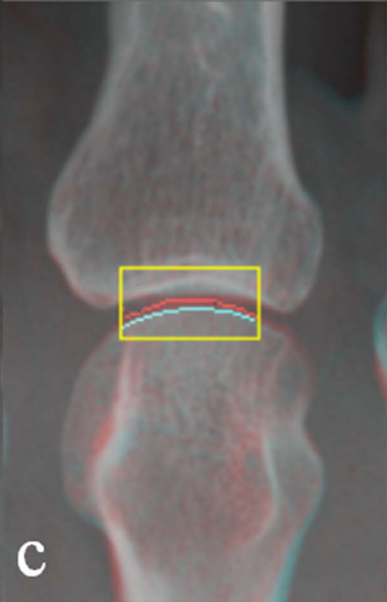
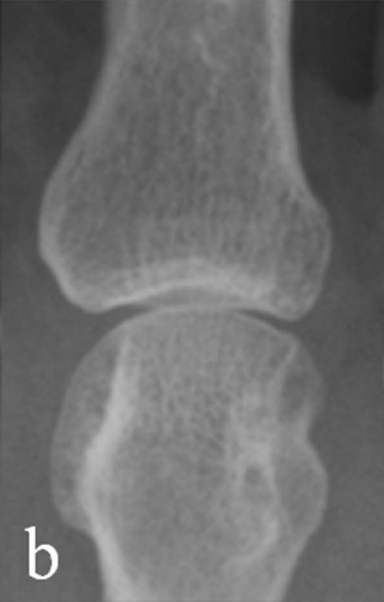
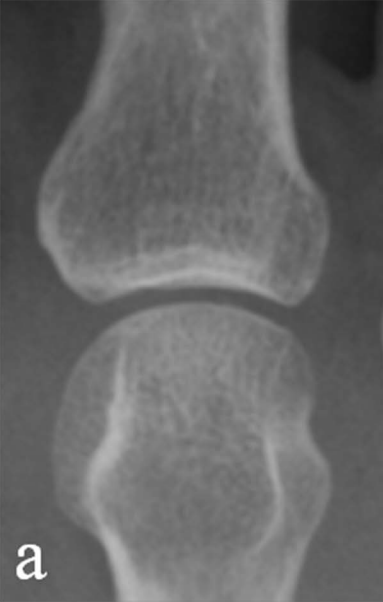


copying pixel value to the red
channel of the fused image

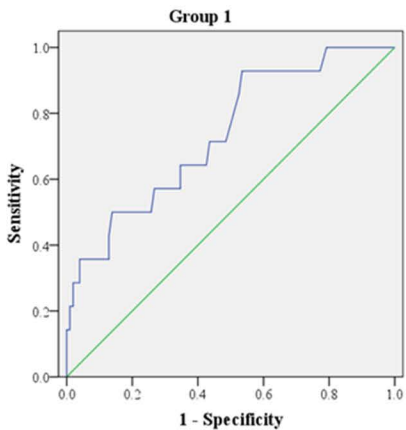


superimposing baseline and
follow-up images

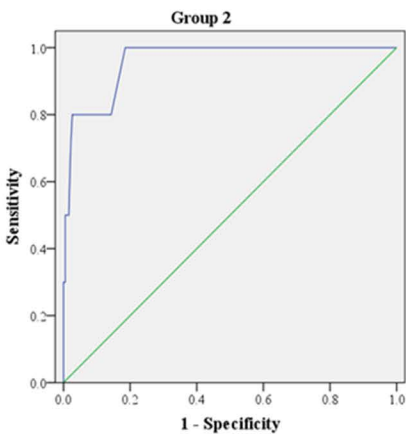




a



b



c

