OPEN ACCESS

CLINICAL SCIENCE

Ultra-low-dose CT detects synovitis in patients with suspected rheumatoid arthritis

Torsten Diekhoff,[1] Sevtap Tugce Ulas,[1] Denis Poddubnyy,[2] Udo Schneider,[3] Sandra Hermann,[3] Robert Biesen,[3] Gerd R Burmester,[3] Bernd Hamm,[1] Kay Geert Hermann[1]

ABSTRACT

Purpose To prove the feasibility and measure the diagnostic accuracy of contrast-enhanced ultra-low-dose CT (ULD-CT) for the depiction of inflammatory soft-tissue changes (synovitis, tenosynovitis and peritendonitis) in patients with arthritis of the hand.

Materials and methods In this institutional review board–approved study, 36 consecutive patients over the age of 50 with suspected rheumatoid arthritis underwent ULD-CT (estimated radiation exposure <0.01 mSv) and MRI of the hand with weight-adapted intravenous contrast administration. ULD-CT subtraction and MR images were assessed for synovitis, tenosynovitis and peritendonitis by three readers using a modified Rheumatoid Arthritis MRI Score (RAMRIS). Patients were asked which modality they would prefer for future examinations. Sensitivity and specificity of ULD-CT for detection of inflammatory changes were calculated using MRI as standard of reference. The sum scores were correlated using Pearson's r.

Results All 36 patients showed synovitis in MRI. ULD-CT had 69% sensitivity on the patient level and 65% on the joint level with 87% specificity. Sensitivity was higher in patients with more severe inflammation (80% for MRI RAMRIS >1). There was almost perfect correlation between the modified RAMRIS sum scores of ULD-CT and MRI (Pearson's r=0.94). Regarding preferences for future examinations, 85% preferred ULD-CT over MRI. ULD-CT detected more differential diagnoses than MRI (8 vs 2/12).

Conclusion Contrast-enhanced ULD-CT of the hand allows for depiction of soft-tissue inflammation at the hand and can be achieved using very low radiation exposure (<0.01 mSv). ULD-CT may evolve to a fast and comfortable alternative to MRI, although it is not as sensitive as MRI for detecting mild disease.

INTRODUCTION

Synovitis, tenosynovitis and peritendonitis are key features of active inflammatory arthritis in patients with peripheral rheumatic disorders.[1] They can be detected using contrast-enhanced MRI or ultrasonography.[2 3] CT is to date not recommended by imaging guidelines for rheumatoid arthritis.[4] With its high resolution and bone contrast, CT may be considered a gold standard for bone destruction,[5] and dual-energy CT depicts gouty depositions and bone marrow oedema.[6–8] However, CT cannot distinguish between inactive and active disease, and there are concerns about the radiation exposure.

Key messages

What is already known about this subject?
► CT can be used as standard of reference for bone destruction in inflammatory diseases; however, it is not able to distinguish between inactive and active disease.

What does this study add?
► Contrast-enhanced ultra-low-dose CT using subtraction allows for a depiction of active soft-tissue inflammation of the wrist and finger joints in patients with suspected rheumatoid arthritis and can be achieved with similar radiation exposure than digital radiography.
► Ultra-low-dose CT showed better accuracy for differential diagnoses; however, it was not as sensitive as MRI for detecting mild disease.
► Despite exhibiting radiation exposure, ultra-low-dose CT was preferred over MRI by the patients due to a shorter examination time.

How might this impact on clinical practice or future developments?
► Ultra-low-dose CT may develop to an alternative imaging technique for patients unwilling or unable to undergo MRI or when arthrosonography is not available.

Recent technical advances such as ultra-low-dose CT (ULD-CT)[9] can reduce CT radiation exposure to that of conventional radiographs. Furthermore, preliminary attempts to detect active inflammation using contrast-enhanced CT have been reported.[10 11]

The aim of our study was to prove the feasibility of contrast-enhanced ULD-CT of the hand and wrist and determine its diagnostic accuracy in arthritis of the hand compared with MRI.

METHODS
Patients

Thirty-seven consecutive patients presenting to the rheumatology department with joint pain and swelling of the wrist and/or finger joints and suspected rheumatoid arthritis between September 2016 and October 2017 were prospectively enrolled. All patients had to be over 50 as requested by the local ethics board. Exclusion criteria were contraindications to MRI and intravenous contrast medium, for example, kidney dysfunction with

a glomerular filtration rate <60 mL/min, and inability to give informed consent. A final diagnosis was established by the expert rheumatologist based on all available data (eg, clinical information, laboratory tests and imaging results including X-ray).

Imaging

All patients underwent a contrast-enhanced ULD-CT and MRI of the same hand in superman position with a maximum interval of 1 hour between the two examinations. The patients were randomised to ULD-CT or MRI first. The ULD-CT protocol included a scanogram and two 16 cm scans on a 320-row detector scanner (Canon Aquilion One Vision; Canon Medical Systems, Japan) without table movement before and 3 min after intravenous injection of iodinated contrast agent. Both scans were performed at 80 kVp to maximise the sensitivity for contrast media. A rotation time of 0.275 s and a tube current of 8.25 mAs was applied to reach a ULD-CT level of radiation exposure. The resulting total dose–length–product was 48 m*Gycm and the estimated effective dose <0.01 mSv. The MRI protocol included clinical standard sequences with coronal T1 and short-tau inversion recovery and a two-plane (coronal and axial) fat-saturated T1-weighted sequence 3 min after contrast agent administration. The total MRI scan time was 25 min. Doses were adjusted to body weight: 1 mL/kg Ultravist 370 (Bayer, Germany) for ULD-CT and 1 mL/kg of a 1:4 mixture of gadolinium–DOTA (Dotarem, Guerbet, France) and isotonic saline for MRI, both at a flow rate of 3 mL/s, respectively. The maximum injected volume was 100 mL.

Precontrast and postcontrast ULD-CT images in soft-tissue kernel were postprocessed using a special software (SureSubtraction Ortho V.5; Canon Medical Systems, Japan) for the reconstruction of colour-coded subtraction images with 3 mm slice thickness.

Image reading

Three readers scored the images independently for synovitis, tenosynovitis and peritendonitis blinded to all identifying or clinical information and the results of the other modality. A modified Rheumatoid Arthritis MRI Score (RAMRIS) including a 0 to 3 rating of flexor and extensor tendons was used.[12] In two separate reading sessions, the readers evaluated MRI and ULD-CT images in consensus for an imaging diagnosis using contrast enhancement for active inflammation and morphological information provided by the respective modality.

Patient comfort

The patients were asked to complete a short questionnaire to assess their concerns regarding radiation exposure, the duration of the examination and contrast agent injection. Specifically, they had to rate the following questions on a 1-to-5 scale: (1) How were your concerns before the (modality) examination (1: no concerns, 5: severe concerns)? (2) How was your comfort during the (modality) examination (1: very good, 5: very poor)? (3) How was your anxiety during the (modality) examination (1: no anxiety, 5: severe anxiety)? (4) Assuming medical equivalence, which examination would you prefer for future examinations?

Statistical analysis

For the comparison of CT and MRI, a location (joint or tendon) was considered positive if two of three readers agreed on the presence of inflammation. For statistical purposes, the scores of joints were grouped, resulting in five groups per patient: (1) wrist, (2) metacarpophalangeal joints, (3) proximal interphalangeal joints, (4) extensor and (5) flexor tendons. Sensitivity and specificity of ULD-CT for detection of synovitis (score >0) on the patient and joint group level were calculated using MRI as standard of reference. A sensitivity analysis on the joint group level was performed defining MRI scores higher than 1 as positive. A Pearson test was applied for significant correlations of MRI and ULD-CT sum scores. Inter-rater reliability was calculated using Fleiss's kappa. The imaging diagnoses derived from the consensus reading were compared descriptively with the final diagnosis established by the rheumatologist. The questionnaire results were compared using Wilcoxon's matched-pairs signed-rank test and McNemar test where appropriate. A p value smaller than 0.05 was considered significant.

RESULTS

Patients

One patient did not undergo contrast-enhanced MRI and was excluded from analysis. Thus, 36 patients (10 men and 26 women) were included. They had a mean age of 60.1 (SD 7.2; range 50–77) years, a mean weight of 77.3 (SD 14.3) kg and a mean C reactive protein of 18 (SD 42.6) mg/L. Twenty-four patients were finally diagnosed and classified with rheumatoid arthritis according to the American College of Rheumatology/European League Against Rheumatism criteria (16 seronegative and 8 seropositive), six with inflammatory osteoarthritis of the hand, three with psoriatic arthritis/peripheral spondyloarthritis, two with calcium pyrophosphate dihydrate deposition disease (CPPD) and one with undifferentiated arthritis.

Image reading

Sixteen patients underwent MRI following ULD-CT, 20 ULD-CT first. All 36 patients had synovitis, tenosynovitis or peritendonitis on MRI (mean sum score 9.9±8.7). ULD-CT revealed inflammation in 69.4% (25/36) of the patients with a mean sum score of 7.5±9.6 (see table 1). Among the false-negative patients, there were six with the diagnosis of RA (one of them seropositive), three with osteoarthritis, one with undifferentiated arthritis and one with CPPD. Imaging examples are presented in figure 1. The results of the consensus reading for the final diagnosis are shown in figure 2.

The specificity on the patient level could not be calculated due to missing true-negative samples. The analysis on the joint group level yielded a combined sensitivity of 65% (95%

Table 1 Scoring results

	ULD-CT	MRI
Synovitis (wrist, MCP and PIP)	11 joints/3 joint groups per patient	
RAMRIS sum score	5.1±6.2	6.8±5.0
Positivity on joint group level	44% (47/108)	74% (80/108)
Tenosynovitis (flexor tendons)	5 tendons/1 group per patient	
mRAMRIS sum score	1.9±2.6	2.3±2.8
Positivity on group level	44% (16/36)	55% (20/36)
Peritendonitis (extensor tendons)	5 tendons/1 group per patient	
mRAMRIS sum score	0.7±1.2	1.1±1.7
Positivity on group level	25% (9/36)	33% (12/36)
Total	21 locations/5 groups per patient	
mRAMRIS sum score	7.5±9.6*	9.9±8.7*
Positivity on joint group level	40%±49%	62%±49%
Positivity on patients' level	69%±47%	100%

For synovitis (according to the RAMRIS score), tenosynovitis of the flexor tendons and peritendonitis of the extensor tendons, the sum scores are given as absolute numbers and SD. The share of positive findings (score >0) is listed in per cent of joint groups/patients.
*The total sum scores correlated with a Pearson's r of 0.94.
MCP, metacarpophalangeal; PIP, proximal interphalangeal; ULD-CT, ultra-low-dose CT; mRAMRIS, modified Rheumatoid Arthritis MRI Score.
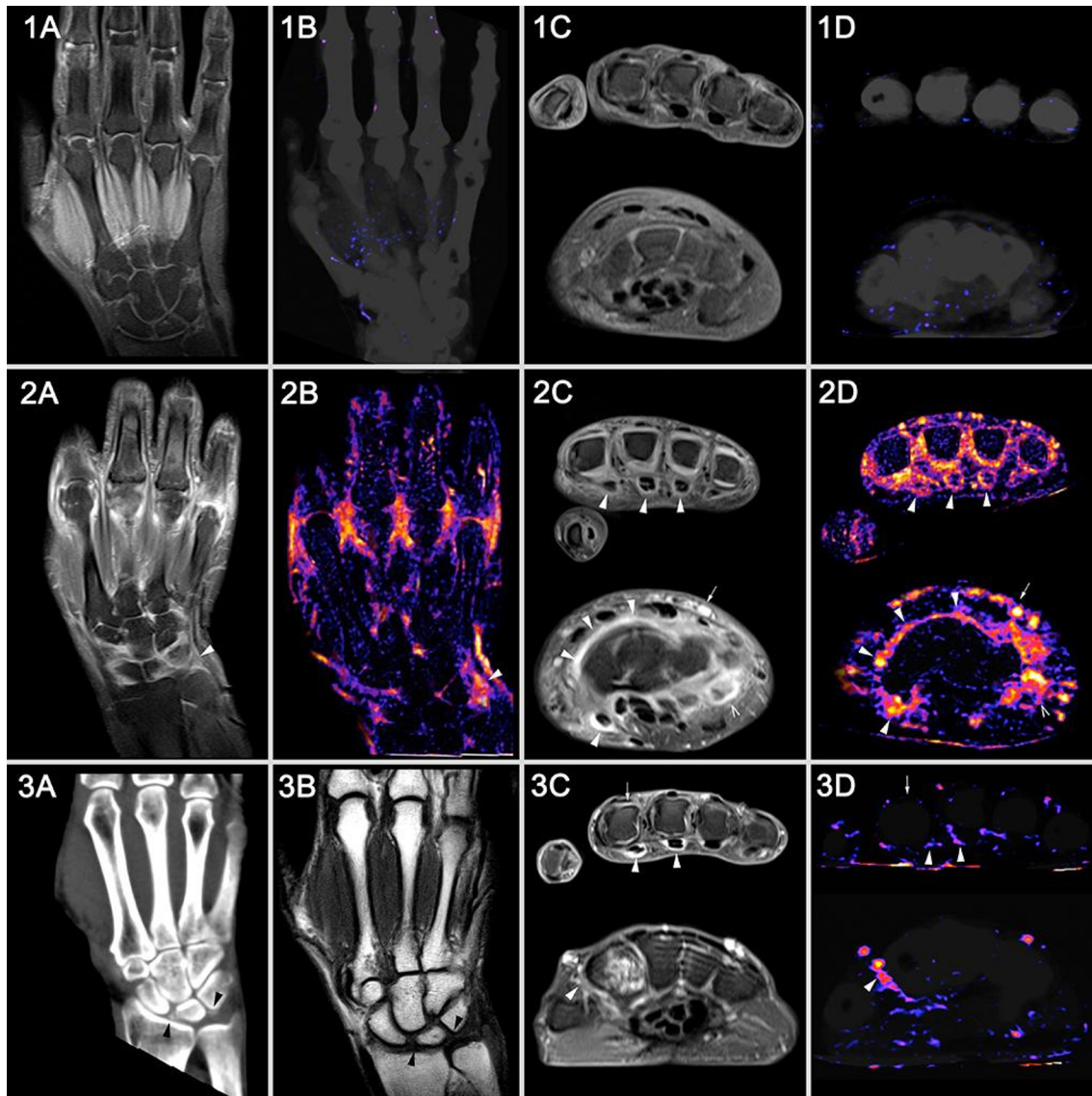
Figure 1 Imaging examples. (1) 68-year-old female patient with seronegative rheumatoid arthritis. (A, C) Coronal (A) and axial (C) T1 with fat saturation shows normal findings at the metacarpophalangeal (MCP) joints and the wrist. There is also no enhancement in ultra-low-dose CT (ULD-CT) subtraction with colour coding (1B, D) in corresponding slice orientation. For better anatomical orientation, the subtraction images were fused with the conventional ULD-CT. Therefore, the bone is faintly visible. (2) A 62-year-old male patient with severe active rheumatoid arthritis. (A) Coronal T1 with fat saturation shows synovitis of the MCP joints and the wrist (white arrowhead). (B) ULD-CT subtraction shows enhancement of the MCP joints and the wrist (white arrowhead) correlating well with MRI. (C and D) Axial MRI (C) and CT subtraction (D) show severe synovitis of the MCP joints and carpus and tenosynovitis of the flexor tendons (white arrowheads). There is also contrast medium in the veins (white arrows). (3) A 67-year-old female patient with calcium pyrophosphate dihydrate deposition disease (CPPD). (A) CT shows calcifications in the scapholunate and lunotriquetral ligament indicating CPPD, which is not visualised by T1-weighted MRI (B) and was occult in radiography (black arrowheads). (C, D) Contrast-enhanced MRI shows tenosynovitis of the second and third flexor tendons and synovitis of the wrist, which was also detected with ULD-CT (white arrowheads). However, the mild synovitis of the second MCP joint was not visualised by ULD-CT (white arrows).

CI 56% to 73%), specificity of 88% (95% CI 78% to 94%), positive predictive value of 90% (95% CI 82% to 95%) and negative predictive value of 59% (95% CI 49% to 68%). Sensitivity for the individual readers ranged from 54% to 84% and specificity from 82% to 94%. Sensitivity increased markedly to 80% for MRI scores >1. A detailed analysis of patients with and without final diagnosis of RA is shown in online supplementary table 1. There was an almost perfect correlation of the ULD-CT sum scores with MRI with a Pearson's r of 0.94. Inter-rater reliability (Fleiss kappa) was 0.55 for MRI and 0.65 for ULD-CT.

Patient comfort

Thirty-four patients completed the questionnaire. The results are presented in online supplementary figure 2. Interestingly, the patients seemed to be more worried about the MRI examination when asked about their concerns. They felt more comfortable during the ULD-CT examination than during MRI and felt less anxiety during the CT scan despite the warm sensation caused by the CT contrast medium. Most patients appreciated the short CT examination time and that there was less noise during the scan. Moreover, 85% (29/34) preferred ULD-CT for future examinations, 3% (1/34) MRI and 12% (4/34) were undecided.
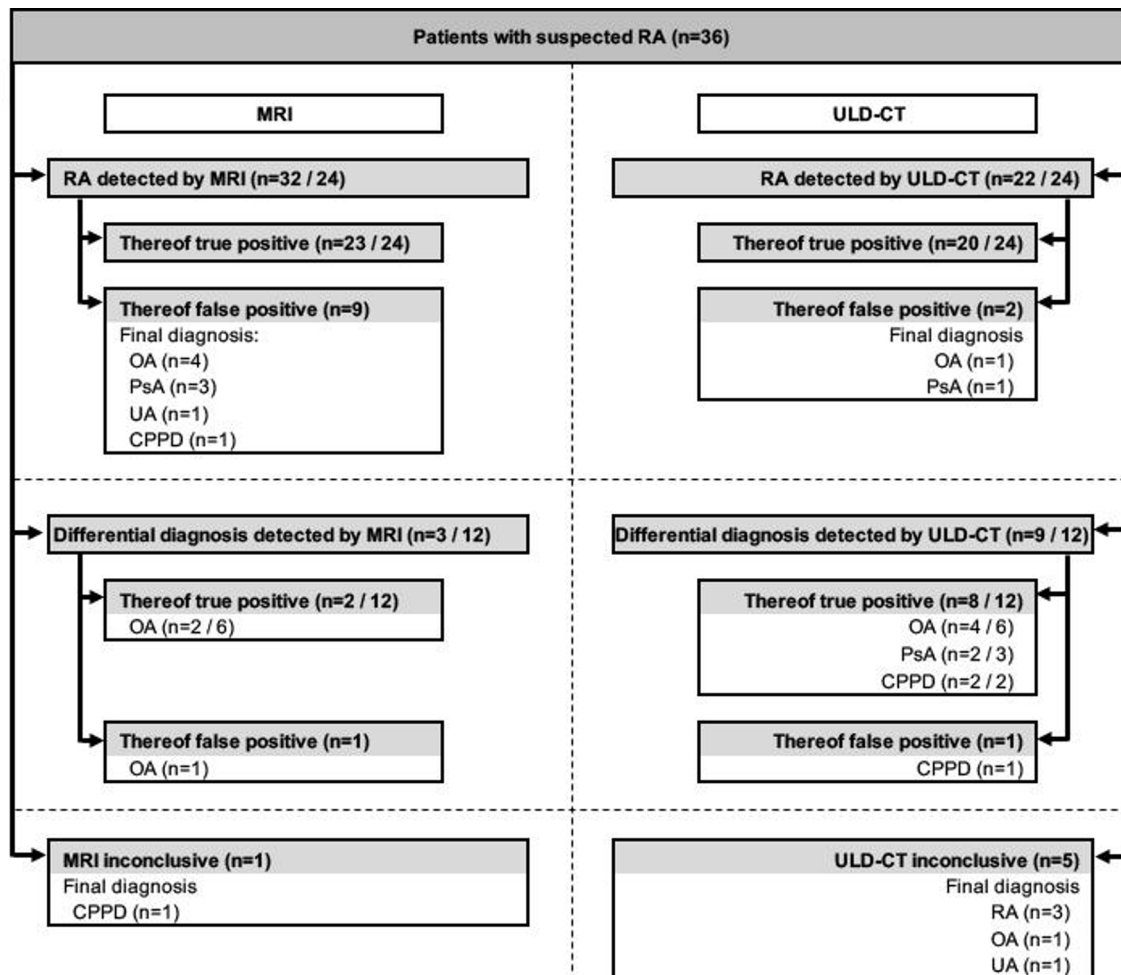
Figure 2 Results of the consensus reading. All patients were included with suspicion of rheumatoid arthritis. Whereas MRI is more sensitive to RA (23 vs 20 true-positive detections), ULD-CT shows better specificity (2 vs 9 false-positive detections) and better differentiation between different differential diagnoses in imaging (8 vs 2 correct differentials). However, ULD-CT was more often inconclusive/normal than MRI (5 vs 1 patients) and imaging results may have biased the final diagnosis. CPPD, calcium pyrophosphate disease; OA, osteoarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; UA, undifferentiated arthritis; ULD-CT, ultra-low-dose CT.

DISCUSSION

To the best of our knowledge, this is the first study to describe ULD-CT subtraction reconstruction for the detection of synovitis. The radiation exposure of ULD-CT was less than 0.01 mSv (10 times less than a chest radiograph and comparable to an X-ray of hands and feet). ULD-CT had limited sensitivity for mild inflammation but reliably detected severe synovitis and tenosynovitis. Specificity was very high and correlation with MRI excellent (r=0.94). ULD-CT yielded a superior inter-rater reliability and capability to detect differential diagnoses. Most patients preferred ULD-CT over MRI due to the short scanning time.

CT is a fast, standardised technique with safe contrast administration in patients without renal dysfunction or hyperthyroidism.[13] State-of-the-art reconstruction algorithms enable low-dose scanning with radiation exposure similar to a radiograph.[14][15] In view of patient preference and recent concerns about gadolinium-based MRI contrast agents,[16] CT may become a suitable alternative, especially for patients with contraindications to MRI or unable to tolerate the rather long examination times. Subtraction after contrast medium may also give additional information of active inflammation in patients who undergo CT for other indications, for example, dual-energy CT

for gout. The reconstruction of the subtraction images takes only 2 min and can be done by a technician. One should also keep in mind that the CT source images offer additional information on bone erosion, new bone formation and soft-tissue calcification that MRI is not able to provide. In our study, 6% of the patients (2/36) were diagnosed with CPPD based on the presence of crystals in typical localisation in CT (and not in radiography). This diagnosis altered treatment, and these patients directly benefited from study participation. Furthermore, some authors suggest that the superior spatial resolution of CT allows for the depiction of enhancement patterns that are not visualised by MRI.[17]

Only a few studies investigated contrast-enhanced CT for the evaluation of active arthritis. Polster et al used postcontrast CT with digital bone subtraction in four patients to delineate synovitis.[11] They also reported that the patients preferred CT over MRI. Fukuda et al used dual-energy CT to generate iodine contrast maps to detect synovitis.[10][17] With 16 patients suffering from psoriatic arthritis, they found 78% sensitivity and 87% specificity.

Despite a well-planned design, our study has some limitations. Our patient cohort is small, but it is the largest number of patients undergoing contrast-enhanced CT in arthritis published to date, and we obtained meaningful statistical results. We obtained a

rather low sensitivity because we used very low radiation exposure. However, sensitivity can be improved by applying higher radiation to reduce image noise. The final diagnosis might be biased by the imaging results because the rheumatologists were not blinded. We did neither compare CT subtraction with other postprocessing techniques (eg, dual-energy iodine map or digital bone masking) nor with sonography. Sonography has proven high diagnostic accuracy in patients with rheumatoid arthritis; however, it has disadvantages in standardisation. We included patients with suspected and not proven rheumatoid arthritis. This leads to a rather inhomogeneous collective. However, we believe that the imaging findings (synovitis) are comparable and our results better reflect daily clinical practice. Finally, our collective was limited to patients over 50 due to requirements of the Federal Office for Radiation Protection. Nonetheless, we do not see technical reasons for ULD-CT losing diagnostic accuracy in younger patients.

In conclusion, our study proves the feasibility of ULD-CT in suspected rheumatoid arthritis. The method is preferred by patients. As such, ULD-CT may be a suitable alternative for patients unable or unwilling to undergo MRI or if arthrosonography is unavailable. Future studies should compare the different techniques in larger patient populations and investigate how image quality can be improved.

REFERENCES

1 Glinatsi D, Baker JF, Hetland ML, *et al*. Magnetic resonance imaging assessed inflammation in the wrist is associated with patient-reported physical impairment, global assessment of disease activity and pain in early rheumatoid arthritis: longitudinal results from two randomised controlled trials. *Ann Rheum Dis* 2017;76:1707–15.

2 Østergaard M, Peterfy CG, Bird P, *et al*. The OMERACT Arthritis Magnetic Resonance Imaging (MRI) Scoring System: Updated Recommendations by the OMERACT MRI in Group. *J Rheumatol* 2017;44:1706–12.

3 Nishino A, Kawashiri SY, Koga T, *et al*. Ultrasonographic efficacy of biologic and targeted synthetic DMARDs therapy in RA from multicenter RA ultrasound prospective cohort in Japan. *Arthritis Care Res* 2018.

4 Colebatch AN, Edwards CJ, Østergaard M, *et al*. EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. *Ann Rheum Dis* 2013;72:804–14.

5 Scharmga A, Geusens P, Peters M, *et al*. Structural damage and inflammation on radiographs or magnetic resonance imaging are associated with cortical interruptions on high-resolution peripheral quantitative computed tomography: a study in finger joints of patients with rheumatoid arthritis and healthy subjects. *Scand J Rheumatol* 2018:1–9.

6 Ramon A, Bohm-Sigrand A, Pottecher P, *et al*. Role of dual-energy CT in the diagnosis and follow-up of gout: systematic analysis of the literature. *Clin Rheumatol* 2018;37:587–95.

7 Jans L, De Kock I, Herregods N, *et al*. Dual-energy CT: a new imaging modality for bone marrow oedema in rheumatoid arthritis. *Ann Rheum Dis* 2018;77:annrheumdis-2018-213152.

8 Diekhoff T, Scheel M, Hermann S, *et al*. Osteitis: a retrospective feasibility study comparing single-source dual-energy CT to MRI in selected patients with suspected acute gout. *Skeletal Radiol* 2017;46:185–90.

9 Ohno Y, Aoyagi K, Chen Q, *et al*. Comparison of computer-aided detection (CADe) capability for pulmonary nodules among standard-, reduced- and ultra-low-dose CTs with and without hybrid type iterative reconstruction technique. *Eur J Radiol* 2018;100:49–57.

10 Fukuda T, Umezawa Y, Tojo S. Initial experience of using dual-energy CT with an iodine overlay image for hand psoriatic arthritis: comparison study with contrast-enhanced mr Imaging. *Radiology* 2017;284:134–42.

11 Polster JM, Winalski CS, Sundaram M, *et al*. Rheumatoid arthritis: evaluation with contrast-enhanced CT with digital bone masking. *Radiology* 2009;252:225–31.

12 Glinatsi D, Bird P, Gandjbakhch F, *et al*. Development and validation of the OMERACT rheumatoid arthritis magnetic resonance tenosynovitis scoring system in a multireader exercise. *J Rheumatol* 2017;44:1688–93.

13 Seeliger E, Sendeski M, Rihal CS, *et al*. Contrast-induced kidney injury: mechanisms, risk factors, and prevention. *Eur Heart J* 2012;33:2007–15.

14 Noël PB, Engels S, Köhler T, *et al*. Evaluation of an iterative model-based CT reconstruction algorithm by intra-patient comparison of standard and ultra-low-dose examinations. *Acta Radiol* 2018;59:1225–31.

15 Lee SH, Yun SJ, Jo HH, *et al*. Diagnostic accuracy of low-dose versus ultra-low-dose CT for lumbar disc disease and facet joint osteoarthritis in patients with low back pain with MRI correlation. *Skeletal Radiol* 2018;47:491–504.

16 Runge VM. Critical questions regarding gadolinium deposition in the brain and body after injections of the gadolinium-based contrast agents, safety, and clinical recommendations in consideration of the EMA's pharmacovigilance and risk assessment committee recommendation for suspension of the marketing authorizations for 4 linear agents. *Invest Radiol* 2017;52:317–23.

17 Fukuda T, Umezawa Y, Asahina A, *et al*. Dual energy CT iodine map for delineating inflammation of inflammatory arthritis. *Eur Radiol* 2017;27:5034–.