

# EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis

Alexandra N Colebatch,<sup>1,2</sup> Christopher John Edwards,<sup>1</sup> Mikkel Østergaard,<sup>3</sup> Désirée van der Heijde,<sup>4</sup> Peter V Balint,<sup>5</sup> Maria-Antonietta D'Agostino,<sup>6</sup> Kristina Forslind,<sup>7,8</sup> Walter Grassi,<sup>9</sup> Espen A Haavardsholm,<sup>10</sup> Glenn Haugeberg,<sup>11</sup> Anne-Grethe Jurik,<sup>12</sup> Robert BM Landewé,<sup>13</sup> Esperanza Naredo,<sup>14</sup> Philip J O'Connor,<sup>15</sup> Ben Ostendorf,<sup>16</sup> Kristina Potočki,<sup>17</sup> Wolfgang A Schmidt,<sup>18</sup> Josef S Smolen,<sup>19</sup> Sekib Sokolovic,<sup>20</sup> Iain Watt,<sup>4</sup> Philip G Conaghan<sup>21</sup>

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For numbered affiliations see end of article.

## Correspondence to

Professor Philip G Conaghan, Division of Musculoskeletal Disease, Section of Musculoskeletal Disease, University of Leeds & NIHR Leeds Musculoskeletal Biomedical Research Unit, 2nd Floor Chapel Allerton Hospital, Chapeltown Road, Leeds LS7 4SA, UK; PConaghan@leeds.ac.uk

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## ABSTRACT

**Objective** To develop evidence-based recommendations on the use of imaging of the joints in the clinical management of rheumatoid arthritis (RA).

**Methods** The task force comprised an expert group of rheumatologists, radiologists, methodologists and experienced rheumatology practitioners from 13 countries. Thirteen key questions on the role of imaging in RA were generated using a process of discussion and consensus. Imaging modalities included were conventional radiography, ultrasound, MRI, CT, dual-emission x-ray absorptiometry, digital x-ray radiogrammetry, scintigraphy and positron emission tomography. Research evidence was searched systematically for each question using MEDLINE, EMBASE and Cochrane CENTRAL. The experts used the evidence obtained from the relevant studies to develop a set of 10 recommendations. The strength of recommendation was assessed using a visual analogue scale.

**Results** A total of 6888 references was identified from the search process, from which 199 studies were included in the systematic review. Ten recommendations were produced encompassing the role of imaging in making a diagnosis of RA, detecting inflammation and damage, predicting outcome and response to treatment, monitoring disease activity, progression and remission. The strength of recommendation for each proposition varied according to both the research evidence and expert opinion.

**Conclusions** Ten key recommendations for the role of imaging in the management of RA were developed using research-based evidence and expert opinion.

## INTRODUCTION

Structural damage in rheumatoid arthritis (RA) can occur early in the disease. Prompt treatment has been shown to reduce inflammation thereby limiting structural damage.<sup>1 2</sup> Although conventional radiography (CR) has been considered the gold standard for imaging in RA, its sensitivity for structural damage in RA diagnosis is low, and disease activity cannot be assessed.<sup>3</sup> Significant advances have been made within the field of imaging in rheumatic diseases over the past decade.<sup>4</sup>

A European League Against Rheumatism (EULAR) task force was therefore convened to develop evidence-based recommendations on the use of imaging of the joints in the clinical management of RA.

## METHODS

An expert group of rheumatologists, radiologists, methodologists and experienced rheumatology practitioners (19 people, representing 13 countries) participated in the study. The objectives were to formulate key clinical questions relating to the role of imaging in RA, to identify and critically appraise the available evidence, and to generate recommendations based on both evidence and expert opinion.

At the initial task force meeting, members contributed clinically relevant questions related to key aspects of the use of imaging in RA. The research questions were agreed by consensus and 13 final research questions were selected, which encompassed the role of imaging in making a diagnosis of RA, detecting inflammation and damage, predicting outcome and response to treatment, monitoring disease progression, and remission (see supplementary material, S1. Research questions, available online only).

A systematic search of articles was performed and the bibliographies of included papers were hand searched for evidence of other studies for inclusion. Specific medical subject headings and additional keywords were used to identify all relevant studies (see supplementary material, S2. Search strategy, available online only).

Titles and abstracts of all citations identified were screened, and potentially relevant articles were reviewed in full text using predetermined inclusion and exclusion criteria. Studies, published in English, on the use of imaging in adults ( $\geq 18$  years of age) with a clinical diagnosis of RA were included. Imaging modalities included were CR, ultrasound, MRI, CT, dual-emission x-ray absorptiometry (DXA), digital x-ray radiogrammetry (DXR), scintigraphy and positron emission tomography (PET). Study types included randomised controlled trials, systematic reviews,

controlled clinical trials, cohort, case-control and diagnostic studies. Studies were considered for inclusion when they provided information on the role of imaging in making a diagnosis of RA, detecting inflammation and damage, predicting outcome and response to treatment, monitoring disease progression and remission.

Following presentation of the data from the literature review, the experts produced 10 recommendations based on the 13 clinical questions with final agreement by a process of discussion and consensus. The experts scored the perceived strength of recommendation (SOR) for each proposition using a 0–10 visual analogue scale (VAS; 0=not recommended at all, 10=fully recommended). Scores reflected both research evidence and clinical expertise.<sup>5</sup>

Evidence was categorised according to study design using a hierarchy of evidence in descending order according to quality.<sup>6</sup> Greater emphasis was given to the best available evidence when answering questions, although all data were collected and reviewed.

Recommendations for future research were agreed by consensus following presentation of the literature review.

## RESULTS

The search of databases (performed in June 2011) resulted in 6888 records, of which 2567 were duplicates. Of the remaining 4321 articles, 3975 were excluded based on title or abstract, leaving 346 articles for detailed review. All full text articles written in English were retrieved for review; 175 articles were excluded after reviewing the full text leaving 171 articles for

inclusion (see supplementary figure S3, available online only). The hand search identified 28 additional articles for inclusion, resulting in a total of 199 articles for inclusion. Articles that were relevant to more than one research question were included in the review more than once. The number of articles included in each question is shown in supplementary table S4 (available online only).

Ten recommendations were produced, and the final wording of the propositions was adjusted using e-mail exchange and at the closing meeting of the group. The recommendations, SOR (mean VAS and 95% CI) and level of evidence are presented in table 1.<sup>5</sup> A full reference list for articles included in each recommendation is given in the supplementary material, S5 (available online only).

### Recommendations

#### Making a diagnosis of RA (in patients with at least one joint with definite clinical synovitis):

**Recommendation 1: When there is diagnostic doubt, CR, ultrasound or MRI can be used to improve the certainty of a diagnosis of RA above clinical criteria alone.**

Strength of recommendation: 9.1 (95% CI 8.6 to 9.6)

Five observational studies described the impact of imaging on confirming a diagnosis of RA when the diagnosis could not be confirmed using conventional methods, two with ultrasound and three with MRI. Three of these studies examined the hand joints (wrist, metacarpophalangeal and proximal interphalangeal joints), but none compared sites.<sup>7–11</sup> One study showed

**Table 1** Recommendations, SOR and level of evidence

Recommendation*	SOR, mean VAS0–10 (95% CI)	Level of evidence
1 When there is diagnostic doubt, CR, ultrasound or MRI can be used to improve the certainty of a diagnosis of RA above clinical criteria alone†	9.1 (8.6 to 9.6)	III
2 The presence of inflammation seen with ultrasound or MRI can be used to predict the progression to clinical RA from undifferentiated inflammatory arthritis	7.9 (6.7 to 9.0)	III
3 Ultrasound and MRI are superior to clinical examination in the detection of joint inflammation; these techniques should be considered for more accurate assessment of inflammation	8.7 (7.8 to 9.7)	III
4 CR of the hands and feet should be used as the initial imaging technique to detect damage. However, ultrasound and/or MRI should be considered if conventional radiographs do not show damage and may be used to detect damage at an earlier time point (especially in early RA)	9.0 (8.4 to 9.6)	IV
5 MRI bone oedema is a strong independent predictor of subsequent radiographic progression in early RA and should be considered for use as a prognostic indicator. Joint inflammation (synovitis) detected by MRI or ultrasound as well as joint damage detected by conventional radiographs, MRI or ultrasound can also be considered for the prediction of further joint damage	8.4 (7.7 to 9.2)	III
6 Inflammation seen on imaging may be more predictive of a therapeutic response than clinical features of disease activity; imaging may be used to predict response to treatment	7.8 (6.7 to 8.8)	III-IV
7 Given the improved detection of inflammation by MRI and ultrasound than by clinical examination, they may be useful in monitoring disease activity	8.3 (7.4 to 9.1)	III
8 The periodic evaluation of joint damage, usually by radiographs of the hands and feet, should be considered. MRI (and possibly ultrasound) is more responsive to change in joint damage and can be used to monitor disease progression	7.8 (6.8 to 8.9)	III
9 Monitoring of functional instability of the cervical spine by lateral radiograph obtained in flexion and neutral should be performed in patients with clinical suspicion of cervical involvement. When the radiograph is positive or specific neurological symptoms and signs are present, MRI should be performed	9.4 (8.9 to 9.8)	III
10 MRI and ultrasound can detect inflammation that predicts subsequent joint damage, even when clinical remission is present and can be used to assess persistent inflammation	8.8 (8.0 to 9.6)	III

\*Recommendations are based on data from imaging studies that have mainly focused on the hands (particularly wrists, metacarpophalangeal and proximal interphalangeal joints). There are few data with specific guidance on which joints to image.

†In patients with at least one joint with definite clinical synovitis, which is not better explained by another disease.

Categories of evidence: Ia, evidence for meta-analysis of randomised controlled trials; Ib, evidence from at least one randomised controlled trial; IIa, evidence from at least one controlled study without randomisation; IIb, evidence from at least one other type of quasi-experimental study; III, evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies; IV, evidence from expert committee reports or opinions or clinical experience of respected authorities, or both. CR, conventional radiography; RA, rheumatoid arthritis; SOR, strength of recommendation; VAS, visual analogue scale (0–10; 0=not recommended at all, 10=fully recommended).

## Recommendation

that ultrasound synovitis improved the certainty of RA diagnosis from 42.0% to 53.2% ( $p$  0.17),<sup>7</sup> and another described how synovitis seen with ultrasound helped confirm (65.2%) or change the diagnosis (11.1%); ultrasound was superior to clinical examination in 75% of patients.<sup>8</sup> Compared to clinical classification criteria, the demonstration of MRI synovitis increased the diagnosis of RA,<sup>9, 10</sup> and was more valuable than anti-cyclic citrullinated peptide antibody (ACPA) determination in the absence of rheumatoid factor (RF).<sup>11</sup>

**Recommendation 2: The presence of inflammation seen with ultrasound or MRI can be used to predict the progression to clinical RA from undifferentiated inflammatory arthritis.**

Strength of recommendation: 7.9 (95% CI 6.7 to 9.0)

Several studies assessed the prognostic value of imaging in patients with undifferentiated inflammatory arthritis (UIA), mainly using ultrasound or MRI. A recent systematic review identified 11 studies relating to MRI.<sup>12</sup> The presence of bone oedema or both synovitis and erosion on MRI increased the likelihood of developing RA (positive likelihood ratio 4.5 and 4.8, respectively), whereas the absence of MRI synovitis decreased the probability of progression to RA (negative likelihood ratio 0.2). A prediction model including clinical hand arthritis, morning stiffness, positivity for RF and bone oedema on MRI correctly predicted progression to RA in 82% of UIA patients.<sup>13</sup> MRI flexor tenosynovitis has also been described as a predictor of early RA (sensitivity 0.60, specificity 0.73).<sup>14</sup> Of the three strongest predictors of RA (MRI flexor tenosynovitis, RF and ACPA), ACPA was found to be the strongest predictor (OR 13.8) and flexor tenosynovitis the weakest (OR 5.0), but its additional value in diagnosing RA was significant.

In a longitudinal study ultrasound significantly increased the detection of joint involvement in all joint regions. When combined with the Leiden prediction rule,<sup>15</sup> power Doppler counts significantly improved area under the curve (AUC) values for the prediction of progression to RA (0.905 to 0.962).<sup>16</sup> Salaffi *et al*<sup>17</sup> described the likelihood of progression of UIA to RA using the presence of power Doppler on ultrasound (scores higher than grade 1), with OR 9.9 if one joint was involved, and 48.7 if more than three were involved; OR with high titre ACPA or RF was 10.9.

### Detecting inflammation and damage:

**Recommendation 3: Ultrasound and MRI are superior to clinical examination in the detection of joint inflammation; these techniques should be considered for a more accurate assessment of inflammation.**

Strength of recommendation: 8.7 (95% CI 7.8 to 9.7)

This recommendation examines the added benefit of assessing joint inflammation by imaging over clinical examination. Sensitivity and specificity were initially extracted from the data; however, as clinical examination was used as the reference these results are difficult to use clinically. To overcome this we recorded detection rates; for example, how many times more (>onefold) or less (<onefold) does imaging detect inflammation over clinical examination. Our chosen approach may increase the number of false positive results.

We identified 51 studies comparing imaging and clinical examination in the detection of inflammation in various joints; 29 with ultrasound,<sup>18–36</sup> 16 with MRI,<sup>21, 26, 29, 30, 37–44</sup> 14 with scintigraphy,<sup>41, 45–47</sup> and two with PET (table 2). In general,

ultrasound and MRI detected joint inflammation more frequently than clinical examination; the mean detection rate for synovitis at the hand and wrist was 2.18-fold for ultrasound and 2.20-fold for MRI.<sup>30</sup> Using scintigraphy and PET were found to provide little benefit over clinical examination.

**Recommendation 4: CR of the hands and feet should be used as the initial imaging technique to detect damage. However, ultrasound and/or MRI should be considered if CR do not show damage and may be used to detect damage at an earlier time point (especially in early RA).**

Strength of recommendation: 9.0 (95% CI 8.4 to 9.6)

Three studies compared tissue damage (erosions or loss of joint space) detected by imaging with abnormal clinical examination. Caution is needed when interpreting these studies as bony involvement shown on imaging was compared with clinical signs of inflammation as reference.

### Prognosis in RA: predicting outcome:

**Recommendation 5: MRI bone oedema is a strong independent predictor of subsequent radiographic progression in early RA and should be considered for use as a prognostic indicator. Joint inflammation (synovitis) detected by MRI or ultrasound as well as joint damage detected by CR, MRI or ultrasound can also be considered for the prediction of further joint damage.**

Strength of recommendation: 8.4 (95% CI 7.7 to 9.2)

Forty-eight longitudinal studies described how baseline changes in imaging predicted outcome, in particular erosive progression; 26 with MRI, 11 with ultrasound, 19 with CR, seven with DXA or DXR and three with scintigraphy. Of these, 46 studies examined the hands and 14 also included the feet; none compared the benefit of imaging different joints.

### Bone marrow oedema

Of baseline MRI features, bone marrow (BM) oedema was a strong, independent predictor of erosive progression. Hetland *et al*<sup>48, 49</sup> have provided compelling data supporting this association; baseline MRI BM oedema was the only independent predictor of radiographic change in their 2 and 5-year follow-up studies (coefficient 0.75,  $p < 0.001$ ; and coefficient 0.82,  $p < 0.001$ , respectively). Haavardsholm *et al*<sup>50</sup> also identified baseline MRI BM oedema (score  $> 2$  RAMRIS units) as an independent predictor of radiographic (OR 2.77, 95% CI 1.06 to 7.21) as well as MRI erosive progression (unstandardised  $\beta$ , B 0.21, 95% CI 0.08 to 0.34). This is supported by McQueen *et al*<sup>51</sup> who described BM oedema to be predictive of MRI erosive progression, OR 6.47,  $p < 0.001$ . This study also demonstrated that the development of radiological erosions at 1 year was highly unlikely in the absence of baseline MRI inflammatory changes (negative predictive value 0.92). Patients with erosive progression on CT also have higher baseline MRI BM oedema scores (relative risk (RR) of CT progression 3.8, 95% CI 1.5 to 9.3).<sup>52</sup>

### Synovitis

Baseline synovitis, detected by MRI or ultrasound, is a predictor of erosive progression. Dohn *et al*<sup>52</sup> reported the RR of CT erosive progression with baseline ultrasound grey-scale synovitis as 11.2, 95% CI 0.65 to 195.7,  $p$  0.1, baseline ultrasound power Doppler activity RR 7.6, 95% CI 0.91 to 63.2,  $p$  0.061, and baseline MRI synovitis RR 0.68, 95% CI 0.04 to 11.5,  $p$  0.79.<sup>52</sup> The predictive value of baseline ultrasound grey-

**Table 2** Recommendation 3: Summary of included studies comparing imaging and CE in the detection of joint inflammation

<b>Ultrasound</b> 29 studies, mean no. of subjects (range): 40.7 (6–100)		<b>MRI</b> 16 studies, mean no. of subjects (range): 47.3 (6–318)		<b>Scintigraphy</b> 14 studies, mean no. of subjects (range): 22.6 (8–38)	
<b>Ultrasound hand/wrist vs CE (article reference)</b>		<b>MRI hand/wrist vs CE (article reference)</b>		<b>Scintigraphy hand/wrist vs CE (article reference)</b>	
Synovitis <sup>18–24</sup>	Detection rate, mean (range) Ultrasound vs CE 2.18-fold (0.55–8.96-fold)	MRI synovitis, vs clinical synovitis <sup>21–24 37–40</sup>	Detection rate, mean (range) MRI vs CE 2.20-fold (0.58–5.43-fold) accuracy: 0.72	vs tenderness/swelling <sup>45 46</sup>	Detection rate, mean (range) Scintigraphy vs CE 1.19-fold Validity: 0.45 Coefficient of association: –0.16
		vs pain <sup>41</sup>	0.71-fold $\kappa$ : 0.36, p 0.009	vs tenderness <sup>41</sup>	0.70-fold $\kappa$ : 0.32, p 0.008
		vs swelling <sup>41</sup>	1.36-fold $\kappa$ : 0.60, p 0.019	vs swelling <sup>41</sup>	1.33-fold $\kappa$ : 0.64, p 0.023
		Correlation with DAS28 <sup>42</sup>	r 0.30–0.40 p < 0.01		
Tenosynovitis <sup>25</sup>	1.06-fold	Relative efficacy for tenosynovitis <sup>26</sup>	2.48–4.69		
Relative efficacy of Ultrasound at detecting any inflammation vs TJC <sup>26</sup>	0.61–1.33	Relative efficacy of MRI synovitis vs TJC <sup>26</sup>	3.03–3.86		
<b>Ultrasound foot/ankle vs CE</b>		<b>MRI foot/ankle vs CE</b>		<b>Scintigraphy feet vs CE</b>	
Effusion <sup>27 28</sup>	0.52–0.99-fold $\kappa$ : 0.04–0.16 % agreement: 71%			vs tenderness/swelling <sup>45</sup>	0.42-fold
Inflammation <sup>29</sup>	2.21-fold % agreement: 63%				
Synovitis <sup>30</sup>	0.87-fold	Synovitis <sup>29 30 40 43</sup>	1.71-fold (0.93–2.8-fold) % agreement: 45.5–71%		
Tenosynovitis <sup>30</sup>	0.58-fold	Tenosynovitis <sup>30</sup>	% agreement: 54.5–90.9%		
<b>Ultrasound knees vs CE</b>		<b>MRI knees vs CE</b>		<b>Scintigraphy knees vs histology</b>	
Baker’s cyst <sup>31–33</sup>	1.88-fold (1.17–2.5-fold)	Synovitis vs clinical synovitis <sup>44</sup>	1.6–3.15-fold	vs histology <sup>47</sup>	1.11-fold
Suprapatellar bursitis <sup>33</sup>	1.7-fold			Swelling vs histology <sup>47</sup>	0.72-fold
Effusion <sup>34</sup>	1.27-fold (1.17–1.4-fold)				
Synovitis vs clinical synovitis <sup>35 36</sup>	r 0.9, p 0.0001				
vs DAS28	Strong correlation, p 0.006				
vs SJC	Weak correlation, p 0.038				

CE, clinical examination; DAS28, disease activity score in 28 joints; TJC, tender joint count; SJC, swollen joint count.

## Recommendation

scale synovitis for MRI erosive progression performed better than MRI synovitis with positive likelihood ratios of 1.75 and 1.47, respectively, and accuracy of 70% and 62%, respectively.<sup>53</sup> Conaghan *et al*<sup>54</sup> described a close correlation between the degree of MRI synovitis and the number of new erosions, with the AUC for MRI synovitis the only significant predictor of erosive progression (AUC for MRI synovitis  $r$  0.420,  $p < 0.007$ ).

### Tenosynovitis

Baseline tenosynovitis on ultrasound appears to be predictive of erosive progression at 1 year (OR 7.18) and 3 years (OR 3.4).<sup>55</sup> This effect has not been seen with MRI tenosynovitis,<sup>56</sup> but baseline MRI tendinopathy has been shown to be predictive of tendon rupture at 1 year (OR 1.57,  $p$  0.02) and 6 years (OR 1.52,  $p$  0.03).<sup>57</sup>

### Erosions

Baseline erosions detected by various imaging techniques appear to be predictive of further erosions at 6 months; MRI erosions ( $\beta$  0.63,  $p < 0.001$ ), radiographic erosions ( $\beta$  0.68,  $p$  0.04), with ultrasound erosions less significant ( $\beta$  0.57,  $p$  0.07).<sup>58</sup> Several studies have reported that baseline MRI erosions are predictive of erosive progression,<sup>59–62</sup> and the absence of baseline MRI erosions predicts that radiographic or MRI erosions are unlikely (negative predictive value 1.0).<sup>61</sup> Baseline radiographic erosions independently predict further radiographic progression (at 3 years, OR 8.47; at 10 years, OR 5.64–18.1).<sup>63–65</sup> In addition, the baseline Larsen score is shown to predict an annual radiological progression rate greater than the median (OR 2.6, 95% CI 1.3 to 5.3).<sup>65</sup>

### Digital x-ray radiogrammetry/dual-emission x-ray absorptiometry

Early hand bone loss measured by change in estimated bone mineral density in the first year of disease by DXR appears to be an independent predictor of erosive progression, even up to 20 years.<sup>53–66–67</sup> Baseline femoral neck osteopenia or osteoporosis are also predictive of radiographic erosive progression.<sup>68</sup>

### Scintigraphy

Baseline inflammatory disease measured by scintigraphy appears to be associated with radiographic progression.<sup>69</sup> In addition, multiple regression analysis has demonstrated that progression of radiographic joint destruction was primarily predicted by <sup>99m</sup>Tc-IgG scintigraphy; joint swelling, ESR and IgM RF were not predictive. This suggests that scintigraphy may be superior to conventional clinical and laboratory measurements in the prediction of joint destruction.<sup>70</sup> However, when comparing scintigraphy to other baseline imaging predictors of progression, baseline MRI BM oedema score (Spearman's correlation,  $r$  0.67), MRI synovitis score ( $r$  0.57), and <sup>99m</sup>Tc-NC scintigraphy uptake ( $r$  0.45) were predictive of change in MRI erosion score from baseline to 2 years. In the multivariate analysis, the BM oedema score was the only baseline variable that predicted erosive progression (OR 4.2, 95% CI 1.3 to 13.8).<sup>71</sup>

### Prognosis in RA: Predicting response to treatment:

**Recommendation 6: Inflammation seen on imaging may be more predictive of a therapeutic response than clinical features of disease activity; imaging may be used to predict response to treatment.**

Strength of recommendation: 7.8 (95% CI 6.7 to 8.8)

Two prospective cohort studies have assessed the use of clinical measures and imaging to predict response to anti-tumour necrosis factor (TNF) therapy. Ellegaard *et al*<sup>72</sup> measured ultrasound Doppler activity and clinical parameters at baseline to predict which patients would benefit from treatment, assessed by treatment persistence at 1 year. They identified ultrasound Doppler activity to be the only baseline parameter to predict treatment persistence ( $p$  0.024); baseline clinical measures including tender and swollen joint counts, C-reactive protein, 28-joint disease activity score (DAS28) and health assessment questionnaire showed no significant association. Elzinga *et al*<sup>73</sup> used changes in PET uptake 2 weeks after treatment to predict future treatment response, according to DAS28. A significant correlation was seen between the changes in PET activity at 2 weeks and DAS28 at 14 and 22 weeks after treatment ( $r$  0.62,  $p < 0.05$ ;  $r$  0.65,  $p < 0.01$  respectively).

### Monitoring disease progression:

**Recommendation 7: Given the improved detection of inflammation by ultrasound and MRI than by clinical examination, they may be useful in monitoring disease activity.**

Strength of recommendation: 8.3 (95% CI 7.4 to 9.1)

No published data were identified that specifically addressed how imaging should be used to monitor RA disease activity. In the absence of this information, data were extracted on each factor separately.

### Comparison of the ability of imaging to detect inflammation

Several studies compared ultrasound and MRI in the detection of joint inflammation, with MRI considered the reference technique. There seems to be significant association between these modalities,<sup>23–24</sup> but aside from access to imaging, there may be advantages to using each technique in certain situations. For example, ultrasound has been shown to detect more joint and tendon sheath effusions than MRI,<sup>58</sup> whereas MRI appears to be more sensitive in identifying tenosynovitis.<sup>74</sup> Comparisons of conventional high-field MRI with dedicated, low-field extremity MRI have shown high agreement for synovitis, with lower agreement for BM oedema and tenosynovitis detected by low-field MRI, with high-field MRI as reference.<sup>75–76</sup> Low-field MRI without contrast also demonstrates poor sensitivity in the detection of synovitis, compared with power Doppler ultrasound.<sup>77</sup> Only one study compared scintigraphy with more modern imaging techniques, and showed strong correlation between uptake on scintigraphy and inflammatory changes seen on MRI.<sup>78</sup>

### Responsiveness to change in inflammation

Ultrasound and MRI appear to show good responsiveness to change. A study of responsiveness of MRI and ultrasound to change in inflammation with treatment has shown that MRI synovitis (standardised response mean (SRM)  $-0.79$  to  $-0.92$ ), MRI tenosynovitis (SRM  $-0.70$  to  $-1.02$ ) and BM oedema (SRM  $-1.05$ – $-1.24$ ) were responsive to change, but ultrasound inflammation (synovitis, tenosynovitis and effusion) was less responsive (SRM  $-0.37$ – $-0.54$ ).<sup>26</sup> A study by Haavardsholm *et al*<sup>79</sup> reported MRI to have a higher potential to detect change in wrist BM oedema than in synovitis over 1 year. The smallest detectable difference for a range of ultrasound measures including power Doppler was low in a large 1-year observational multiple-reader study of RA patients treated with anti-TNF agents, demonstrating both the reliability of this measure and the ability to detect individual-level important

change. At the group level, there were significant changes in all ultrasound synovial assessments in parallel with DAS28 changes.<sup>80</sup> When comparing the changes in power Doppler and grey-scale ultrasound activity with response to treatment, grey-scale ultrasound appears to perform better,<sup>81</sup> as does the addition of contrast enhancement.<sup>82</sup>

**Which joints to assess**

Only one study directly compared the assessment of inflammation by imaging different areas; Calisir *et al*<sup>40</sup> described MRI synovitis and BM oedema in the hands and feet of patients with early RA and found no significant difference in MRI inflammation in these regions.

**Recommendation 8: The periodic evaluation of joint damage, usually by radiographs of the hands and feet, should be considered. MRI (and possibly ultrasound) is more responsive to change in joint damage and can be used to monitor disease progression.**

Strength of recommendation: 7.8 (95% CI 6.8 to 8.9)

As for the previous recommendation, there were no specific data on the recommended frequency of imaging in the assessment of progressive joint damage.

**Comparison of the ability of imaging to detect damage**

Dohn *et al*<sup>52</sup> performed comparison studies of the ability of CR, CT, ultrasound and MRI to detect erosive damage.<sup>53 83</sup> With CT as the reference technique, CR was shown to have an accuracy of 81%, MRI of 89% and ultrasound of 80%, with high specificities and lowest sensitivity for CR.<sup>52 83</sup> A previous systematic review has described ultrasound to be more effective for erosion detection than CR, with comparable efficacy to MRI.<sup>84</sup> A summary of data comparing the different imaging modalities in the detection of erosions is given in table 3.<sup>24 26 29 39 43 52 58 75 76 83 85–102</sup>

Studies assessing tendon damage have shown ultrasound to be more sensitive than MRI in the detection of finger extensor tendon tears later confirmed at surgery;<sup>103</sup> and moderate agreement between ultrasound and MRI (used as the reference technique) in the assessment of shoulder tendon involvement.<sup>104</sup>

**Responsiveness to change in damage**

CR is the standard imaging technique used to detect and monitor joint damage. There are some data suggesting that CR

is responsive to change in erosions on an individual level, particularly after the first 12 months of disease.<sup>26</sup> Radiographic progression appears to be most rapid in the first 2 years of disease, with 75% of all damage seen in the first 5 years of a 10-year study.<sup>105</sup> MRI seems to be more responsive to change at earlier time points, but measures of annual progression rates are similar with MRI and CR.<sup>26</sup> This is supported by Østergaard *et al*,<sup>106</sup> who found that 78% of new radiographic bone erosions were seen at least 1 year earlier by MRI, in fact MRI detection of new erosions preceded CR by a median of 2 years.

**Which joints to assess**

Early erosive changes on CR appear to be more common in the feet than in the hands, but from year 3 onwards these areas are more equally affected.<sup>105 107</sup>

**Recommendation 9: Monitoring of functional instability of the cervical spine by lateral radiograph obtained in flexion and neutral should be performed in patients with clinical suspicion of cervical involvement. When the radiograph is positive or specific neurological symptoms and signs are present, MRI should be performed.**

Strength of recommendation: 9.4 (95% CI 8.9 to 9.8)

Thirteen studies described the assessment of cervical spine involvement in RA, summarised in table 4.<sup>108–120</sup> No studies explored the appropriate frequency for monitoring change in the cervical spine; Yurube *et al*<sup>118</sup> investigated baseline features on CR predictive of future cervical instability and found that patients with baseline deforming hand changes, cervical vertical subluxation (VS), and subaxial subluxation showed more progression in VS and subaxial subluxation at 5 years, and Reijnierse *et al*<sup>120</sup> identified that baseline MRI atlas erosions and reduced subarachnoid space were associated with clinical neurological dysfunction at 1 year.

Comparison studies of different imaging modalities of the cervical spine have shown variation in the detection of the different pathologies, according to the imaging technique used. Fezoulidis *et al*<sup>108</sup> found CR and CT to be comparable and better than MRI in detecting atlanto-axial and atlanto-occipital lesions, but MRI to be superior in identifying odontoid lesions. MRI also seems to be better at showing erosions of the dens.<sup>117</sup>

Independent of the imaging modality used, dynamic lateral views of the cervical spine are more useful than static, neutral views in detecting atlanto-axial subluxation (AAS), in particular

**Table 3** Recommendation 8: Summary of included studies comparing imaging in the detection of erosions

Comparator vs reference technique (article reference)	Sensitivity	Specificity	Accuracy	κ	Detection rate, mean (range)
<b>Hand/wrist erosions:</b>					
MRI vs CT <sup>52 83 85–87</sup>	0.61–0.68	0.92–0.96	0.77–0.89	0.63	0.71-fold (0.60–0.81-fold)
Ultrasound vs CT <sup>52 83</sup>	0.42–0.44	0.91–0.95	0.80–0.84	0.44	
CR vs CT <sup>52 83 85–88</sup>	0.14–0.54	0.92–1.0	0.63–0.81	0.29	0.34-fold (0.16–0.60-fold)
CR vs MRI <sup>24 26 39 58 75 89 90–100</sup>	0.0–0.55	0.5–1.0	0.23–0.92		0.38-fold (0.06–0.80-fold)
CR vs ultrasound <sup>24 58 97–101</sup>	0.48	1.0			0.60-fold (0.18–1.21-fold)
Ultrasound vs MRI <sup>24 58 97–100</sup>	0.33–0.87	0.68–1.0	correlation coefficient 0.68–0.9	p<0.0005–<0.001	0.77-fold (0.35–1.51-fold)
Low vs high-field MRI <sup>75 76 91 95</sup>	0.46–0.94	0.93–0.94	0.55–0.94		0.94-fold (0.46–1.16-fold)
<b>Feet erosions:</b>					
CR vs MRI <sup>29 43</sup>	0.32–0.80	0.85–0.98		0.65 p 0.002	1.19-fold (0.55–1.83-fold)
CR vs ultrasound <sup>29 102</sup>					0.53-fold (0.42–0.64-fold)
Ultrasound vs MRI <sup>29</sup>	0.79	0.97	0.96		1.3-fold

CR, conventional radiography.

**Table 4** Recommendation 9: Summary of included studies comparing imaging in the assessment of the cervical spine

Article year, (reference)	No. of subjects	Cervical spine imaging modality	Parameter assessed	Outcome
1989 <sup>108</sup>	55	CR (AP, lateral F/E, OM) MRI CT	Atlanto-axial lesions Atlanto-occipital lesions Odontoid lesions Odontoid fibro-ostosis	Atlanto-axial lesions: CR = CT > MRI Atlanto-occipital lesions: CR = CT > MRI Odontoid lesions: MRI > CR/CT Odontoid fibro-ostosis: CR = CT > MRI
2000 <sup>109</sup>	5 known AAS	CR (F/E) MRI (F/E)	AAS	More detail seen with MRI, and using F/E views
2005 <sup>110</sup>	31	CR (F/E) MRI (F/E)	ADI Dense erosions	CR showed greater ADI in flexion than MRI, p 0.001 No significant difference in neutral/extension Assessment of dens erosions easier with MRI
1998 <sup>111</sup>	65 unstable AAS	CR (lateral N/F/E)	AAS	Significant difference between AAS in neutral and flexion/extension, p<0.0001
1998 <sup>112</sup>	28 symptomatic	CR (AP, lateral N/F, OM) MRI CT	AAS Odontoid erosions/cysts	Combination on MRI with CR showed more involvement than CT with CR (1.25-fold more VS; 1.13-fold more erosions/cysts)
2000 <sup>113</sup>	42 symptomatic	MRI (N/F)	Reduction in subarachnoid space Brainstem compression	Flexion views showed more: brainstem compression (1.17-fold) reduction in the subarachnoid space at the atlanto-axial level (1.06-fold) and below C2 (1.13-fold)
2000 <sup>114</sup>	25	CR (AP, lateral F/E, OM)	Odontoid erosions	Lateral views showed more erosions (1.57-fold) than open mouth views
2011 <sup>115</sup>	56 symptomatic	CR (lateral) CT	CT factors predictive of VS on CR	VS greater in presence of odontoid erosions, p<0.05 Odontoid erosions significantly associated with odontoid osteoporosis, p<0.05
1995 <sup>116</sup>	136 symptomatic	CR (AP, lateral F/E) MRI	MRI findings in normal CR	All MRI abnormal with normal CR: Effusion: 28% Pannus: 62%
2009 <sup>117</sup>	40	CR (lateralN/ F/E, OM) MRI (N/F/E) CT	AAS Dens erosions	% patients with C-spine involvement on: CR 47.5%, MRI 70%, CT 28.2% Anterior AAS seen more in flexion on CR than MRI, p<0.005 CT best at detecting lateral AAS Dens erosions: CR 12.5%, MRI 67.5%, CT 41%
2011 <sup>118</sup>	267	CR (lateral N/F/E)	Baseline features predictive of VS and SAS at 5 years	Prediction of VS: AAS, p 0.01; VS, p<0.01; SAS, p 0.06 Prediction of SAS: AAS, p 0.29; VS, p<0.01; SAS, p<0.01
1987 <sup>119</sup>	18 symptomatic	CR (AP, lateral F/E) MRI	AAS CS SAS Dens erosions	MRI vs CR: AAS: 0.88-fold CS: 1.0-fold SAS: 0.5-fold Dens erosions: 1.27-fold
2001 <sup>120</sup>	46 symptomatic	CR (lateral N/F, OM) MRI	Baseline CR and MRI features predictive of clinical neurological dysfunction at 1 year	CR not predictive (odontoid erosions, AAS) Dysfunction according to MRI (OR): Dens erosion: 1.5; atlas erosion: 4.9 Decreased subarachnoid space: 12.0 Decreased atlanto-axial space: 2.4 Brainstem compression: 2.3

AAS, atlantoaxial subluxation; ADI, atlanto-dental interval; AP, anteroposterior; CR, conventional radiography; CS, craniocervical settling; E, extension; F, flexion; N, neutral; OM, open mouth; SAS, subaxial subluxations; VS, vertical subluxations.

anterior AAS.<sup>111</sup> Flexion and neutral views are used commonly, with evidence to suggest greater change in the atlanto-dental interval with these views.<sup>110</sup> The open mouth view is used for imaging the odontoid peg and to assess for lateral and rotatory AAS; whereas posterior AAS can be measured with neutral and extension views, and VS with a lateral neutral view, although these types of AAS are much less common than anterior AAS.<sup>117</sup> When using CR to assess odontoid erosions, lateral cervical spine views appear to be more sensitive than open mouth views.<sup>114</sup>

#### Imaging in clinical remission:

**Recommendation 10: Ultrasound and MRI can detect inflammation that predicts subsequent joint damage, even when clinical remission is present and can be used to assess persistent inflammation.**

Strength of recommendation: 8.8 (95% CI 8.0 to 9.6)

The role of imaging in the detection of inflammation and subsequent prediction of outcome has been discussed previously (recommendation 5). There is good evidence to support the disparity between clinical remission and evidence of ongoing inflammation seen with various imaging modalities. Power Doppler activity has been found in 15–62% of patients in clinical remission according to DAS28, American College of Rheumatology or simplified disease activity index remission criteria,<sup>121–124</sup> MRI synovitis in 96% and BM oedema in 52%.<sup>124 125</sup> In one study, 60% of patients in disease activity score remission had increased uptake on scintigraphy.<sup>126</sup>

The significance of persistent inflammation, shown in a number of studies, is summarised in table 5.<sup>127–133</sup> The presence of ultrasound synovial hypertrophy, power Doppler activity and MRI synovitis at baseline in clinical remission has been shown to be significantly associated with structural progression at 1 year, even in asymptomatic joints.<sup>127</sup> Baseline ultrasound

**Table 5** Recommendation 10: Summary of included studies describing outcome in the presence of image-detected inflammation in clinical remission

Article year (reference)	No. of subjects	Duration of follow-up (months)	Baseline assessment modality	Outcome parameter assessed	Results
2008 <sup>127</sup>	102	12	Ultrasound SH, PD synovitis	CR progression (Genant score)	SH: OR 2.31, p 0.032 PD synovitis: OR 12.21, p<0.001 OR 2.98, p 0.002
2011 <sup>128</sup>	94	12	MRI synovitis Ultrasound SH, PD synovitis, remissions (no SH or PD synovitis)	Relapse rate	% patients having flare: in ultrasound remission: 20.0% With ultrasound PD activity: 47.1%, p 0.009
2009 <sup>129</sup>	106	24	Ultrasound joint count, PD synovitis	Relapse rate	Unsustained remission vs sustained remission: higher PD: OR 12.8, p<0.05 Higher ultrasound joint count: OR 4.6, p<0.05
2005 <sup>130</sup>	32	12	Ultrasound RI	Relapse rate	Relapse rate higher with low RI se 0.80, sp 1.0, acc 0.96, p<0.01
2007 <sup>131</sup>	169	24	Sustained ACR/DAS remission	CR progression (Larsen score)	Increase in Larsen score in (unsustained vs sustained): ACR remission: p 0.017 DAS remission: p<0.001
2004 <sup>132</sup>	187	24	Sustained ACR/DAS remission	CR progression (SHS)	Increase in SHS score in (unsustained vs sustained): ACR remission: p 0.053 DAS remission: p 0.017
2012 <sup>133</sup>	535	24	Remission according to DAS, SDAI, CDAI, ACR/EULAR	CR progression (SHS)	% patients with CR progression with baseline remission: DAS: 30% SDAI: 24% CDAI: 19% ACR/EULAR: 20%

ACR, American College of Rheumatology; CDAI, clinical disease activity index; CR, conventional radiography; DAS, disease activity score; EULAR, European League Against Rheumatism; PD, power Doppler; RI, resistive index; SDAI, simplified disease activity index; SH, synovial hypertrophy; SHS, Sharp/van der Heijde score.

inflammatory activity in clinical remission also seems predictive of future disease flare, with 20% of patients experiencing a flare within 12 months in the absence of baseline ultrasound power Doppler activity, compared with 47% in patients with baseline power Doppler activity (p 0.009).<sup>128</sup> Although radiographic progression can still be seen in clinical remission, individuals with sustained clinical remission show fewer signs of structural progression compared with patients with clinically relapsing disease.<sup>131–133</sup>

### Future research agenda

The most important topics for future research according to currently available evidence and clinical practice were formulated by the group, shown in table 6.

**Table 6** Future research agenda

Research agenda
1 Further evaluation of the specific joints to be assessed, timing of assessment(s) and the evaluation system to be employed in order to optimise the role of modern imaging modalities in diagnosis, prognosis and outcome measurement of RA
2 To assess algorithms using established and modern imaging modalities to examine their cost-effectiveness in clinical practice diagnosis, prognosis and outcome measurement of RA
3 To elucidate further the importance of subclinical (imaging-alone detected) inflammation, including synovitis, bone marrow oedema and tenosynovitis, especially in low disease activity states and to define key thresholds to guide intervention
4 To assess further the importance of imaging, in particular MRI and ultrasound, in the evaluation of damage, including joint space narrowing and cartilage loss
5 Assessing the feasibility, costs and appropriate training required to use ultrasound and MRI in clinical practice

RA, rheumatoid arthritis.

### DISCUSSION

These are the first recommendations produced by a EULAR task force on imaging in RA clinical practice. The recommendations were developed by an international group of experts with detailed literature review, and aimed to address clinical questions relevant to current practice. We acknowledge there is still a large amount of research required to optimise the use of imaging tools in routine clinical practice, in particular which joints should be used for disease assessment and monitoring and consideration of the feasibility, costs and appropriate training required to use ultrasound and MRI in clinical practice. In view of a lack of literature at the time of the review, these recommendations have not focused on detecting joint space narrowing, which is important to consider in view of the impact on functional status.<sup>134</sup> We have made specific reference to this in our proposed future research agenda.

In summary, we have developed 10 recommendations on various aspects of imaging in RA. These are based on the best available evidence and clinical expertise supported by an international panel of experts. We aimed to produce recommendations that are practical and valuable to clinical practice.

### Author affiliations

<sup>1</sup>Department of Rheumatology, University Hospital Southampton, Southampton, UK

<sup>2</sup>Department of Rheumatology, Yeovil District Hospital, Yeovil, UK

<sup>3</sup>Copenhagen Center for Arthritis Research, Center of Rheumatology and Spine Diseases, Copenhagen University Hospital at Glostrup, Copenhagen, Denmark

<sup>4</sup>Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands

<sup>5</sup>3rd Department of Rheumatology, National Institute of Rheumatology and Physiotherapy, Budapest, Hungary

<sup>6</sup>Department of Rheumatology, Ambroise Paré Hospital, Boulogne-Billancourt, France

<sup>7</sup>Department of Medicine, Section of Rheumatology, Helsingborg Hospital, Helsingborg, Sweden

<sup>8</sup>Section of Rheumatology, Institution of Clinical Science, University Hospital, Lund, Sweden

<sup>9</sup>Department of Rheumatology, Università Politecnica delle Marche, Ancona, Italy

<sup>10</sup>Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway

- <sup>11</sup>Department of Rheumatology, Hospital of Southern Norway, Kristiansand, Norway  
<sup>12</sup>Department of Radiology, Aarhus University Hospital, Aarhus, Denmark  
<sup>13</sup>Department of Clinical immunology and Rheumatology, Academic Medical Centre, Amsterdam, The Netherlands  
<sup>14</sup>Rheumatology Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain  
<sup>15</sup>Department of Radiology, Leeds General Infirmary, Leeds, UK  
<sup>16</sup>Centre for Rheumatology, Heinrich-Heine University of Düsseldorf, Düsseldorf, Germany  
<sup>17</sup>Institute of Diagnostic and Interventional Radiology, University Hospital Center Zagreb, Zagreb, Croatia  
<sup>18</sup>Immanuel Krankenhaus Berlin, Medical Centre for Rheumatology Berlin-Buch, Berlin, Germany  
<sup>19</sup>Institute of Rheumatology, Medical University of Vienna, Vienna, Austria  
<sup>20</sup>Rheumatology Department, Clinic of Heart and Rheumatic Diseases, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina  
<sup>21</sup>Division of Musculoskeletal Disease, Section of Musculoskeletal Disease, University of Leeds & NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK

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