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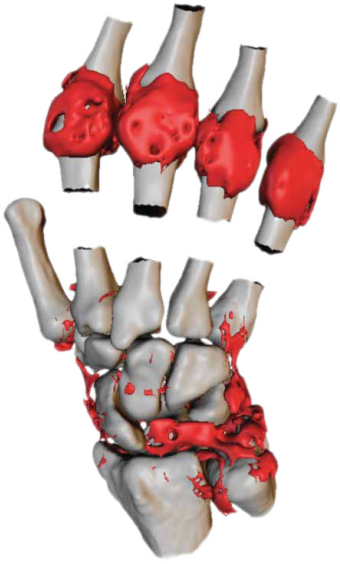

White Paper:

An Overview of RAMRIQ:

An Automated MRI Rheumatoid Arthritis Quantitative Assessment System

At left: Volume of synovitis in the hand and wrist. Areas of enhancement (shown in red) on MRI images using Gd-contrast indicate synovitis at the the MCP and wrist joints

In the study of Rheumatoid Arthritis (RA), imaging techniques have played an important role in the understanding and assessment of disease progression and treatment response. Traditionally RA has been assessed using radiographic or x-ray images. However, only late stage structural joint damages can be visualised in these images.

Imaging in RA

The measurement of structural changes, as opposed to clinical changes, in subjects with rheumatoid arthritis (RA) is based on radiological imaging. Early intervention with effective DMARDs in patients presenting with inflammation due to RA means that x-rays are increasing irrelevant in diagnosis and the tracking of disease progression since significant joint narrowing and erosions are often not seen. This problem can be addressed by using MR imaging with its excellent soft tissue contrast.

MRI in the Assessment of RA

For the measurement of synovial inflammation and structural joint damage in rheumatoid arthritis clinical trials, MRI measures provide improved sensitivity versus conventional radiography[1]. Furthermore, MRI is able to detect inflammatory activity such as bone marrow oedema and synovitis, both markers of bone pathology and future bone damage. The validated, semi-quantitative assessment of multiple pathologies using the Outcome Measures in Rheumatology Clinical Trials (OMERACT) RA MRI score (RAMRIS)[2] evaluates bone erosions, synovitis, and bone edema and is increasingly being used as an outcome measure in clinical trials.

The RAMRIS evaluation is performed using MR images of the hand by expert readers who produce semi-quantitative scores for each of the measures of pathology in the MCP and wrist joints and then assign a score to each joint (0-3 for synovitis and oedema, 0-11 for erosion)[3]. In order to assess synovitis, gadolinium (Gd)-based contrast agent is injected intravenously. Recently the OMERACT RAMRIS group have introduced the use of joint space narrowing as a fourth semi-quantitative measure[4].

Development of RAMRIQ

Sufficient reproducibility is a prerequisite feature for any scoring method to be considered of clinical value. It has been demonstrated that the OMERACT RAMRIS system can exhibit good and very good intra-reader reliability for assessment of status as well as scoring of change, when carried out by trained, calibrated readers[2]. However, fully automated, quantitative MRI measures offer the opportunity to improve on the responsiveness of semi-quantitative scoring further, and should be more rapid and more scalable than finding numerous expert readers.

Automation

With the development of the Rheumatoid Arthritis MRI Quantification (RAMRIQ) system, Imorphics set out to duplicate the measures and anatomical constructs recommended by OMERACT RAMRIS with a system of automated measurements. The construct validity of each of the component measures has been widely validated by a number of groups and we believe that these are good constructs to measure, that have clear associations with the disease. The aim of developing the RAMRIQ system was to produce fully quantitative versions of the same constructs.

Underlying Technology

To provide automated image analysis, the RAMRIQ system makes use of Active Appearance Models (AAMs)[5]. AAMs and Active Shape Models (ASMs)[6] have proved to be amongst the most successful approaches to medical image segmentation with over 6,000 citations for the original ASM paper. The underlying idea is to use a set of examples that represent the statistical variability of an object's shape and appearance to train a deformable model. This model can be altered in shape and appearance to best match a new, unseen example of the object, but only within the limits of what was previously learnt. This prevents the model from taking up implausible shapes when representing an object. Figure 1 illustrates how a 3D AAM is used to segment the bones of the hand and define regions of interest for the accurate measurement of synovial enhancement.

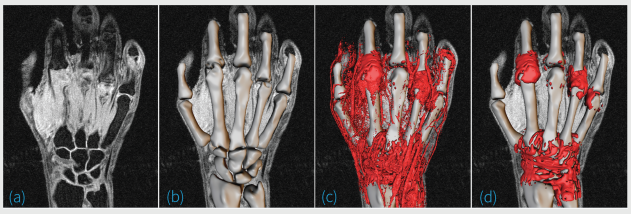

Figure 1: Using AAM to automatically identify bone and soft tissue, and generate regions of interest

Figure (a) shows a single slice in a typical T2-TSE image. The 3D image is searched using an active appearance model (AAM), which generates bone surfaces for all the bones in the hand (b). Figure (c) shows all of the areas containing contrast agent before regions of interest have been applied. AAMs are then used to apply anatomical masks which correspond to the synovial capsule of each joint. These 3D regions of interest are then examined for voxels which enhance.

RAMRIQ Measures

The quantitative measures computed from RAMRIQ are designed to parallel those of the RAMRIS scoring system. They are set out below, with a short description of the measurement and how it is calculated.

1. Quantitative Analysis of Synovitis Volume

This measure calculates the volume which is enhanced by Gadolinium in the region around the hand and wrist joints in which hypertrophy of the synovium may occur. This is achieved by fitting a bone model to each image; this process also creates a 3-dimensional mask around each joint. This mask is chosen carefully to exclude gadolinium enhancement in the tendon sheaths (tenosynovitis) and blood vessels.

Difference images for the images without and without Gadolinium are created, and the volume within the mask area which is enhanced by each joint is calculated. The joints used are analogous to those of the RAMRIS system (MCP joints 2 to 5, wrist, radius-carpal and radius-ulna), allowing direct comparison with the RAMRIS scores.

2. Quantitative Analysis of Joint Space Width

This measure calculates the distance in 3-dimensional space between two bones. This is achieved by fitting bone models to each bone, and then calculating a series of measurements across the joint space. This can be expressed as a mean distance, or in more complex ways.

This measure is slightly different in nature to the joint space width used within the RAMRIS system, which deals with joints which break down almost completely. The 3D measure is most meaningful for those joints which are still recognisable as joints (i.e. have both surfaces covered by cartilage, fairly normal ligaments and capsule, with minor erosions). Any change in joint space width is likely to be a result of loss of cartilage, or possibly loss of fluid or tightening of the capsule.

The joints used are identical to those of the RAMRIS system (MCP joints 2 to 5, and all carpel joints), allowing direct comparison with the RAMRIS scores.

3. Quantitative Analysis of Bone Erosions
This measure calculates the volume of eroded bone, after fitting a bone model to each bone in the hand and wrist. The bone model which is fitted to each bone is built from non-diseased subjects, or bones which are close to normal shape. They therefore provide a good approximation of the shape of the subject's original bone before disease. Total healthy bone is reported, along with the percentage of bone lost from the estimate of normal bone.

The bones used are identical to those of the RAMRIS system (15mm each side of the MCP joins 2 to 5, whole wrist bones, distal radius to a depth of 15mm and distal ulna to a depth of 15mm), allowing direct comparison with the RAMRIS scores.

Note: this measure cannot be used on the wrist MR images of some patients, where the carpal bones appear to fuse together. In studies of mild to moderate disease these patients usually form less than 10% of the population, in early RA (as in this study) they are less common. In the RAMRIS system these are scored as '10'.

4. Quantitative Analysis of Bone Marrow Oedema
This measures the volume of bone in the T2 or STIR images which have a higher intensity than normal bone might be expected to exhibit. As with the previous 3 measures, the bone area is identified using a statistical shape model, and the volume of bone inside the shape which exhibits a high signal is calculated.

Again, the bones used are identical to those of the RAMRIS system (15mm each side of the MCP joins 2 to 5, whole wrist bones, distal radius to a depth of 15mm and distal ulna to a depth of 15mm), allowing direct comparison with the RAMRIS scores.

5. Quantitative Analysis of Tenosynovitis
The semi-quantitative assessment of tenosynovitis has been suggested as an addition to he standard set of RAMRIS scores. Therefore, we have more recently extended the statistical shape model which identifies synovitis of the joints to automatically identify the tendons in the hand, and measure volume in the region around each tendon. This method measures Gd enhancement around the wrist flexor tendons within the common synovial sheath, see Figure 2.

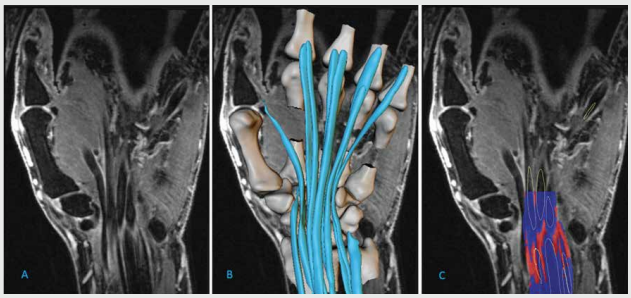

Figure 2 – Using appearance models to automatically identify bone, and generate 3D regions of interest.

Figure A shows a single slice in a typical post-contrast VIBE image from this study. The 3D image is searched using an active appearance model (AAM), which generates surfaces for all the bones and flexor tendons in the hand (B). C shows the areas which enhance in the 3D region of interest around the flexor tendons in the ulnar bursa group of flexor tendons (enhanced voxels coloured red, region of interest coloured blue)

RAMRIS+

We can also include the thumb and first row of PIP joints (sometimes called RAMRIS* or RAMRIS+). We have found however that it can be difficult in some centres to obtain good images which contain all of the standard RAMRIS joints at the same time as the thumb and PIP joints.

If the imaging protocol correctly visualises these joints, we can include them in the analysis.

Validation of RAMRIQ

Previous work during the development of RAMRIQ in an open label study with a single cycle of rituximab has suggested improved responsiveness over RAMRIS[7]. A more recent study has demonstrated good concordance between results obtained using RAMRIS and RAMRIQ in the same patient population treated with tofacitinib plus methotrexate (MTX), tofacitinib monotherapy and MTX monotherapy[8].

All measures were analysed blind to time order, adding to the robustness of the evaluation. The improved differentiation of tofacitinib groups from MTX monotherapy enabled by the RAMRIQ quantitative MRI system compared with the semiquantitative RAMRIS method further validates its use as improved tool for outcome assessment, see Figure 3.

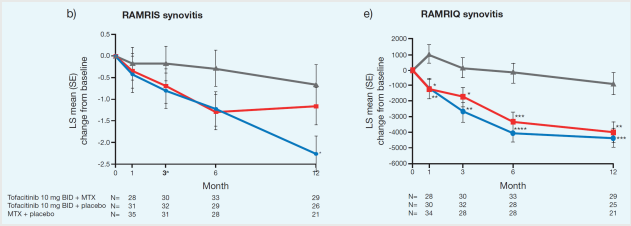

Figure 3: Least squares (LS) mean change from baseline in wrist and metacarpophalangeal (MCP) joints

(b) RAMRIS synovitis, (e) RAMRIQ synovitis, (evaluable set). *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 vs methotrexate (MTX) monotherapy, using a mixed-effect model for repeated measures. MRI measurements were based on one hand (most symptomatic at baseline). RAMRIS and RAMRIQ scores relate to MRIs of the index hand (MCP joints 1–5 and 2–5, respectively) and wrist. BID, twice daily.

A Note on Accuracy and Reproducibility

For RAMRIQ, only those acquisition sequences which support the standard RAMRIS system are required. These were originally chosen to be easily acquired at any clinical imaging facility. The required images include T1 high resolution 3D images with fat-saturation or water-excitation, both pre- and post-Gadolinium contrast; and either T2 or STIR images.

We strongly prefer the use of a knee coil to image the whole hand, as this improves image quality across the whole hand.

MRI Image Acquisition Requirements

In the academic literature regarding RAMRIS and radiographic scoring, the most widely used method to calculate repeatability is the smallest detectable change (SDC). In this method, it is not the difference in raw scores for a read-reread that is calculated, but instead the change found by reader 1 on a pair of images is compared with reader 2 on the same pair of images. This is not a meaningful test for an automated system, as the computer finds exactly the same answer on each image however many times it is run.

To test the repeatability of software it is necessary to run a genuine double baseline image (repeat the image within a few hours, or within a day). This is not a common procedure and we do not have access to a large number of patients for whom this has been this done.

Study Results

We have performed a study on 9 who subjects were imaged twice at baseline (separated by one week), to perform repeatability tests. One baseline image and one 3 or 6 month image from each patient were assessed using manual segmentation. We calculated accuracy, the RMS Coefficient of Variation (CoV), and the smallest detectable difference (SDD) which is calculated as 1.96 x standard deviation of the change. Results showed good accuracy and reproducibility:

- The bone search (from which all of our measures hangs) is very repeatable and accurate with a mean point-to-surface accuracy of 0.27 mm, or about half a pixel.
- Repeatability of erosion measurement expressed as CoV was 1.6%, and SDD for the method was 2.5%

The CoV of the JSW measurement was 8.8% and the SDD was 0.188 mm approximately half a pixel.

Conclusion

The use of MR images with OMERACT RAMRIS scoring is already changing the way that DMARD clinical trial image data is analysed by offering analysis of soft tissue changes and inflammation compared to radiographic scoring. By developing RAMRIQ, a quantitative analogue of the RAMRIS scoring method, Imorphics can offer improved sensitivity as well as a reduction of the time taken to produce analysis compared with the RAMRIS method due to its automation.

In addition, the continuous variables produced provide for the employment of more powerful statistical techniques than those that are used with the categorical scoring of RAMRIS. For these reasons, RAMRIQ is already being employed in numerous retrospective and prospective studies of clinical trial image data.

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Contact Us.

Email. info@imorphics.com
Twitter: @imorphics
LinkedIn: imorphics Ltd

Worthington House,
Towers Business Park,
Manchester, M20 2HJ

For more information please visit
www.imorphics.com