Overview of Current Imaging as Applied to OA Diagnostics and Clinical Studies:

What Methods are Currently Used and What are the Limitations?

Frank W. Roemer, M.D.

Overview

- Radiography
- MRI
- Ultrasound
- CT
- Others
- Relevance
- Summary
Disclosure

- CMO and shareholder of Boston Imaging Core Lab, LLC
- Consultant to Merck Serono, NIH
Radiography

- First line diagnostic imaging tool in a clinical setting
- Most of the time sufficient for clinical diagnostic purposes
- X-ray detected joint space narrowing only accepted imaging endpoint in clinical phase III trials (EMEA/FDA)
- Important for inclusion into clinical trials and subject stratification

Radiographic OA assessment

- Semiquantitative assessment (K/L grading and OARSI Atlas)
- Joint space width measurement: manual/semi-automated/automated
- JSW only indirect surrogate of cartilage and meniscal damage and extrusion \(^1,2,3\)

---

Semiquantitative Xray assessment - Kellgren Lawrence Grading: composite score

Grade 0: no feature of OA
Grade 1: Doubtful JSN and possible osteophytic lipping
Grade 2: **Definite osteophytes** and possible JSN
Grade 3: Moderate multiple osteophytes, **definite JSN**, and some sclerosis and possible deformity of bone ends
Grade 4: Large osteophytes, marked JSN, severe sclerosis, and definite deformity of bone ends


Definition Radiography

Images courtesy of Richard Frobell, KANON Trial
Semiquantitative Xray assessment -
OARSI Grading: Atlas-based

- Medial femoral osteophyte: 0-3
- Medial tibial osteophyte: 0-3
- Lateral femoral osteophyte: 0-3
- Lateral tibial osteophyte: 0-3
- Medial tibio-femoral JSN: 0-3
- Lateral tibio-femoral JSN: 0-3


Methods - Radiography

Atlas-based assessment

Longitudinal within-grade change

sensitivity to change?
No longitudinal joint space narrowing
an indirect marker of cartilage integrity?

X-ray non-sensitive

Longitudinal joint space narrowing
an indirect marker of cartilage loss?

X-ray non-specific

Methods - Radiography
**Radiographic OA assessment:**  

<table>
<thead>
<tr>
<th>MRI Predictor</th>
<th>Progression of JSN</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of features worsening</td>
<td>Absence</td>
<td>Presence</td>
</tr>
<tr>
<td>No worsening of all 3 features</td>
<td>366 (69.2%)</td>
<td>18 (3.4%)</td>
</tr>
<tr>
<td>Worsening of 1 feature</td>
<td>85 (16.1%)</td>
<td>27 (5.1%)</td>
</tr>
<tr>
<td>Worsening of 2 features</td>
<td>10 (1.9%)</td>
<td>11 (2.1%)</td>
</tr>
<tr>
<td>Worsening of 3 features</td>
<td>2 (0.4%)</td>
<td>9 (1.7%)</td>
</tr>
</tbody>
</table>


**Minimum joint space width**

Software automatically delineates joint margins and determines mJSW


Digital Tomosynthesis

### Methods - Radiography

#### Prevalence, Sensitivity, and Specificity

<table>
<thead>
<tr>
<th>Compartments</th>
<th>Prevalence</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>X-ray</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lat Fem</td>
<td>35 (44)</td>
<td>0.73</td>
<td>1.00</td>
</tr>
<tr>
<td>Med Fem</td>
<td>31 (39)</td>
<td>0.79</td>
<td>1.00</td>
</tr>
<tr>
<td>Lat Tib</td>
<td>42 (53)</td>
<td>0.87</td>
<td>0.91</td>
</tr>
<tr>
<td>Med Tib</td>
<td>42 (53)</td>
<td>0.90</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>DTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lat Fem</td>
<td>48 (60)</td>
<td>0.98*</td>
<td>0.97</td>
</tr>
<tr>
<td>Med Fem</td>
<td>39 (49)</td>
<td>0.97*</td>
<td>0.98</td>
</tr>
<tr>
<td>Lat Tib</td>
<td>49 (61)</td>
<td>1.00*</td>
<td>0.89</td>
</tr>
<tr>
<td>Med Tib</td>
<td>42 (53)</td>
<td>1.00</td>
<td>0.93</td>
</tr>
</tbody>
</table>
Fractal signature analysis

Texture or 'fractal' signatures are computed at a number of scales in the vertical and horizontal direction.

The radiograph gives a 2D projection of trabecular structure

Methods - Radiography

Fractal signature analysis

- Texture Analysis of macroradiographs of OA knees using fractal signature has long history
- Conflicting results in regard to prediction of OA progression
- Different dimensions of trabecular architecture are assessed
- Validation with histomorphometry and µCT needed

Wolozszynski T, Arthritis Rheum 2012;64:688-95
Magnetic Resonance Imaging

MRI

- Tomographic technique
- No radiation
- Superior soft tissue contrast
- Clinically relevant for differential diagnosis
- Direct visualization of all joint structures: semiquantitative whole-joint assessment
- 3D quantitative analysis
MRI

- Biochemical/compositional/metabolic/vascular analysis: T2 mapping, dGEMRIC, T1rho, Na\(^{++}\), spectroscopy, diffusion, CEST, DCE MRI
- Imaging technique easily reproducible in multicenter studies and longitudinally
- Major drawback: costs
- Contraindications (e.g. pacemaker, claustrophobia)

MRI: Hardware

- Different MRI systems available that are suitable for image acquisition and MRI assessment in OA studies and clinical trials:
  - 1.0 T extremity systems
  - 1.5 T large bore systems
  - 3.0 T large bore systems
**MRI: Relevance of sequences**

[Images of MRI scans]

**MRI: Novel sequences – relevance for OA assessment**

[Images of MRI scans]

References:
• Different imaging approaches to OA joint assessment using MRI available:
  - Quantitative Analysis
    (cartilage, meniscus, muscle)
  - Compositional Analysis
    (cartilage, meniscus)
  - Semiquantitative Analysis
    (all joint tissues)

SQ MRI Assessment

• Semi-quantitative whole joint assessment
  - Assessment of articular cartilage directly
  - Assessment of other important articular structures
    - Meniscus
    - Osteophytes
    - Attrition
    - Subchondral bone marrow lesions and cysts
    - Ligaments
    - Synovium
    - Effusion
    - Periarticular structures
**Semiquantitative MRI Scoring Systems**

- **WORMS = Whole-Organ Magnetic Resonance Imaging Score**

- **KOSS = Knee Osteoarthritis Scoring System**

- **BLOKS = Boston Leeds Osteoarthritis Knee Score**

- **SQ Synovitis Assessment Score**

- **MOAKS = MRI Osteoarthritis Knee Score**

- **HOAMS = Hip Osteoarthritis MRI Score**

- **OHOA = Oslo Hand Osteoarthritis MRI Score**

**Methods - MRI**

**Semiquantitative MRI Scoring Systems:** subregional division

- **BLOKS:** 8 articular subregions for cartilage, bone marrow lesion (BML) and subchondral cyst assessment
- **WORMS/MOAKS:** 15 articular subregions for cartilage, bone marrow lesion (BML) and subchondral cyst assessment
Quantitative MRI

- Cartilage (+++); sensitive to change
- May be applied in other joint structures (menisci, bone, synovium)
- Less observer dependent (more objective)
- Ordered values approach possible for analysis
- Minimal changes over large areas can be depicted
- Less sensitive than SQ to small focal (early) changes


Methods - MRI

Regional assessment of cartilage (Courtesy of Chondrometrics)

Segmentation of synovitis (IV+)
Compositional MRI

- Compositional MRI detects cartilage alterations before surface damage is evident.
- Changes in GAG, collagen and water content detectable by sophisticated MR techniques.
- Applicable on most clinical MR scanners but at present not in clinical routine due to unknown relevance and difficult implementation.
  - T2 and T2* mapping
  - T1 rho
  - dGEMRIC
  - Sodium MRI
  - Diffusion MRI / Diffusion Tensor Imaging
  - CEST
Compositional MRI: T2 Mapping

- T2 values reflect collagen and water content
- High inter- and intraindividual variability
- T2 maps may be useful to identify subjects with sites of early degeneration (normal surface morphology).
- Available in OAI
- T2 maps may be used in the future for monitoring surgical cartilage repair

Compositional MRI: dGEMRIC

- Negatively charged Gad molecules diffuse into the cartilage and will inversely distribute according to the concentration GAG molecules
- Depletion of negatively charged GAG: Gd-DTPA2-
- Needs IV administration of contrast; time-consuming
- Applied also to the menisci
- Longitudinal effect on cartilage morphology not yet well understood
Methods - MRI

Compositional MRI: dGEMRIC

Baseline Baseline 24 months follow-up

Ultrasound
Ultrasound

- Visualization of soft tissue structures in multiple planes
- Real time, mobile scanners
- Dynamic exam
- No radiation
- Inexpensive
- No contrast agent needed for synovial assessment
- Good soft-tissue contrast


Ultrasound: Synovitis and Effusion

Methods - Ultrasound

Ultrasound

- User-dependent
- Physical properties of sound limit its application
  - => no visualization of subchondral bone and deep intra-articular structures!
- Low negative predictive value for cartilage assessment
- Not yet validated as an outcome tool in OA
- Documentation difficult (screenshots)

Computed Tomography

Methods - CT

CT

- Widespread availability
- Fast exam
- Few artifacts
- Non-invasive
CT

- High spatial resolution
- Not user-dependent
- Multiplanar reconstructions possible with MDCT
- Large scanning volumes possible

CT

- Depicts cortical bone and soft tissue calcifications superiorly to MRI
- High sensitivity in detection of intraarticular loose bony fragments
- Established clinical role in assessment and treatment of facet joint OA of spine
- Radiation exposure
- Poor soft tissue contrast

Dual Energy CT

Potential application of dual energy CT: assessment of synovitis (?)


CT-Arthrography

- Potentially very useful in OA assessment
- Limited access to MR facilities
- Contraindications to MR imaging
- No 1 in depiction of superficial cartilage damage (superior to MRI due to high resolution)
- Invasive
- Subchondral bone marrow, synovitis, extraarticular ligaments, periarticular structures not visualized


Images courtesy of Prof. B. Vande Berg, Brussels
CT-Arthrography

- Intrachondral GAG composition
- Good correlation with EPIC-µCT
- High radiation dose
- Presently only ex vivo application
Optical Coherence Tomography

- FDA-approved for ophthalmology and cardiology
- Analogous to ultrasound
- Measuring back-reflected infrared light
- Incorporated into arthroscope
- High resolution
- 2-5 mm wide, 1-2 mm depth

Optical Coherence Tomography

- invasive
- covers only small area of articular surface
- smaller devices in development
- validation still ongoing

Nuclear medicine

- Assesses metabolic activity of different joint tissues
- $^{99m}$Tc-HDP scintigraphy
  - Increased tracer uptake during bone phase
- $^{2-18}$F-fluoro-2-deoxy-D-glucose (FDG) PET
  - Injection of radioactively marked glucose
  - Increased uptake in the periarticular region, intercondylar notch, subchondral bone marrow

FDG-PET

PET-MRI

Nuclear Medicine

- Non specific: trauma, tumor, degeneration, infection, inflammation
- Sensitive concerning hypermetabolism
- Radiation exposure
- Very low spatial resolution
- New hybrid techniques (PET-CT/PET-MRI)
Relevance: Research and Clinical Trials

- Radiography and MR imaging are valuable tools for diagnosis and assessment of progression of OA in clinical trials
- X-ray-detected JSN has limitations
  - Not sensitive to change, "too slow" in longitudinal studies
  - Indirect (does not visualize cartilage directly)
  - Non-specific (meniscal subluxation can mimic cartilage loss)
  - Positioning difficult to reproduce, e.g. in multicenter studies

Relevance: Research and Clinical Trials

- MRI offers advantages
  - Direct visualization of cartilage using multiple parameters
  - Direct visualization of other features of OA: Bone marrow abnormalities, synovitis, effusion, menisci, ligaments, osteophytes
- MRI reproducible in multicenter studies
- MRI detects pre-radiographic OA features
Summary

- Multiple imaging tools are available with MRI the most important one today
- MRI induced change of perception from "wear and tear" to "multi-tissue / whole organ" disease
- Strong associations between imaging findings and symptoms
- Clinical role of MRI today still minor, in a research setting No 1 tool to investigate structural changes
- Further validation of other methods needed


Thank You!