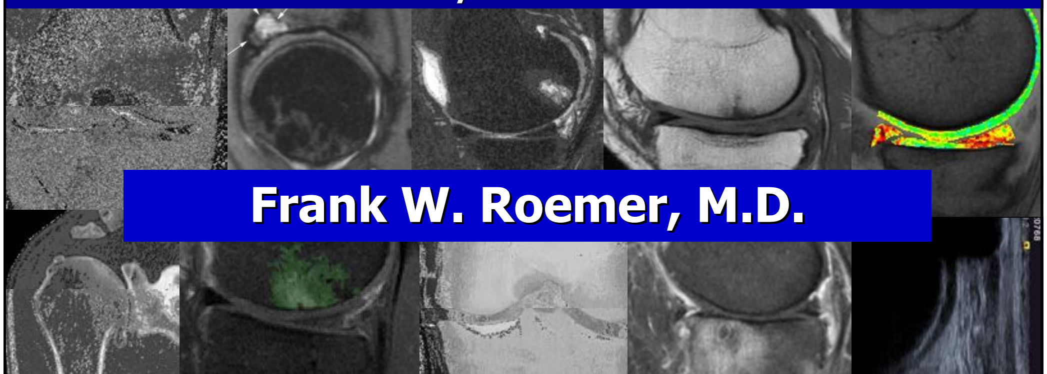
Overview of Current Imaging as Applied to OA Diagnostics and Clinical Studies:

What Methods are Currently Used and What are the Limitations?



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Overview

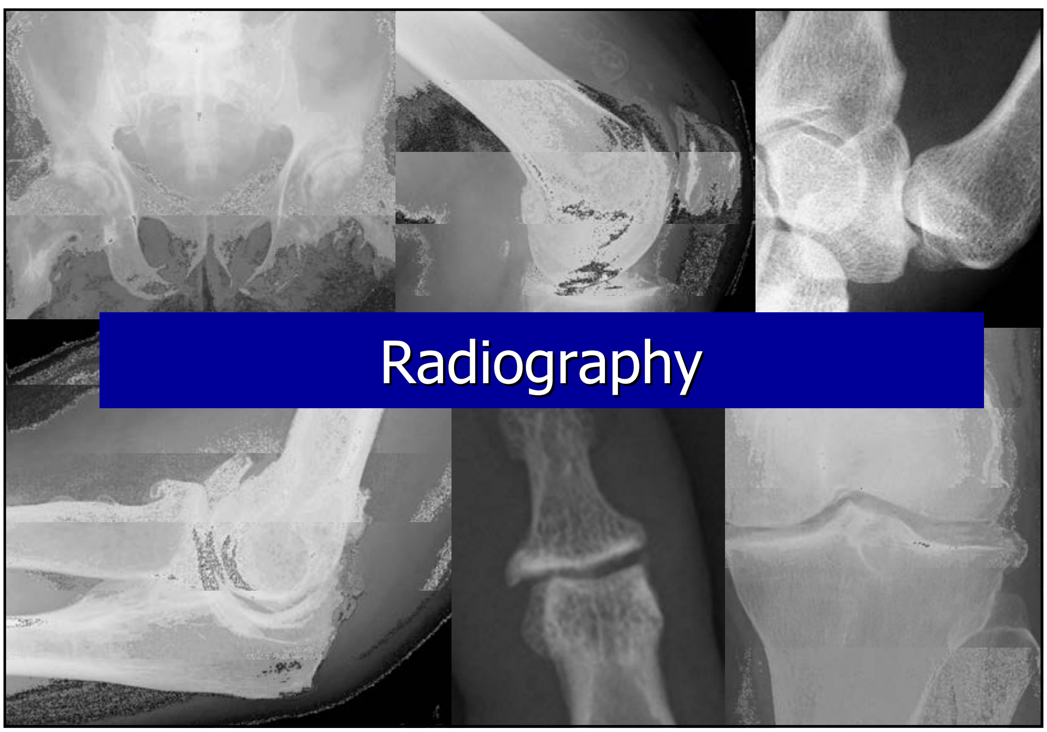
- Radiography
- MRI
- Ultrasound
- CT
- Others
- Relevance
- Summary

OABiomarker Global Initiative OARSI

Disclosure

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

OABiomarker Global Initiative



Radiography

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]

[1]Gale DR, et al.Osteoarthritis Cartilage. 1999 Nov;7(6):526-32.
[2]Hunter DJ, et al. Arthritis Rheum. 2006 Aug;54(8):2488-95.
[3]Crema M et al. Osteoarthritis Cartilage 2011;19(Suppl 1): S173.

Semiquantitative Xray assessment -
Kellgren Lawrence Grading: composite score

Grade 0: no feature of OA

Grade 1: Doubtful JSN and possible osteophytic lipping

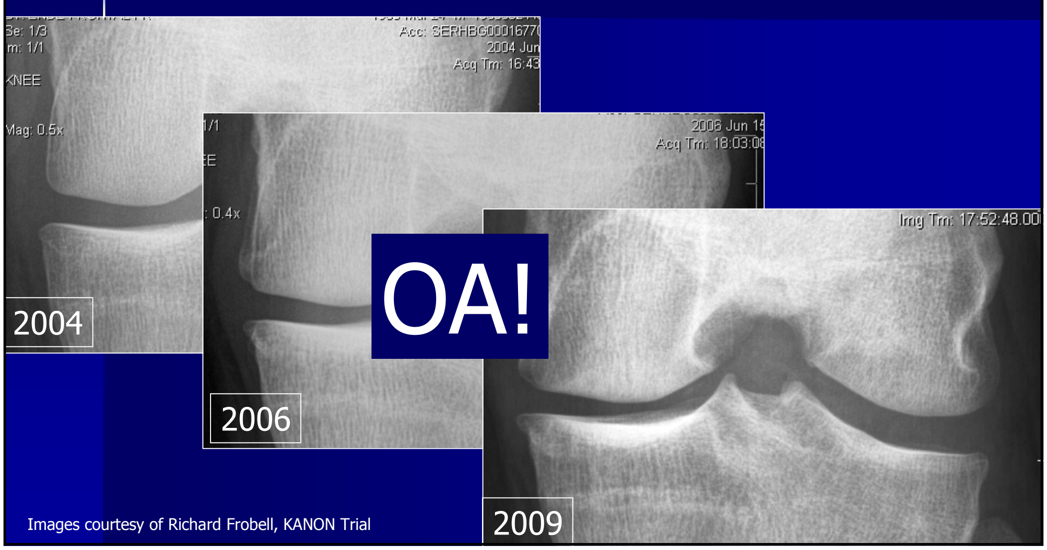
Grade 2: **Definite osteophytes** and possible JSN

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

Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502.

Definition Radiography
Kellgren Lawrence



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

Altman RD, Hochberg M, Murphy WA, et al. Atlas of individual radiographic features in osteoarthritis. Osteoarthritis Cartilage 1995;3(Suppl A):3-70
Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage 2007;15 Suppl A:A1-56

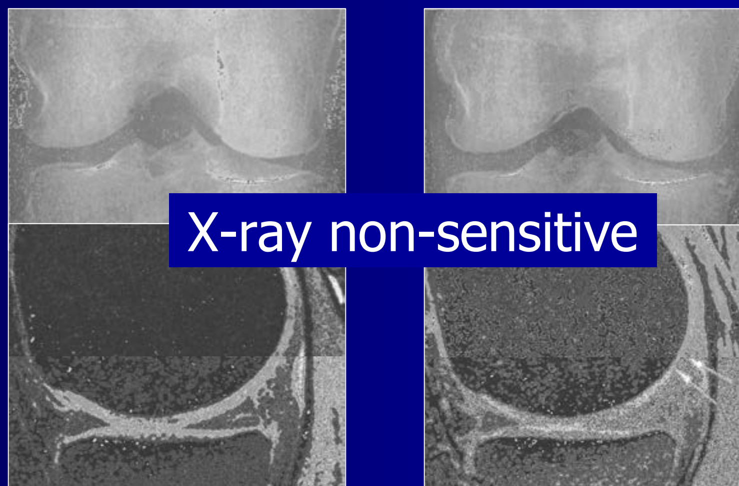
Methods - Radiography

Atlas-based assessment

Felson DT, et al. J Rheumatol. 2008 ;35(10):2047-54.

No longitudinal joint space narrowing

an indirect marker of cartilage integrity?



Roemer FW, et al. Osteoarthritis Cartilage 2009;17(Suppl 1):S224

Longitudinal joint space narrowing

an indirect marker of cartilage loss?

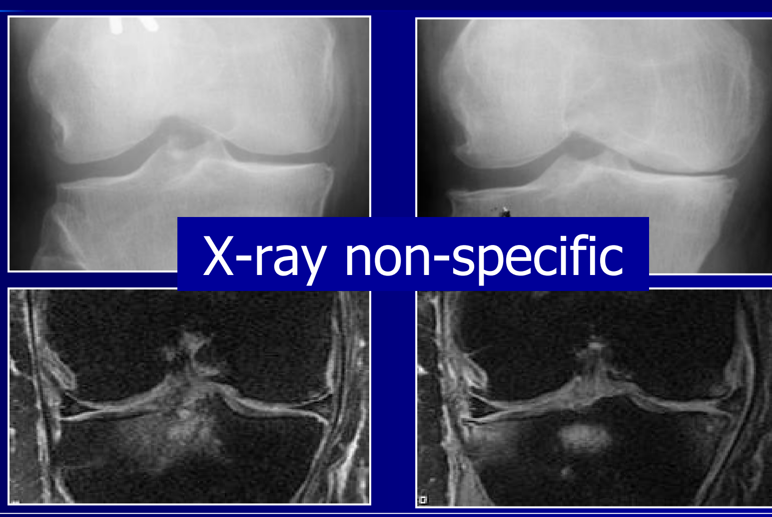
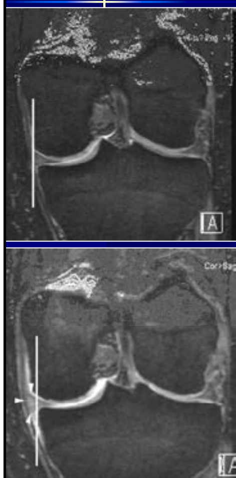


image from: Amin S, et al. Arthritis Rheum 2005;52:3152-9, Hunter DJ et al. A&R 2006, Gale D 1999

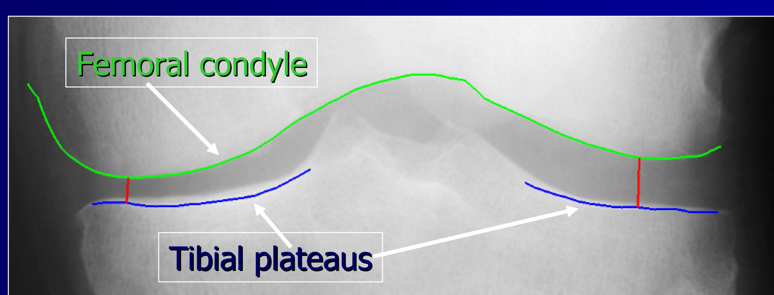
Radiographic OA assessment: JSW



MRI Predictor	Progression of JSN		Adjusted OR (95% CI)
Number of features worsening	Absence	Presence	
No worsening of all 3 features	366 (69.2%)	18 (3.4%)	1.0 (reference)
Worsening of 1 feature	85 (16.1%)	27 (5.1%)	6.5 (3.4;12.2)
Worsening of 2 features	10 (1.9%)	11 (2.1%)	22.5 (8.8,57.5)
Worsening of 3 features	2 (0.4%)	9 (1.7%)	92.6 (18.7, 457.4)

Crema M et al. The association of worsening of cartilage damage and meniscal pathology with increase in radiographic tibiofemoral joint space narrowing in persons with knee OA. Osteoarthritis Cartilage 2011;19(Suppl 1): S173

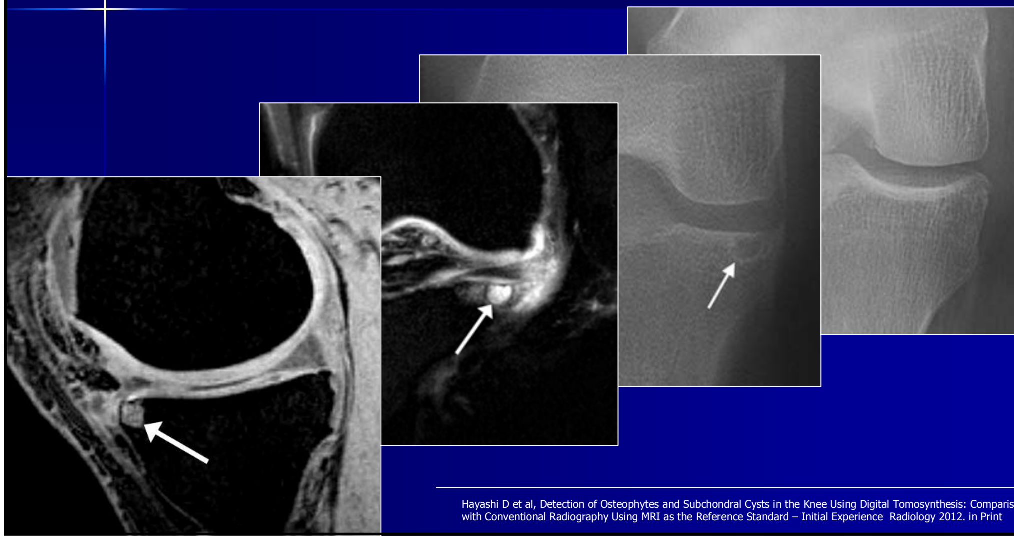
Minimum joint space width



Software automatically delineates joint margins and determines mJSW

•Duryea J, et al. Osteoarthritis Cartilage 2003;11:102-110
•Duryea J, et al. Arthritis Care Res (Hoboken). 2010 Jul;62(7):932-7.

Digital Tomosynthesis



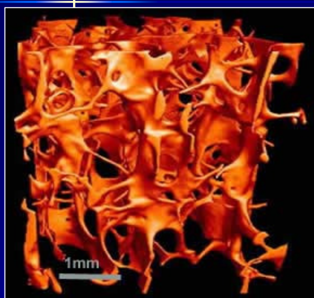
Hayashi D et al, Detection of Osteophytes and Subchondral Cysts in the Knee Using Digital Tomosynthesis: Comparison with Conventional Radiography Using MRI as the Reference Standard – Initial Experience Radiology 2012. in Print

Digital Tomosynthesis

Compartments		Prevalence N	(%)	Sensitivity	Specificity
X-ray	Lat Fem	35	(44)	0.73	1.00
	Med Fem	31	(39)	0.79	1.00
	Lat Tib	42	(53)	0.87	0.91
	Med Tib	42	(53)	0.90	0.83
DTS	Lat Fem	48	(60)	0.98*	0.97
	Med Fem	39	(49)	0.97*	0.98
	Lat Tib	49	(61)	1.00*	0.89
	Med Tib	42	(53)	1.00	0.93

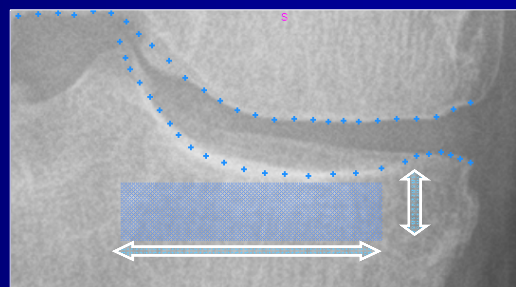
Hayashi D et al., Detection of Osteophytes and Subchondral Cysts in the Knee Using Digital Tomosynthesis: Comparison with Conventional Radiography Using MRI as the Reference Standard – Initial Experience Radiology 2012. in Print

Fractal signature analysis



The radiograph gives a 2D projection of trabecular structure

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

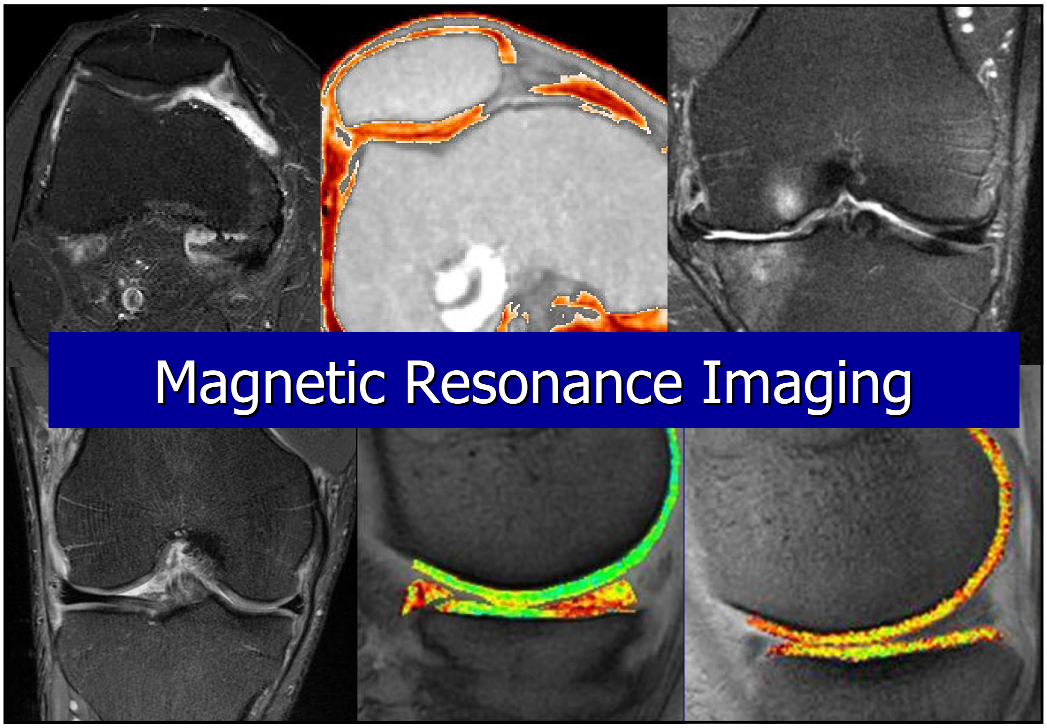


Images courtesy of Optasia

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 histomorhometry and µCT needed

Lynch JA et al, Phys Med Biol 1991;36(6):709-22)
Messent EA, et al. Osteoarthritis Cartilage 2005;13:463–70.
Kraus VB, et al. Arthritis Rheum. 2009;60:3711-22.
Buckland-Wright JC, et al. Rheumatology (Oxford) 2007; 46:257–64.
Wolozszynski T, Arthritis Rheum 2012;64:688-95



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

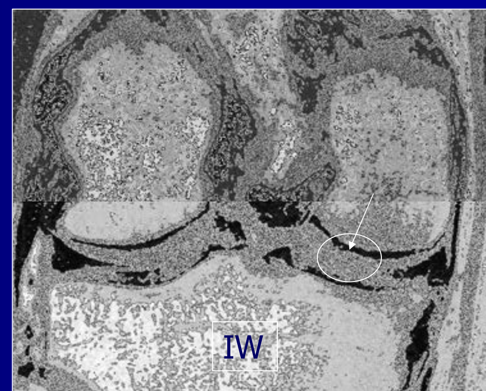
MRI

- 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

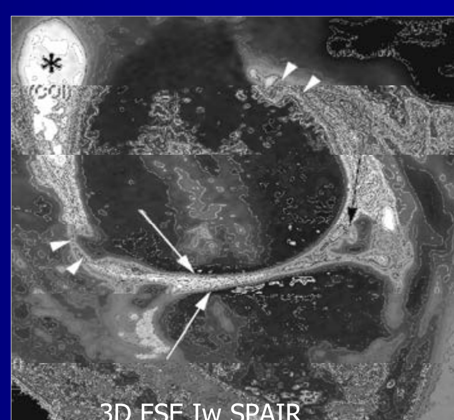
- Different MRI systems available that are suitable for image acquisition and MRI assessment in OA studies and clinical trials:
  - 1.0 T extremity systems
  - 1.5 T large bore systems
  - 3.0 T large bore systems

MRI: Relevance of sequences



1Roemer FW et al., Eur J Radiology, Eur J Radiol. 2011 Nov;80(2):e126-31. 2Mohr et al., Skeletal Radiol 2003; 32:396-402; 3Stahl R, et al.. Skeletal Radiol 2008; 37:627-638; 4 Roemer FW, et al. Advances in Osteoarthritis and Cartilage Imaging. Radiology

MRI: Novel sequences – relevance for OA assessment



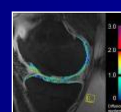
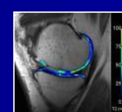
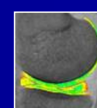
Crema MD,et al. Comparison between 2D and 3D Intermediate-weighted Fast Spin-Echo MRI for Semiquantitative Whole Organ Assessment of the Knee in Osteoarthritis Research. - RSNA 96th Scientific Assembly and Annual Meeting, Chicago, IL, November 28-December 3, 2011. SSM12-04

MRI-based OA Assessment

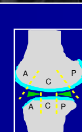
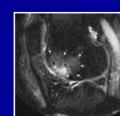
- Different imaging approaches to OA joint assessment using MRI available:
  - Quantitative Analysis (cartilage, meniscus, muscle)



  - Compositional Analysis (cartilage, meniscus)

  - Semiquantitative Analysis (all joint tissues)

SQ MRI Assessment

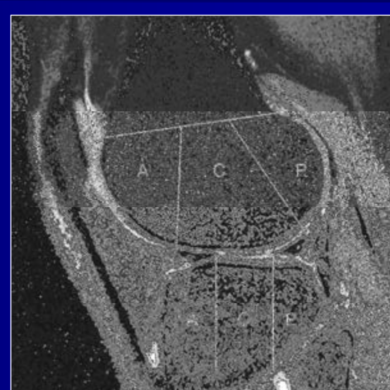
- Semi-quantitative whole joint assessment
  - Assessment of articular cartilage directly
  - Assessment of other important articular structures
    - Meniscus
    - Osteophytes
    - Attrition
    - Subchondral bone marrow lesions and cysts
    - Ligaments
    - Synovium
    - Effusion
    - Periarticular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

Semiquantitative MRI Scoring Systems

- WORMS = Whole-Organ Magnetic Resonance Imaging Score
  Peterfy CG, et al. Osteoarthritis Cartilage 2004;12:177-190
- KOSS = Knee Osteoarthritis Scoring System
  Kornaat PR, et al. Skeletal Radiol 2005;34:95-102
- BLOKS = Boston Leeds Osteoarthritis Knee Score
  Hunter DJ, et al. Ann Rheum Dis 2008;67:206-211
- SQ Synovitis Assessment Score
  Guermazi A, et al. Ann Rheum Dis. 2011;70(5):805-11
- MOAKS = MRI Osteoarthritis Knee Score
  Hunter DJ, et al. Osteoarthritis Cartilage. 2011;19(8):990-1002
- HOAMS = Hip Osteoarthritis MRI Score
  Roemer FW, et al. Osteoarthritis Cartilage. 2011;19(8):946-62
- OHOA = Oslo Hand Osteoarthritis MRI Score
  Haugen IK, et al. Ann Rheum Dis. 2011 Jun;70(6):1033-8.

Semiquantitative MRI Scoring Systems:
subregional division

BLOKS



WORMS/MOAKS

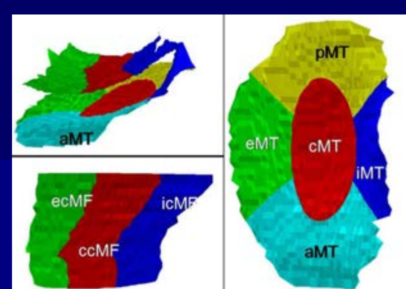
BLOKS: **8 articular subregions** for cartilage, bone marrow lesion (BML) and subchondral cyst assessment

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

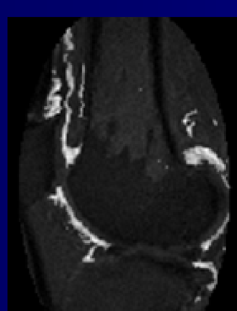
Quantitative MRI

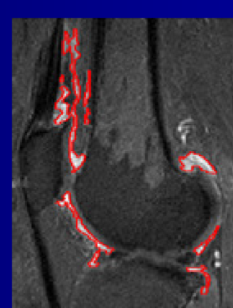
- Cartilage (+++); sensitive to change
- May be applied in other joint structures (menisci, bone, synovium)
- Less observer dependent (more objective)
- Ordered values approach possible for analysis
- Minimal changes over large areas can be depicted
- Less sensitive than SQ to small focal (early) changes

Eckstein F et al. Radiol Clin N Am 2009;47:655-673
Wirth W et al. Magn Reson Med 2010;63:1162-71
Wirth W et al. Osteoarthritis Cartilage 2011;19:689-99
Fotinos-Hoyer AK et al. Magn Reson Med 2010;64:604-9



Regional assessment of cartilage (Courtesy of Chondrometrics)



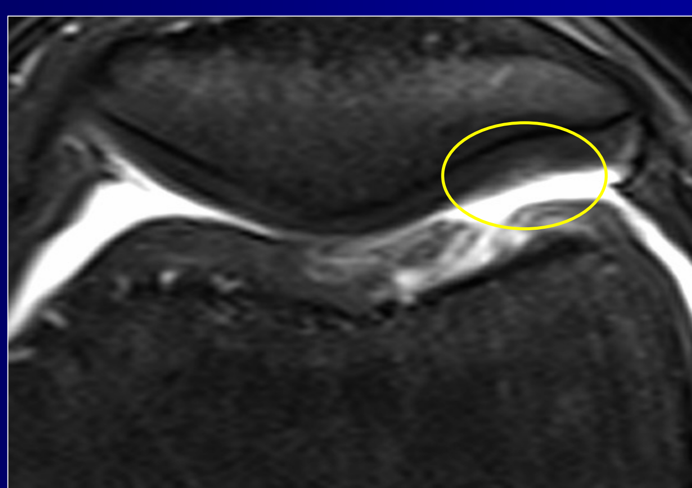


Segmentation of synovitis (IV+)

Compositional MRI

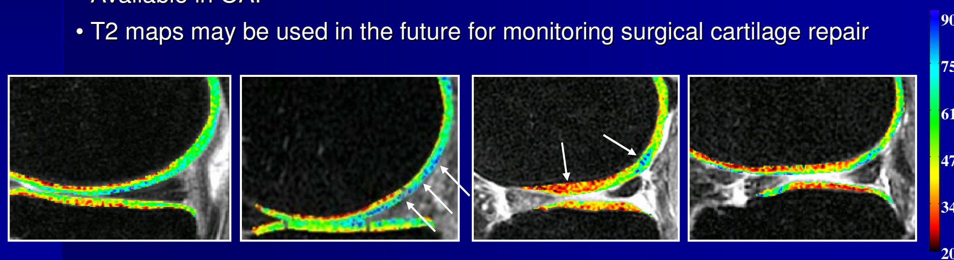
- Compositional MRI detects cartilage alterations before surface damage is evident
- Changes in GAG, collagen and water content detectable by sophisticated MR techniques
- Applicable on most clinical MR scanners but at present not in clinical routine due to unknown relevance and diffcult implementation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

Compositional MRI



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

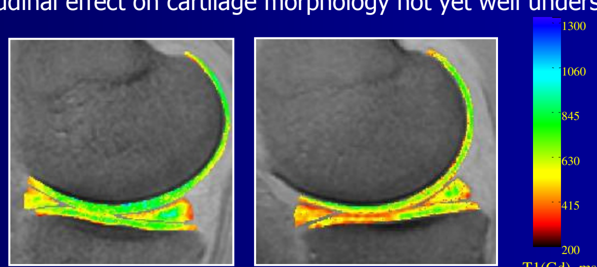


•Baum T et al. J Magn Reson Imaging 2012;35:370-8
•Pan J et al. Radiology 2011;261:507-15
•Zarins ZA et al. Osteoarthritis Cartilage 2010;18:1408-16
•Mosher TJ, et al. Arthritis Rheum. 2004;50:2820-8.
•Dunn TC, et al. Radiology 2004;232:592-8.

Methods - MRI

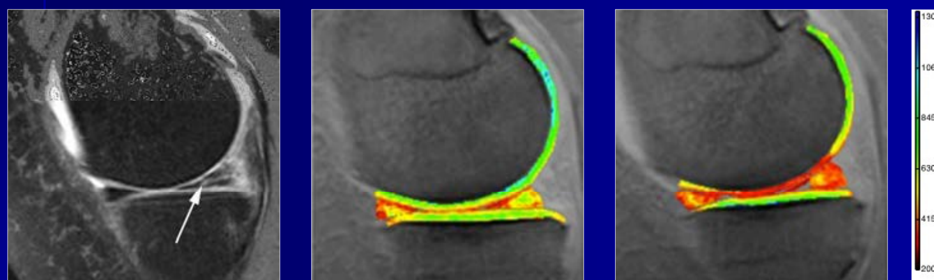
Compositional MRI: dGEMRIC

- Negatively charged Gad molecules diffuse into the cartilage and will inversely distribute according to the concentration GAG moleculules
- 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



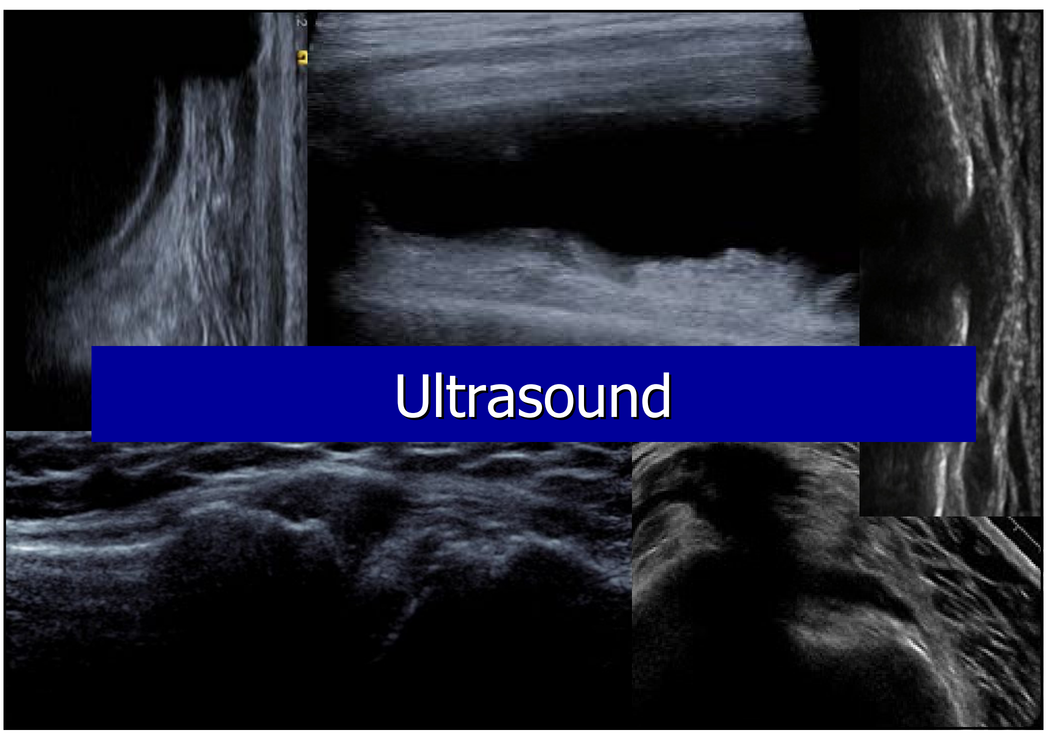
Burstein D, Velyvis J, Scott KT, et al. Magn Reson Med 2001;45:36-41.
Williams A, Sharma L, McKenzie CA, et al. Arthritis Rheum 2005;52:3528-35.

Compositional MRI: dGEMRIC



Baseline Baseline 24 months follow-up

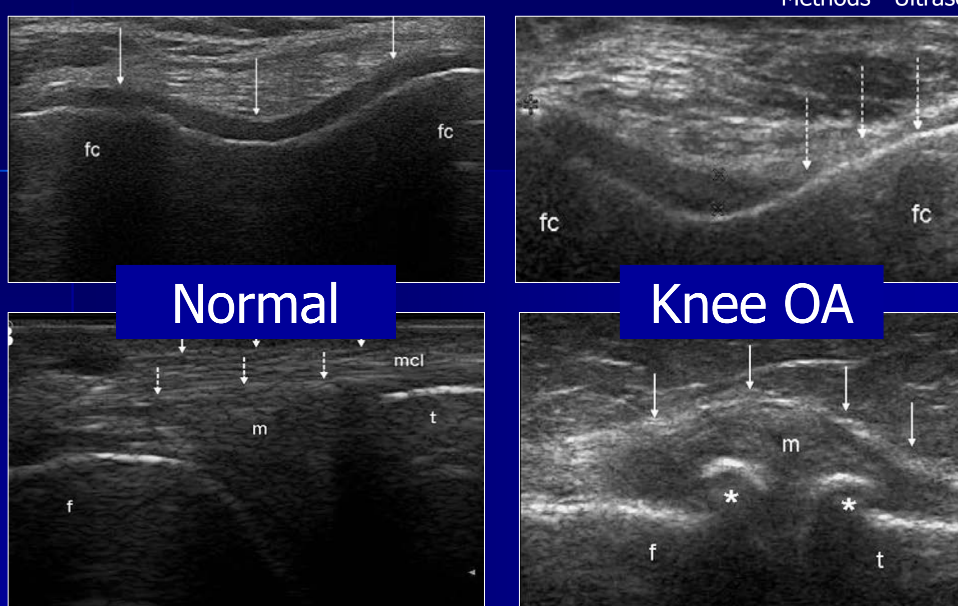
Crema MD, et al.; Osteoarthritis Cartilage 2011;19(Suppl 1): S161.
Crema MD et al.; Osteoarthritis Cartilage 2011;19(Suppl 1): S163.



Ultrasound

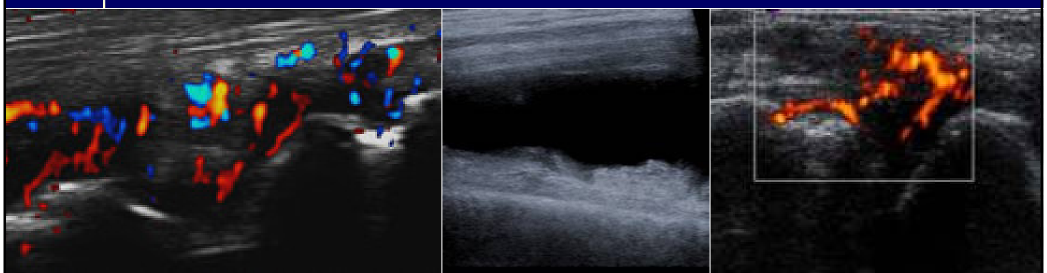
- Visualization of soft tissue structures in multiple planes
- Real time, mobile scanners
- Dynamic exam
- No radiation
- Inexpensive
- No contrast agent needed for synovial assessment
- Good soft-tissue contrast

Keen HI, et al. A systematic review of ultrasonography in osteoarthritis. Ann Rheum Dis. 2009 May;68(5):611-9. Review

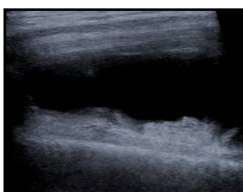


Keen HI, Conaghan PG. Radiol Clin North Am 2009;47:581-94

Ultrasound: Synovitis and Effusion



Wakefield RJ et al. J Rheumatol 2005;32:2485-7
D'Agostino MA et al. Ann Rheum Dis 2005;64:1703-9
Conaghan PG et al. Ann Rheum Dis 2005;64:1710-4
Conaghan PG et al. Ann Rheum Dis 2010;69:644-7

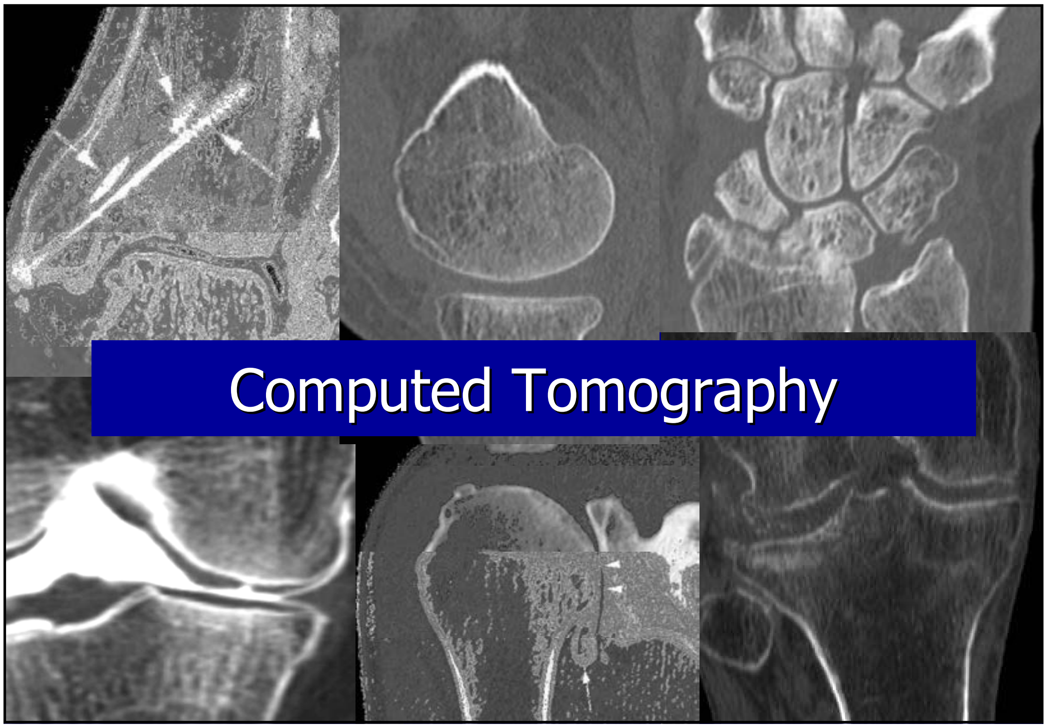


Ultrasound

- User-dependent
- Physical properties of sound limit its application

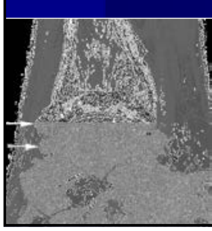
  => no visualization of subchondral bone and deep intra-articular structures!
- Low negative predictive value for cartilage assessment [1]
- Not yet validated as an outcome tool in OA [2]
- Documentation difficult (screenshots)

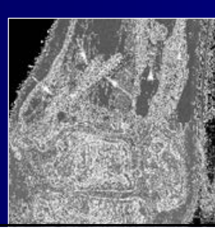
1 Saarakkala S et al. Osteoarthritis Cartilage 2012 Feb 1 [Epub ahead of print]
2 Keen HI et al. Ann Rheum Dis 2008;67:651-5

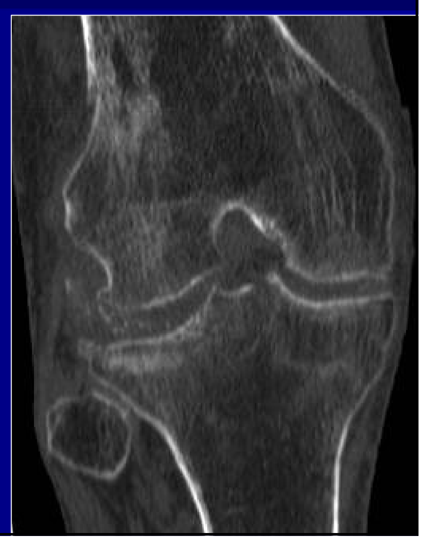


CT

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

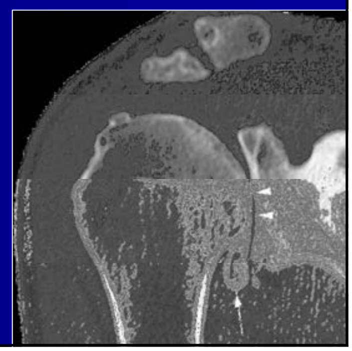






CT

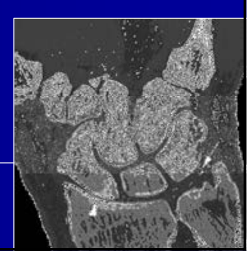
- High spatial resolution
- Not user-dependent
- Multiplanar reconstructions possible with MDCT
- Large scanning volumes possible



Methods - CT

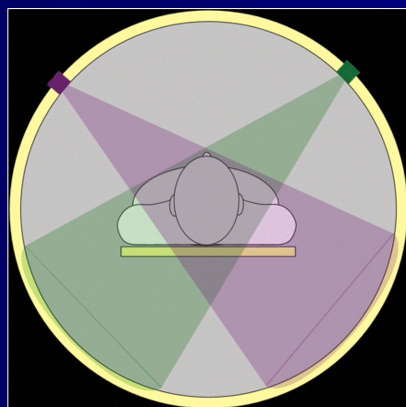
CT

- Depicts cortical bone and soft tissue calcifications superiorly to MRI[1]
- High sensitivity in detection of intraarticular loose bony fragments[2,3]
- Established clinical role in assessment and treatment of facet joint OA of spine[4,5]
- <u>Radiation exposure</u>
- <u>Poor soft tissue contrast</u>



[1]Gerster JC, et al. Ann Rheum Dis. 2002 Jan;61(1):52-4.
[2]Dubberley JH, et al. J Bone Joint Surg Br. 2005 May;87(5):684-6.
[3]Zubler V, et al. AJR Am J Roentgenol. 2010 Jun;194(6):W515-20.
[4]Meleka S, Patra A, Minkoff E, Murphy K. AJNR Am J Neuroradiol. 2005 May;26(5):1001-3.
[5]Kalichman L, et al. Spine 2008 Nov 1;33(23):2560-5.

Dual Energy CT



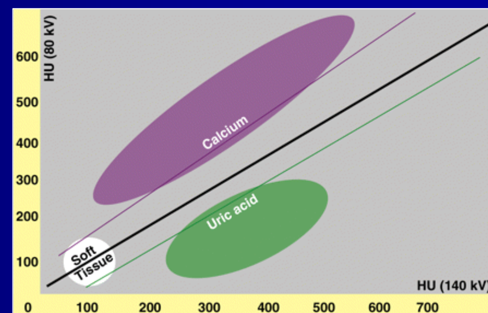
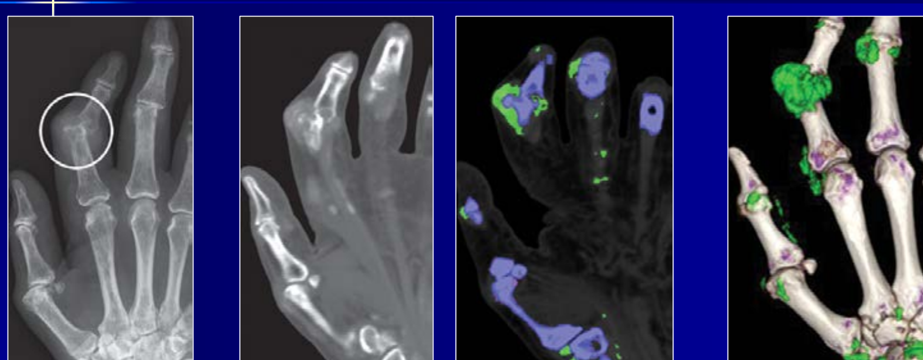


Image from: Desai MA, et al. Clinical Utility of Dual-Energy CT for Evaluation of Tophaceous Gout. Radiographics 2011;31:1365-75

Dual Energy CT



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

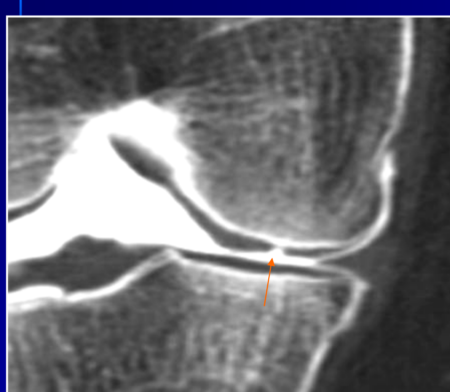
Bacani AK, et al. Dual energy computed tomography for quantification of tissue urate deposits in tophaceous gout: help from modern physics in the management of an ancient disease. Rheumatol Int 2009 Dec 17. [Epub ahead of print]
Desai MA, et al. Clinical Utility of Dual-Energy CT for Evaluation of Tophaceous Gout. radiographics 2011;31:1365-75

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

Vande Berg BC, et al. Eur Radiol. 2002 Jul;12(7):1800-10.
Vande Berg BC, et al. Skeletal Radiol. 2002 Nov;31(11):643-9.
Moser T, et al. Radiology. 2008 Jan;246(1):193-7.
Kraniotis P et al Skeletal Radiol 2012:41:803-9

CT-Arthrography



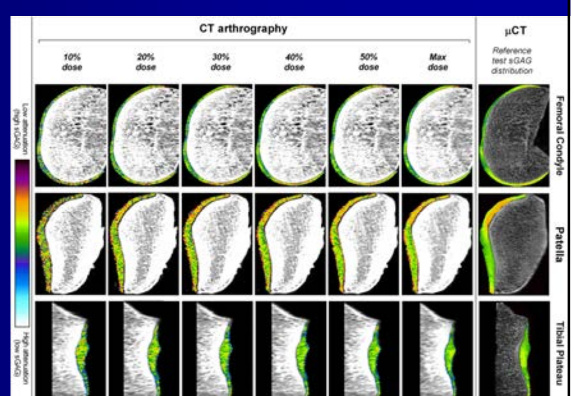
Images courtesy of Prof. B. Vande Berg, Brussels

CT-Arthrography


Images Kraniotis P et al Skeletal Radiol 2012;41:803-9

CT-Arthrography

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

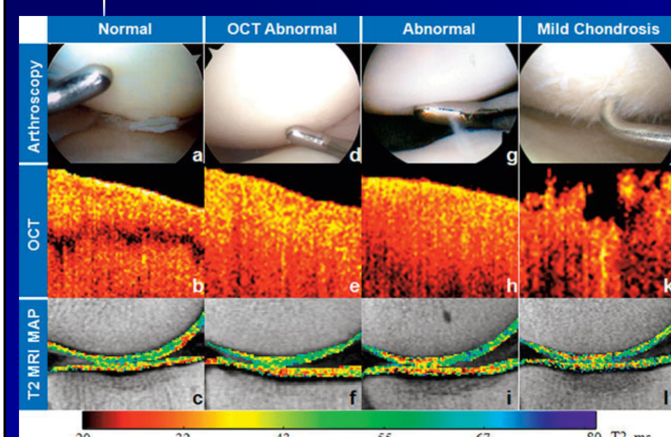


Van Tihiel J et al., Osteoarthritis Cartilage;20::678-85

Optical Coherence Tomography

- FDA-approved for ophtalmology 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



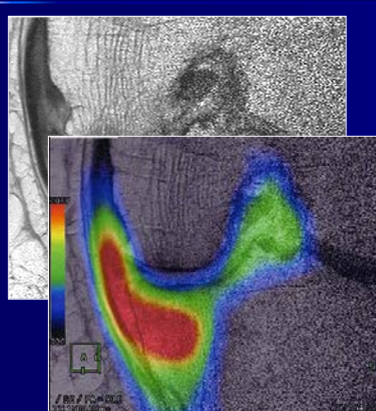
- invasive
- covers only small area of articular surface
- smaller devices in development
- validation still ongoing

image from: Chu C, et al. Arthritis Rheum 2010,62,1412-1420

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



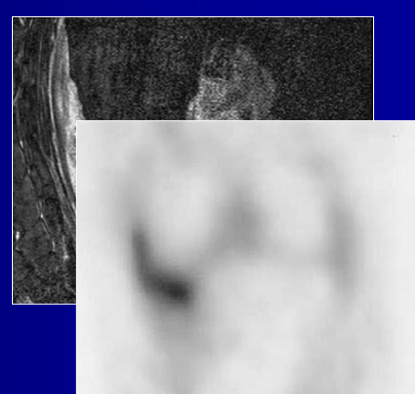


Image: Nakamura H et al. Positron emission tomography with 18F-FDG in osteoarthritic knee. Osteoarthrits Cartilage 2007;15:673-81.

PET-MRI

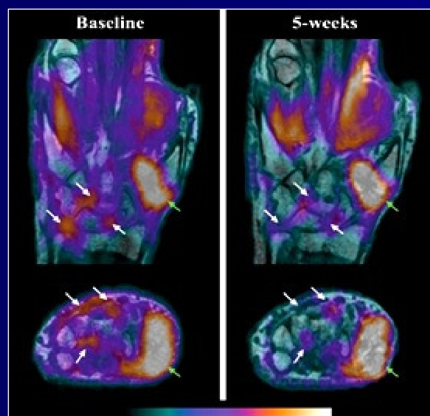


Image: Chaudhari AJ, Eur J Nucl Med Mol Imaging (2010) 37:1047

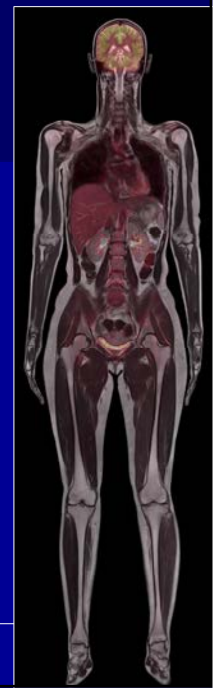


Image:
Siemens Healthcare

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

Roemer FW, Crema MD, Trattnig S, Guermazi A. Advances in imaging of osteoarthritis and cartilage. Radiology. 2011 Aug;260(2):332-54.