Advanced Cartilage Imaging: Cartilage Repair and Management

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Target audience: Radiologists and imaging scientists interested in assessing cartilage repair, including the use of quantitative techniques to assess repair tissue biochemistry.

Outcome/Objectives:

1. To become familiar with different appearance of cartilage repair techniques
2. To become familiar with both morphologic and quantitative assessment of repair

Purpose: Articular cartilage has little to no inherent capacity for self-repair. The presentation will outline both scaffold and cell-based repair techniques, demonstrating both surgical approach and both early and longer term MR appearance of the repair tissue.

Methods and Results: Review of pertinent literature of MRI of cartilage repair

Cartilage Repair: Methods of Repair'

- Articular cartilage has little to no capacity to undergo spontaneous repair
  - avascular; unable to regenerate across a physical gap
- Marrow stimulation (microfracture +/- augmentation)
- Osteochondral transfer
  - autologous (mosaicplasty; OATS, AOT)
  - allograft (fresh cadaveric tissue)
- Tissue Engineered Cartilage (three requirements)
  - matrix scaffold to support tissue formation → chemical composition and physical structure attract endogenous cells ("cell homing")
    - carbohydrate based polymers (polylactic acid)
    - protein based polymers (collagen, fibrin)
  - cells
    - chondrocytes
    - chondroprogenitor cell pools (cambial layer of periosteum and perichondrium)
    - mesenchymal stem cells from the bone marrow or synovial membrane
- signaling molecules (cytokines): PRP, FGF18 appear promising
  - Signaling by fibroblast growth factor (FGF) 18 promotes chondrocyte proliferation and differentiation

Works through activation of FGF receptor 3 *(Moore et al; OA & Cart 2005)*

MRI as Primary Outcome Measure: Cartilage Repair

- Signal intensity of tissue (ROI)
- Integrity/hypertrophy of periosteal flap
- Morphology; presence/absence of displacement (ACI/ OCA)
- Interface with native cartilage
- Volume of repair "fill"
- Appearance/morphology of subchondral bone
- Assess adj./opp. articular cartilage
- Presence/absence of inflammatory synovitis
- MR observation of cartilage repair tissue (MOCART)
  Marlovits et al; Eur J Radiol 2006; 57:16-23
  - Correlated to KOOS and VAS; significant correlation for fill, structure, subchondral bone, SI
  - ICC (3 readers); κ range: 0.765-1.00

Imaging of Cartilage Structure

- Water proton pools:
  - Free water (accounts for bulk of MRI signal)
  - Bound to PG by electrostatic charge (assess fixed charge density)
    - Sodium MRI

- GAG CEST
- Gd-DTPA^{-2} techniques (dGEMRIC)
    - T1 rho imaging
- Associated with collagen fibrils Quantitative T2 mapping:
    - Assess alterations in collagen orientation
- Diffusion tensor weighted imaging

Increased failure rate of autologous chondrocyte implantation after previous treatment with marrow stimulation techniques

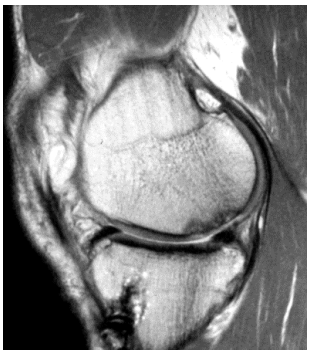
Minas et al, AJSM 2009

- 321 patients treated with autologous chondrocyte implantation
- Prior marrow stimulation: 26% failures (29/111)
- No prior marrow stimulation: 8% failures (17/214)

Imaging of Microfracture

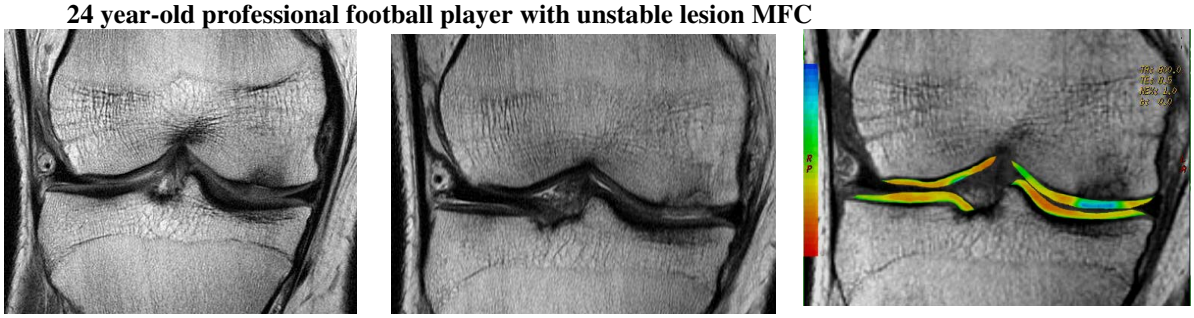
- Prospective study of 48 patients treated with microfracture evaluated by validated clinical outcome instruments and cartilage sensitive MRI
    - bony overgrowth was noted in 25% of patients, but did not have a negative effect on clinical outcome scores
    - adverse functional scores after 24 months did correlate with poor percentage fill

J Bone Joint Surg 2005; 87(9):1911-1920



Four years post microfracture

24 year-old professional football player with unstable lesion MFC



Preop 4/05 4 months post microfracture 8/05

- **Welsch et al *(Radiology 2008; 247:154-161)* studied 20 pts following MFX or MACT with mean F/U 28.6 vs 27.4 mo**
- **MFX tissue showed reduced mean T2 whereas MACT showed mean T2 similar to control tissue (56.4msec); MFX showed no stratification while MACT did from deep to superficial areas**

Cell-Based Approaches for Cartilage Repair

- Cell-based approaches hold great promise but there are still limitations to overcome
- Just adding pluripotent cells and hoping something good will happen may not be enough!
- Implanted cells need appropriate signals to drive differentiation
- The composition (specific matrix proteins) is often made by the cells but the structure of hyaline cartilage is not completely reformed

Matrix-Induced Autologous Chondrocyte Implantation (MACI)

- 3D scaffold supports maintenance of chondrocyte phenotype in culture
- Also serves as delivery vehicle for cells
- Autologous cells seeded on a hyaluronic acid or collagen scaffold
- Implantation approximately 4 weeks later
- Reduced technical complexity
    - No periosteum harvest
    - No suturing
    - Fibrin glue fixation
    - Arthroscopic implantation
- Used since 2001 in Europe & Australia

- Significant limitation of cell-based techniques is de-differentiation of cells in culture → variable expression of cartilage-forming genes
  - Chondroselect" technique (Tigenix, Inc.) selects a subset of cells that express chondrocyte phenotype in culture

Tissue Engineering Strategies

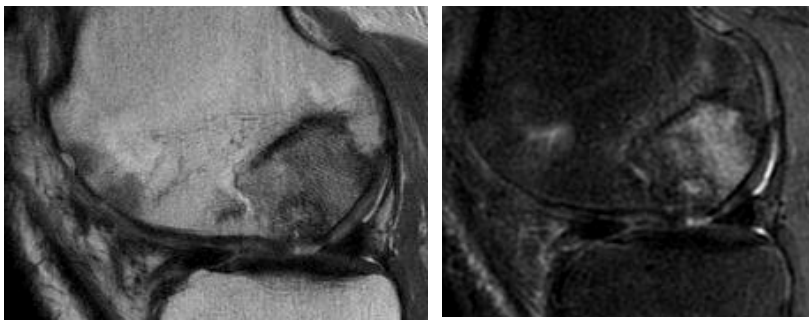
- Paradigm: cells + scaffold + cytokines + mechanical stimulation
- NeoCart (Histogenics, Waltham, MA)
- Cartilage biopsy → Chondrocytes expanded in culture
- Cells then seeded on a bovine type-I collagen 3-D honeycomb matrix
- Culture in bioreactor – hydrostatic pressure controlled
- Bioreactor conditions support chondrocyte phenotype
- Average implant development time 67 days

Tissue Transplantation

- Direct implantation of osteochondral tissue with hyaline cartilage
- Indications: Osteochondral defect - bone loss
- Allows restoration of architecture/geometry
- Autograft OATS: lesion size under 15mm diameter
  - Limitation: donor site morbidity
- Allograft OATS for larger lesions
  - Limitation: tissue availability
    - fresh tissue requires immediate transplantation

Imaging of Osteochondral Allografts

- ♦ Prospective, longitudinal study of cartilage defects treated with hypothermically stored fresh osteochondral allografts using validated clinical outcome instruments and MRI
- ♦ Allografts remain intact without displacement
  - fissures noted at the graft/host interspace in 14/18 (78%) grafts
  - poor incorporation was noted in 4/18 (22%) grafts, 1 had intense bone marrow edema pattern and 3 had frank subchondral marrow fibrosis (low signal on all pulse sequences)
  - collapse of the subchondral bone in the graft was correlated to lack of bony integration based on signal characteristics
- Sirlin et al. correlated MRI of shell osteochondral allografts to the results of antihuman leukocyte antigen antibody screening (*Radiology* 2001;219:35-43)
  - Pts. who expressed positive humoral immune responses were associated with decreased incorporation, greater marrow edema pattern and a higher proportion of surface collapse of their graft



J Bone Joint Surg 2007; 89A(4):718-726

Juvenile Articular Cartilage Allograft

DeNovo NT Graft (Natural Tissue Graft®)

- Minced cartilage derived from juvenile human donors (allograft)
- There is a dramatic age-related decline in human chondrocyte chondrogenic potential
- Juvenile tissue has much higher proliferative capacity
- The material is suspended in fibrin glue and attached to lesion site using fibrin glue

Quantitative MRI: Issues of Data Acquisition

- Ideally assess both PG and collagen
- Clinical trial challenges for reproducibility: QMRI
  - Add to scan time!!
  - Software availability
  - Magnetic field strength (Na^{23}, T1rho)
  - Contrast agents (dGEMRIC)
  - Magic angle prolongation (T2, T1rho)
  - Coil choice (Na^{23})
  - Parameters of acquisition (SNR, resolution, # echoes)
  - Post-processing algorithm (2 vs. 3 parameter fit)
  - Registration software

Table 2. Recommendations for Use of Magnetic Resonance Imaging (MRI) in Multicenter Cartilage Repair Trials

Recommendation	Concerns/Variables
Establish imaging core laboratory with expertise in cartilage repair	Allows for standardized and reproducible assessment of RC and compliant registry of patient data
MRI data points (scoring system, pulse sequences, biochemical assessment) in phase I should parallel those used in preclinical models	Preclinical data will allow for relative range of relaxation times and expected morphological appearance of RC
Standardize magnetic field strength	Field strength will affect signal intensity and tissue relaxation times
Standardize imaging coils	Coil design will affect signal-to-noise ratio and image quality
Use cartilage pulse sequence validated for accuracy and reproducibility	MRI treated as an outcome measure
Use published and previously applied morphology assessment system (e.g., MOCART)	MRI treated as an outcome measure
Assess RC fixed charge density (proteoglycan) compared with NC	dGEMRIC; T1rho
Assess RC collagen orientation compared with NC	T2 mapping
Assess zonal (deep, superficial) relaxation times for RC, NC, and tissue at peripheral integration between RC and NC	Provides objective and quantifiable tissue characterization of RC and tissue at peripheral integration with host tissue
Define time points for data collection: 6 months, 1 year, 2 years, etc.	Coordinate MRI metrics with acquisition of subjective clinical outcome instruments
QA concerns: biyearly phantom assessment of relaxation times	Will detect site-specific issues that may lead to inaccuracies in quantitative assessment of RC and NC
Standardize postprocessing algorithm for quantitative assessment	Different algorithms may affect RC and NC relaxation times by up to 20% to 30%

Note: RC = repair cartilage; MOCART = magnetic resonance observation of cartilage repair tissue; NC = native cartilage; dGEMRIC = delayed gadolinium-enhanced MRI of cartilage; QA = quality assurance.

Adapted from Trattnig S, Winalski CS, Marlovits S, Jurvelin JS, Welsch GH, Potter HG. Magnetic resonance imaging of cartilage repair: A review. Cartilage 2011; 2(1):5-26

MRI of cartilage repair

- Future repair strategies will require appropriate combination of cells, scaffolds and signals (cytokines)
- We can form "cartilage-like" tissue but the overall microstructure and architecture are not normal
- Need strategies to regenerate tissue with appropriate mechanical function (i.e., strength) → "Functional tissue engineering" (? links to QMRI)
- ♦ Standardized, reproducible MR sequences should be utilized
- ♦ Objective evaluation of cartilage following repair
  - ♦ Secondary (primary!) end point for FDA trials
- ♦ Quantitative MR evaluation:
  - ♦ should ideally assess both PG and collagen
- Registration methodology and careful attention to acquisition parameters (2D, 3D, etc.) and post-processing necessary for multi-institutional trials

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