Defining Failure in Articular Cartilage Surgery

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Abstract

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Articular cartilage injury remains a challenging condition for orthopedic surgeons to address. While multiple treatment options exist and have reported improvement in patient symptoms, sustained and successful treatment of symptomatic chondral defects remains elusive in many cases. Physicians may define failure in a multitude of ways such as subsequent surgery, progression to arthroplasty, lack of improvement in outcome measures, lack of hyaline-like repair tissue, or poor appearance on imaging studies. This chapter reviews the current standards for defining treatment failure in order to address the importance of consistent and clear goals for treating cartilage injuries and understanding the outcome tools currently available.

Keywords

Cartilage restoration
Failure
Outcomes
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Introduction

Injury to the articular cartilage remains a difficult problem for patients and a challenging condition for orthopedic surgeons. Chondral lesions are commonly encountered in knee arthroscopy, with full-thickness lesions noted in more than 60% of knee arthroscopies [1, 2]. Additionally, osteoarthritis is one of the leading causes of worldwide disability, and the utilization of total knee arthroplasty continues to rise to attempt to address this condition.

Multiple treatment options are available to address articular cartilage lesions, and there has been great progress in developing novel cartilage restoration techniques. Microfracture remains an option for initial treatment for many lesions and is frequently used as a comparative therapy in clinical trials [3, 4]. This procedure involves penetrating the subchondral bone to stimulate a healing response with fibrocartilage. In 1994, Brittberg et al. published and popularized autologous chondrocyte implantation [5]. This technology utilizes a patient's native chondrocytes expanded in culture and then reimplanted to restore hyaline cartilage to an injured area. Novel matrix-associated autologous chondrocyte implantation (MACI) techniques have been introduced recently in an attempt to improve upon the results of ACI [6]. Osteochondral autograft transfer (OATS) and osteochondral allograft implantation are further treatment options that allow for the restoration of both the bone and cartilage at

the site of a defect [7, 8]. Numerous other novel therapeutics including surface allograft transplantation are early in the clinical adoption cycle or in development to address symptomatic chondral injuries.

Successful and sustained treatment of symptomatic chondral lesions, however, remains elusive in many cases. As new therapeutic options are introduced, it becomes even more important to have consistent and clear goals for treating cartilage injuries and to understand what outcome tools are available to determine which treatments will lead to excellent long-term outcomes. Additionally, the current level of evidence of the majority of the cartilage repair literature is limited at best [9]. The purpose of this chapter is to review current standards for defining treatment failure and explore methods that will be used in future studies to determine success and failure of cartilage restoration procedures.

Objective Endpoints

Clinical Definitions of Failure

Survival analysis is frequently used to evaluate cartilage restoration procedures with conversion to total knee arthroplasty or reoperation utilized as the endpoint in disease treatment. Sterett et al. reported 91% survival of microfracture and high tibial osteotomy at a mean follow-up of 7 years [10]. While conversion to TKA is easy to measure and objective, this may not capture all patients who are unsatisfied, symptomatic, or persistently limited in function after cartilage restoration procedures. Bae et al. followed a cohort of 134 knees following microfracture of symptomatic chondral lesions and defined failure as conversion to TKA or pain scores worse than the preoperative value or less than 60. With this more stringent definition of failure, success of microfracture was 88.8% at 5 years, 67.9% at 10 years, and 45.6% at 12 years after surgery [11].

Pestka et al. evaluated patients treated with ACI and compared patients with and without a prior history of microfracture. Failure in this study was defined as reoperation of any kind, with patients who had a prior microfracture having a significantly higher failure rate (25% vs 3.6%; $p = 0.024$). Patient satisfaction levels, however, showed no difference between these groups, with 25.9% of patients with prior microfracture reporting unsatisfactory results compared to 28.6% of patients without a history of prior microfracture [12]. Reoperation is an important outcome after cartilage restoration, but it is imperative to incorporate other variables to capture patient satisfaction, symptoms, and function. Additionally, understanding patient goals and expectations is necessary in interpreting conversion to TKA as a measure of failure as some patients may be satisfied with a procedure that bridges them to replacement, while others have goals of longer-term joint preservation with a desire for more complete symptom relief.

Histologic Evaluation of Cartilage Repair

Histologic assessment of cartilage repair can determine if repair tissue has similar biochemical and structural composition to native cartilage. An ideal repair technique would reproduce the complex architecture of articular cartilage; the appropriate levels of collagen, water, and glycosaminoglycans; and the interaction between the cartilage and subchondral bone. Animal studies are often used to test possible cartilage restoration procedures with a major advantage being the ability to perform histologic analysis on cartilage repair tissue. A biopsy during second-look arthroscopy may also be used in clinical studies; however this is an invasive procedure and may even damage the area of cartilage repair. The International Cartilage Repair Society (ICRS) has also provided recommendations on specific variables to control when performing histologic analysis of cartilage repair tissue [13]. These variables include the location of the biopsy sample, timing of recovery, processing methodology, staining method, and blind comparison to a control group.

After obtaining a cartilage sample in either a preclinical model or from arthroscopic biopsy, different stains are available to differentiate the types of tissue present at the repair site. Hematoxylin and eosin (H&E) staining is commonly used, with dark pink staining representing mineralized collagen and light pink staining signifying fibrous tissue [14]. Safranin O staining is used to determine the presence of proteoglycans [15]. Tissue stained with toluidine blue shows collagen matrix as blue and glycosaminoglycans as purple [16].

The stained samples are then evaluated with various scoring systems, including the Pineda system, O'Driscoll system, and ICRS-1 and ICRS-2 systems. The Pineda system rates four features, including defect fill, osteochondral junction integrity, matrix stain, and morphology of the cells [17]. The O'Driscoll system includes a rating of the tissue surface on regularity and integrity, thickness, integration with surrounding tissue, cellularity and cell clustering, and degenerative changes in surrounding tissue [18]. The ICRS rating systems include evaluation of the tissue surface, matrix, cellularity, cell viability, subchondral bone, and mineralization. For ICRS-1, the components are rated from 0 to 3, while ICRS-2 uses a continuous VAS rating from 0 to 100 [19, 20]. The use of these scoring systems in both animal and human cartilage trials allows for a consistent reporting of outcomes and evaluation of parameters linked to successful and sustained clinical results.

Macroscopic scoring systems have been developed to evaluate the gross appearance of cartilage restoration procedures at the time of second-look arthroscopy. One scale is the ICRS score. This score ranges from 0 to 12 and includes three categories rated as 0–4: amount of defect fill, integration with adjacent cartilage, and macroscopic appearance of the repair tissue [21]. A second score is the Oswestry Arthroscopy Score, which is scored from 0 to 10. Components of this score include graft fill, integration with adjacent cartilage, surface appearance, graft color, and stiffness of repair tissue [22]. Van den Borne et al. reviewed the reproducibility and validity of both measurements and found both scoring systems to be reproducible methods for evaluating cartilage restoration procedures [23].

While histologic and macroscopic appearance of cartilage repair tissue would intuitively predict clinical outcomes, defining failure based on these measures alone is insufficient. For instance, Knutsen et al. compared microfracture and ACI in a randomized trial and found no correlation between histologic appearance of repair tissue from a biopsy at 2 years after surgery and clinical outcomes or failure (23% in both groups), defined in this study as reoperation for a symptomatic defect before the final follow-up of 5 years [24]. In comparing microfracture and ACI, Saris et al. reported better histologic appearance of ACI at 1 year postoperative [25], though in a follow-up report on the same cohort, Vanlauwe et al. showed no difference between clinical outcomes between the groups at 5 years after surgery [26]. Finally, Gudas et al. reported on the ICRS macroscopic score at second-look arthroscopy in a randomized controlled trial comparing OATS and microfracture [27]. There was no difference in the clinical outcomes for groups with low-grade or high-grade ICRS scores. Future research will define which histologic and macroscopic properties are able to predict success and failure after cartilage repair procedures.

Subjective Outcomes

Patient-reported outcomes are an attractive metric to use when defining procedure-specific success and failure. These scores are collected in the form of survey questions and can be obtained at both scheduled follow-up visit and remotely through electronic- or telephone-based surveys. General health-related quality of life scores, such as the Short Form (SF)-36, are often collected to follow patients after cartilage restoration procedures, in addition to joint-specific scores and activity ratings. Patient-reported outcome measures help focus the definition of success and failure on the patient's perceived benefit from any intervention.

Joint-specific scores evaluate the symptoms, function, and level of disability and may better isolate the effects of a chondral injury and its treatment. The International Knee Documentation Committee (IKDC) Subjective Knee Form is a joint-specific outcome tool used to evaluate symptoms and function in the setting of knee ligament, meniscus, and chondral injury [28]. The IKDC score ranges from 0 to 100, with higher scores reflecting better knee function. The Knee Injury and Osteoarthritis Outcome Score (KOOS) is a second knee-specific score that is validated in measuring knee symptoms and function for osteoarthritis, meniscal injuries, and ligamentous injuries. The KOOS encompasses five sub-scores, including scores for activities of daily living, sports and recreation function, pain, symptoms, and knee-related quality of life. This score is also reported from 0 to 100, with higher scores reflecting better outcomes and function.

The Lysholm score was originally described to measure functional outcomes after knee ligament injury and has been validated to monitor cartilage repair procedures, as well [29, 30]. In a meta-analysis of cartilage repair

studies that included the results of 61 studies and 3987 operations, the Lysholm score was the most frequently reported clinical outcome score [9]. This score may be monitored prior to and after treatment, and a Lysholm score <64 has been described as a marker of clinical failure [31]. The WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) also measures function and symptoms as a result of knee conditions [32]. This survey has been tested most in the setting of osteoarthritis though it was shown to have similar responsiveness as the IKDC Subjective Knee Form in a group of chondral injury patients [33]. Other scores, such as the HSS and Cincinnati scores, are also utilized to monitor the response to treatment of articular cartilage injuries.

These various survey instruments show different responses in patients after cartilage restoration procedures. Ebert et al. compared responses to the KOOS, SF-36, Tegner, and Lysholm outcome measures 5 years after matrix-induced autologous chondrocyte transplantation [34]. The KOOS sports and quality of life sub-scores were the most responsive scores that showed the best correlation with a patient satisfaction. The Tegner score and SF-36 had the lowest responsiveness in this patient cohort. Hambly and Griva compared the KOOS and IKDC in patients with a history of knee articular cartilage repair surgery [35]. The IKDC Subjective Knee Form was found to perform better than the KOOS in this heterogeneous patient population. In general, the IKDC Subjective Knee Form should be recorded and reported in clinical trials on the treatment of articular cartilage injuries.

In addition to measuring patient symptoms and function, defining patient activity levels is also important when interpreting results from cartilage-resurfacing studies. Multiple activity scales are used, including the Tegner activity score and Marx activity rating scale. The Tegner activity score is a 0–10 scale that asks patients to rate their level of function, ranging from disability due to a knee condition to competing in elite-level sports. The Marx activity rating scale has four domains and asks patients to rate their ability to participate in running, cutting, pivoting, and decelerating. The use of activity ratings, both before and after cartilage restoration procedures, can reflect how successful a procedure is at restoring patients to a desired level of function.

For athletes, return to play and return to prior performance rates may provide even more guidance regarding the optimal treatment. Krych et al. performed a meta-analysis to evaluate return to play rates for various cartilage procedures. In this evaluation of 44 studies, osteochondral autograft transfer (OATS) showed the highest rate of return at 92%, while microfracture had the lowest rate at 58%. The rate for ACI was 82% and for osteochondral allograft was 88%. Additionally, OATS patients returned the quickest following the procedure, at a mean of 5.2 months, as compared to 9.1 months for microfracture, 9.6 months for osteochondral allografts, and 11.8 months for ACI. The overall return to sport rate in this study including 2549 patients was 76%. When treating an athletic patient, the definition of failure may become even more stringent with return to play as the primary criterion. Related to that endpoint is the fact that many athletes withdraw from sports for a variety of reasons unrelated to their clinical outcome and true return to play frequency may be underestimated.

Imaging-Based Endpoints

Imaging modalities can allow for a noninvasive and objective assessment after cartilage repair procedures. Magnetic resonance imaging (MRI) is commonly used in clinical trials to provide an in vivo assessment after cartilage procedures. This imaging modality is attractive as there is no ionizing radiation used and there is excellent soft tissue contrast. Additionally, multiple quantitative imaging techniques have been developed and applied specifically to cartilage to evaluate the biochemistry and microscopic structure of repair tissue.

First, MR images may be evaluated in a semiquantitative method. One such scoring system commonly utilized is the magnetic resonance observation of cartilage repair tissue (MOCART) system. This scoring system has excellent interobserver agreement and includes evaluation of defect fill, integration with surrounding tissue, surface integrity, signal intensity, subchondral bone status, the presence of adhesions, and degree of synovitis [36]. Studies have demonstrated correlations of the MOCART score with a VAS pain score [37, 38], with the KOOS [38, 39], and with IKDC scores. However a recent systematic review found inconsistent relationships of MOCART with clinical outcomes, perhaps because of the multiple components of the scoring system [40]. For instance, defect fill alone has been shown to be correlated with clinical outcomes after microfracture [41, 42].

Multiple quantitative imaging sequences offer the ability to probe the biochemical and structural makeup of tissue. First, delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC) utilizes intravenous gadolinium contrast material to measure the proteoglycan content in the cartilage. A preinjection scan is completed, followed by the administration of contrast material, a period of exercise, and a re-scan of the affected joint. Due to the negative charge of gadolinium, the results of this scan give a direct measurement of proteoglycan content. The dGEMRIC relaxation rate has been correlated with IKDC, Lysholm, and KOOS scores after treatment of chondral lesions with osteochondral allograft and ACI [43, 44].

Multiparametric MR sequences, such as T1rho and T2 mapping, can also provide detailed information on the biochemical composition of the cartilage without exogenous contrast. The T1rho relaxation time is proportional to the proteoglycan content in the tissue and has been used to monitor changes in the composition of cartilage repair tissue [45, 46]. T2 mapping provides information on the collagen structure of cartilage and repair tissue [45]. There have been variable reports on whether T2 mapping values are correlated with subjective outcome scores after different cartilage repair surgeries [43, 44, 47, 48].

While the relationships between imaging parameters and clinical outcomes are not fully defined, there is great potential for these studies to serve as objective, noninvasive biomarkers for success and failure after cartilage repair procedures. Characterizing the macroscopic and microscopic properties of repair tissue through MRI can provide an alternative to second-look arthroscopy and biopsy. These imaging techniques offer the possibility for an earlier definition of the likelihood success or failure of new repair procedures before the deterioration of clinical function.

Conclusions

Defining success and failure is a complex question with regard to outcomes after cartilage restoration surgery. Failure may be variably defined as subsequent surgery, progression to arthroplasty, lack of improvement in outcome measures, lack of hyaline-like repair tissue, or poor appearance on imaging studies. When designing and reporting on clinical trials for cartilage injuries, multiple definitions of failure should be included. Early endpoints should encompass factors such as imaging parameters that may be predictive of long-term function, while longer-term studies may focus more on reoperation rates, ability to meet predefined outcome score thresholds, and conversion to arthroplasty surgery. All trials should incorporate patient-reported outcome measures, activity measures, and satisfaction scores to gauge whether patient-defined goals are met with specific procedures. Once this information is widely available, surgeons can better counsel and provide guidance on success and failure rates based on specific patient goals.

References

1. Curl WW, Krome J, Gordon ES, Rushing J, Smith BP, Poehling GG. Cartilage injuries: a review of 31,516 knee arthroscopies. Arthroscopy J Arthroscopic Relat Surg. 1997;13:456–60.

2. Hjelle K, Solheim E, Strand T, Muri R, Brittberg M. Articular cartilage defects in 1,000 knee arthroscopies. Arthroscopy J Arthroscopic Relat Surg. 2002;18:730–4.

3. Steadman JR, Briggs KK, Rodrigo JJ, Kocher MS, Gill TJ, Rodkey WG. Outcomes of microfracture for traumatic chondral defects of the knee: average 11-year follow-up. Arthroscopy J Arthroscopic Relat Surg. 2003;19:477–84.

4. Mithoefer K, McAdams T, Williams RJ, Kreuz PC, Mandelbaum BR. Clinical efficacy of the microfracture technique for articular cartilage repair in the knee: an evidence-based systematic analysis. Am J Sports Med. 2009;37:2053–63.

5. Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. N Engl J Med. 1994;331:889–95.

6. Kon E, Verdonk P, Condello V, et al. Matrix-assisted autologous chondrocyte transplantation for the repair of cartilage defects of the knee. Am J Sports Med. 2009;37:156S–66S.

7. Gudas R, Kalesinskas RJ, Kimtys V, et al. A prospective randomized clinical study of mosaic osteochondral autologous transplantation versus microfracture for the treatment of osteochondral defects in the knee joint in young athletes. Arthroscopy J Arthroscopic Relat Surg. 2005;21:1066–75.

8. Bugbee WD, Convery FR. Osteochondral allograft transplantation. Clin Sports Med. 1999;18:67–75.

9. Jakobsen RB, Engebretsen L, Slauterbeck JR. An analysis of the quality of cartilage repair studies. J Bone Joint Surg Am. 2005;87:2232–9.

10. Sterett WI, Steadman JR, Huang MJ, Matheny LM, Briggs KK. Chondral resurfacing and high tibial osteotomy in the varus knee: survivorship analysis. Am J Sports Med. 2010;38:1420–4.

11. Bae DK, Song SJ, Yoon KH, Heo DB, Kim TJ. Survival analysis of microfracture in the osteoarthritic knee —minimum 10-year follow-up. Arthroscopy J Arthroscopic Relat Surg. 2013;29:244–50.

12. Pestka JM, Bode G, Salzmann G, Südkamp NP, Niemeyer P. Clinical outcome of autologous chondrocyte implantation for failed microfracture treatment of full-thickness cartilage defects of the knee joint. Am J Sports Med. 2012;40:325–31.

13. Hoemann C, Kandel R, Roberts S, et al. International Cartilage Repair Society (ICRS) recommended guidelines for histological endpoints for cartilage repair studies in animal models and clinical trials. Cartilage. 2011;2:153–72.

14. Gilmore R, Palfrey A. A histological study of human femoral condylar articular cartilage. J Anat. 1987;155:77.

15. Rosenberg L. Chemical basis for the histological use of safranin O in the study of articular cartilage. J Bone Joint Surg Am. 1971;53:69–82.

16. Henderson I, Tuy B, Connell D, Oakes B, Hettwer W. Prospective clinical study of autologous chondrocyte implantation and correlation with MRI at three and 12 months. Bone Joint J. 2003;85:1060–6.

17. Pineda S, Pollack A, Stevenson S, Goldberg V, Caplan A. A semiquantitative scale or histologic grading of articular cartilage repair. Cells Tissues Organs. 1992;143:335–40.

18. O'Driscoll SW, Keeley FW, Salter RB. Durability of regenerated articular cartilage produced by free autogenous periosteal grafts in major full-thickness defects in joint surfaces under the influence of continuous passive motion. A follow-up report at one year. J Bone Joint Surg Am. 1988;70:595–606.

19. Mainil-Varlet P, Aigner T, Brittberg M, et al. Histological assessment of cartilage repair. J Bone Joint Surg Am. 2003;85:45–57.

20. Mainil-Varlet P, Van Damme B, Nesic D, Knutsen G, Kandel R, Roberts S. A new histology scoring system for the assessment of the quality of human cartilage repair: ICRS II. Am J Sports Med. 2010;38:880–90.

21. Brittberg M, Peterson L. Introduction of an articular cartilage classification. ICRS Newsl. 1998;1:5–8.

22. Smith GD, Taylor J, Almqvist KF, et al. Arthroscopic assessment of cartilage repair: a validation study of 2 scoring systems. Arthroscopy J Arthroscopic Relat Surg. 2005;21:1462–7.

23. Van Den Borne M, Raijmakers N, Vanlauwe J, et al. International Cartilage Repair Society (ICRS) and Oswestry macroscopic cartilage evaluation scores validated for use in Autologous Chondrocyte Implantation (ACI) and microfracture. Osteoarthr Cartil. 2007;15:1397–402.

24. Knutsen G, Drogset JO, Engebretsen L, et al. A randomized trial comparing autologous chondrocyte implantation with microfracture. J Bone Joint Surg. 2007;89:2105–12.

25. Saris DB, Vanlauwe J, Victor J, et al. Characterized chondrocyte implantation results in better structural repair when treating symptomatic cartilage defects of the knee in a randomized controlled trial versus microfracture. Am J Sports Med. 2008;36:235–46.

26. Vanlauwe J, Saris DB, Victor J, Almqvist KF, Bellemans J, Luyten FP. Five-year outcome of characterized chondrocyte implantation versus microfracture for symptomatic cartilage defects of the knee: early treatment matters. Am J Sports Med. 2011;39:2566–74.

27. Gudas R, Gudaitė A, Pocius A, et al. Ten-year follow-up of a prospective, randomized clinical study of mosaic osteochondral autologous transplantation versus microfracture for the treatment of osteochondral defects in the knee joint of athletes. Am J Sports Med. 2012;40:2499–508.

28. Irrgang JJ, Anderson AF, Boland AL, et al. Development and validation of the international knee documentation committee subjective knee form. Am J Sports Med. 2001;29:600–13.

29. Lysholm J, Gillquist J. Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. Am J Sports Med. 1982;10:150–4.

30. Kocher MS, Steadman JR, Briggs KK, Sterett WI, Hawkins RJ. Reliability, validity, and responsiveness of the Lysholm knee scale for various chondral disorders of the knee. JBJS. 2004;86:1139–45.

31. Knutsen G, Drogset JO, Engebretsen L, et al. A randomized multicenter trial comparing autologous chondrocyte implantation with microfracture: long-term follow-up at 14 to 15 years. J Bone Joint Surg Am. 2016;98:1332–9.

32. McConnell S, Kolopack P, Davis AM. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties. Arthritis Care Res. 2001;45:453–61.

33. Greco NJ, Anderson AF, Mann BJ, et al. Responsiveness of the International Knee Documentation Committee subjective knee form in comparison to the Western Ontario and McMaster Universities Osteoarthritis Index, modified Cincinnati Knee Rating System, and Short Form 36 in patients with focal articular cartilage defects. Am J Sports Med. 2010;38:891–902.

34. Ebert JR, Smith A, Wood DJ, Ackland TR. A comparison of the responsiveness of 4 commonly used patient-reported outcome instruments at 5 years after matrix-induced autologous chondrocyte implantation. Am J Sports Med. 2013;41:2791–9.

35. Hambly K, Griva K. IKDC or KOOS? which measures symptoms and disabilities most important to postoperative articular cartilage repair patients? Am J Sports Med. 2008;36:1695–704.

36. Marlovits S, Striessnig G, Resinger CT, et al. Definition of pertinent parameters for the evaluation of articular cartilage repair tissue with high-resolution magnetic resonance imaging. Eur J Radiol. 2004;52:310–

9.

37. Dhollander A, Huysse W, Verdonk P, et al. MRI evaluation of a new scaffold-based allogenic chondrocyte implantation for cartilage repair. Eur J Radiol. 2010;75:72–81.

38. Marlovits S, Singer P, Zeller P, Mandl I, Haller J, Trattnig S. Magnetic resonance observation of cartilage repair tissue (MOCART) for the evaluation of autologous chondrocyte transplantation: determination of interobserver variability and correlation to clinical outcome after 2 years. Eur J Radiol. 2006;57:16–23.

39. Robertson W, Fick D, Wood D, Linklater J, Zheng M, Ackland T. MRI and clinical evaluation of collagen-covered autologous chondrocyte implantation (CACI) at two years. Knee. 2007;14:117–27.

40. de Windt TS, Welsch GH, Brittberg M, et al. Is magnetic resonance imaging reliable in predicting clinical outcome after articular cartilage repair of the knee? A systematic review and meta-analysis. Am J Sports Med. 2013;41:1695–702.

41. Mithoefer K, Williams RJ, Warren RF, et al. The microfracture technique for the treatment of articular cartilage lesions in the knee. J Bone Joint Surg Am. 2005;87:1911–20.

42. Kreuz PC, Steinwachs MR, Erggelet C, et al. Results after microfracture of full-thickness chondral defects in different compartments in the knee. Osteoarthr Cartil. 2006;14:1119–25.

43. Tadenuma T, Uchio Y, Kumahashi N, et al. Delayed gadolinium-enhanced MRI of cartilage and T2 mapping for evaluation of reparative cartilage-like tissue after autologous chondrocyte implantation associated with Atelocollagen-based scaffold in the knee. Skelet Radiol. 2016;45:1357–63.

44. Brown DS, Durkan MG, Foss EW, Szumowski J, Crawford DC. Temporal in vivo assessment of fresh osteochondral allograft transplants to the distal aspect of the femur by dGEMRIC (delayed gadolinium-enhanced MRI of cartilage) and zonal T2 mapping MRI. J Bone Joint Surg Am. 2014;96:564–72.

45. Li X, Cheng J, Lin K, et al. Quantitative MRI using T1rho and T2 in human osteoarthritic cartilage specimens: correlation with biochemical measurements and histology. Magn Reson Imaging. 2011;29:324–34.

46. Theologis AA, Schairer WW, Carballido-Gamio J, Majumdar S, Li X, Ma CB. Longitudinal analysis of T1ρ and T2 quantitative MRI of knee cartilage laminar organization following microfracture surgery. Knee. 2012;19:652–7.

47. Domayer S, Kutscha-Lissberg F, Welsch G, et al. T2 mapping in the knee after microfracture at 3.0 T: correlation of global T2 values and clinical outcome–preliminary results. Osteoarthr Cartil. 2008;16:903–8.

48. Jungmann PM, Brucker PU, Baum T, et al. Bilateral cartilage T2 mapping 9 years after mega-OATS implantation at the knee: a quantitative 3T MRI study. Osteoarthr Cartil. 2015;23:2119–28.