

Image-Guided Chondrocyte Harvesting for Autologous Chondrocyte Implantation

Initial Feasibility Study with Human Cadaver and Pilot Clinical Experience

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Background: Autologous chondrocyte implantation (ACI), a promising modality for repairing full-thickness cartilage defects, requires 2 consecutive arthroscopic procedures for chondrocyte harvesting and implantation. In the present study, we assessed the feasibility and efficacy of image-guided chondrocyte harvesting as an alternative to arthroscopic biopsy.

Methods: We induced full-thickness cartilage defects in 10 human cadaveric knees. Computed tomographic arthrography (CTA) was performed following the intra-articular administration of Omnipaque 350 to measure the diameters of the induced cartilage defects. Subsequently, 2 independent operators conducted CTA-guided chondrocyte harvesting (from the medial and lateral trochlear ridges) in each knee. The time for chondrocyte harvesting, accuracy (distance between the predefined target on CTA and the final insertion site of the needle), and number of needle readjustments were recorded. In the institutional review board-approved clinical study, informed consent was obtained and chondrocyte harvesting was performed both with use of a conventional arthroscopic biopsy method and with use of a needle through an arthroscopy access site in 10 subjects for whom ACI was indicated. The samples were processed and cultured blindly, and the quantity and quality of the samples were determined.

Results: CTA measurements of full-thickness cartilage defects showed high to perfect absolute agreement and consistency when compared with direct measurements (overall interclass correlation coefficient, 0.933 to 0.983; $p < 0.05$). For both operators, image-guided chondrocyte harvesting from the lateral ridge was more accurate ($p = 0.007$ and 0.040) and faster ($p = 0.056$ and 0.014) in comparison with harvesting from the medial ridge. In the clinical study, no significant difference was observed for the growth index of samples between the needle-harvest and conventional methods ($p = 0.897$).

Conclusions: CTA can be used for precise measurement of full-thickness cartilage defects. Image-guided chondrocyte harvesting is a viable alternative to traditional arthroscopic biopsy for ACI.

Clinical Relevance: We recognize the current pivotal role of arthroscopic biopsy, as a part of ACI, for chondrocyte harvesting as well as for delineating the nature of the lesion. However, on the basis of our results, image-guided chondrocyte retrieval may obviate the need for arthroscopic biopsy in some patients in the future.

Full-thickness cartilage defects are associated with knee pain and mechanical symptoms and are predictors of end-stage osteoarthritis^{1,2}. Several surgical methods, including microfracture, osteochondral autograft transplantation, and autologous chondrocyte implantation (ACI), have been used to provide fibrocartilage or hyaline cartilage to the defect sites³⁻⁶. Although these methods restore cartilage integrity, there is a paucity of data on their protective effect with regard to pain and osteoarthritis progression³⁻⁶. Among all of these methods,

ACI and especially matrix-associated ACI (MACI) have been considered to be promising modalities to provide viable chondrocytes to a large articular injured area, with favorable clinical outcomes^{3,7,8}.

To perform a standard ACI or MACI, chondrocytes are initially harvested arthroscopically from a non-weight-bearing cartilage surface region (e.g., the medial or lateral trochlear ridge or the femoral intercondylar notch)⁹⁻¹¹. The harvested samples are cultured on a collagen membrane and then are

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implanted into the defect via a second arthrotomy or arthroscopic surgery^{9,10}. Despite the positive experiences that have been reported in association with ACI and MACI, these methods have numerous limitations, including hypertrophy and overgrowth of the periosteal patch, unpredictable long-term chondrocyte viability, and extraordinary cost¹². The requirement for 2 consecutive operations can limit the clinical application of ACI because of the morbidity and complications associated with these procedures^{13,14}.

Image-guided tissue harvesting is a well-established minimally invasive procedure that has been primarily used for the diagnosis of bone and soft-tissue abnormalities^{15,16}. This method currently is performed with use of computed tomography (CT), ultrasound, and magnetic resonance imaging (MRI) in the outpatient setting, and it is feasible and comparable with open biopsy in terms of costs, complications, and patient satisfaction^{17,18}.

The purpose of the present study was to investigate the feasibility of image-guided chondrocyte harvesting as an alternative to arthroscopic surgery for the first stage of ACI or MACI. The present investigation was performed in 2 parts. In the first part, a human cadaveric study was performed to assess the feasibility and accuracy of image-guided chondrocyte harvesting with use of CT arthrography (CTA) as well as to evaluate the accuracy of CTA in determining the diameters of cartilage defects. In the second part, a pilot clinical study was performed to investigate the quantity and quality of obtained chondrocytes.

Materials and Methods

Study Samples

We obtained 10 human cadaveric lower extremities in accordance with Health Insurance Portability and Accountability Act (HIPAA) recommendations. Full-thickness

cartilage defects (average height and width, 18.3 and 12.4 mm, respectively) were induced in all specimens, and CTA-guided needle chondrocyte harvesting was performed as described below.

For the institutional review board-approved, HIPAA-compliant clinical study, 10 human subjects were recruited from an orthopaedic sports medicine clinic between January 2015 and January 2016. As part of the informed-consent process, all subjects were informed about the 2 applied methods of chondrocyte harvesting. All 10 subjects had full-thickness cartilage defects and were candidates for standard ACI, and all underwent same-day needle harvesting and conventional arthroscopic retrieval of chondrocytes.

Introducing Full-Thickness Cartilage Defects (Cadaveric Study)

An arthrotomy was performed with use of a medial parapatellar approach¹⁹. The incision was made from 5 cm above the superior patellar margin to the tibial tubercle in a curvilinear fashion. Articular cartilage in the femoral epiphysis was inspected in 3 locations (the trochlea, medial femoral condyle, and lateral femoral condyle). At each site, 1 full-thickness cartilage defect was induced with use of straight and curved microcurets. The cartilage defects had distinct margins. In 1 sample, the medial condylar cartilage had a large full-thickness cartilage defect, and no additional injury was induced in that location. In another sample, the lateral condylar cartilage was completely denuded, and we were not able to create any defect at that site. The height and width of the cartilage defects were measured by an observer who was not involved in the CTA measurements; the average height was 18.3 mm (range, 11 to 42 mm), and the average width was 12.4 mm (range, 5 to 38 mm). The joint capsule, fascia, and skin were then closed.

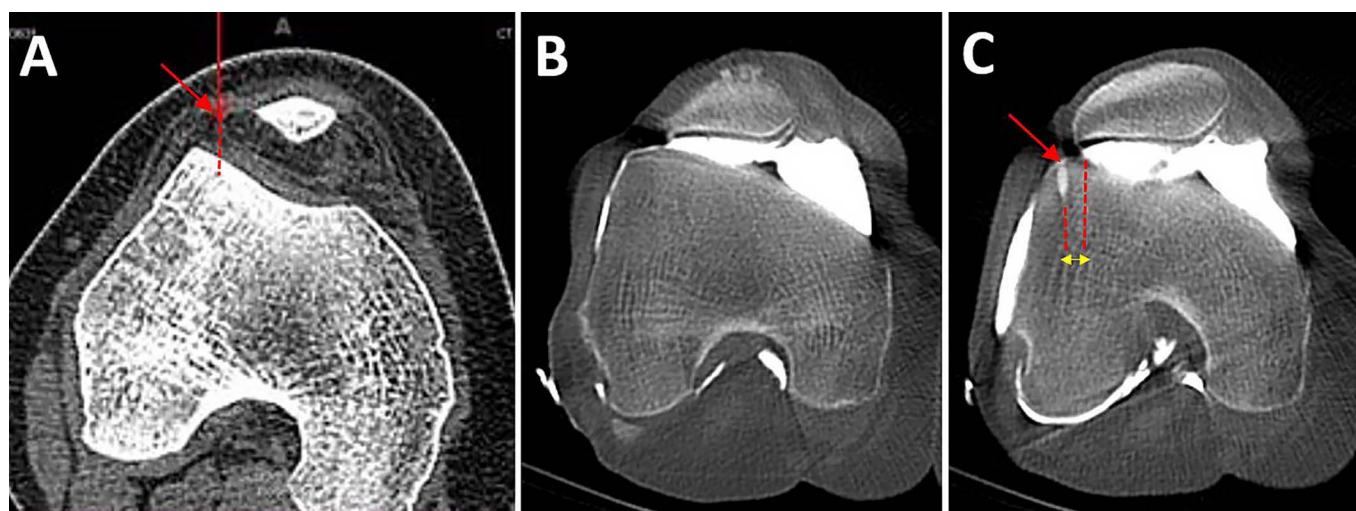


Fig. 1

Fig. 1-A Preprocedural axial CT scan used for the determination of the target site (red arrow and dashed line) for the performance of image-guided chondrocyte retrieval. **Fig. 1-B** Axial CTA scan made following the intra-articular administration of Omnipaque 350, used to measure the size of the cartilage defect. **Fig. 1-C** Axial CTA scan made after CTA-guided chondrocyte harvesting; the distance between the predefined target on the preprocedural CT scan and the final insertion site of the needle (red arrow) was calculated as the distance between the 2 red dashed lines (marked by the yellow bidirectional arrow).

CTA and CTA-Guided Needle Harvesting (Cadaveric Study)

Following the creation of the cartilage defects, CTA and CTA-guided chondrocyte harvesting were performed on all cadaveric knees. All scans were performed with use of a Siemens CT scanner (Siemens Medical Systems) according to CT parameters that are routinely used in clinical practice (120 kVp and 150 to 200 mA).

First, preprocedural CT acquisition was performed and the target site for performing chondrocyte retrieval was marked and recorded (Fig. 1). Next, following the intra-articular administration of 20 mL of Omnipaque 350 (Nycomed), CTA was performed to visualize the joint space and the full-thickness cartilage defects (Fig. 1). Multiplanar reconstructions of the scanned data were examined on a picture archiving and communication system (Emageon Workstation; Emageon). After image acquisition, a musculoskeletal radiologist with 8 years of clinical experience reviewed and measured the height and the width of the cartilage defects (in millimeters) on CTA.

Subsequently, the specimens underwent CTA-guided chondrocyte harvesting. An Osteo-Site bone biopsy needle (product number, G13761; description, Murphy M1M; size, 11 gauge \times 10 cm) was used for chondrocyte retrieval (Fig. 2). Two operators (1 musculoskeletal radiologist and 1 orthopaedic surgeon) performed the procedures. Each operator performed 1 sampling from the medial ridge of the trochlea and 1 sampling from the lateral ridge. Time (in seconds), accuracy (the distance [in millimeters] between the predefined target on the preproce-

dural CT scan and the final insertion site of the needle) (Fig. 1), and the number of needle readjustment attempts were recorded.

Chondrocyte Retrieval with Use of Standard Arthroscopic Versus Needle Harvesting (Clinical Study)

Cartilage samples were obtained arthroscopically from a non-weight-bearing area on the femoral intercondylar notch of the damaged knee with use of the conventional technique to ensure the standard of care regarding the adequacy of samples for planned ACI^{9,10}. Simultaneously during the routine arthroscopic chondrocyte retrieval, an Osteo-Site coaxial bone biopsy needle set (product number, G13761; description, Murphy M1M; size, 11 gauge \times 10 cm; M2-S) was inserted through the arthroscopy probe access site to obtain additional chondrocytes from the non-weight-bearing lateral trochlear ridge. The retrieved samples were placed in a sterile medium and were submitted for cell culture separately.

Isolation and Culture of Chondrocytes (Clinical Study)

In vitro culture of the obtained cells was performed with use of the method described by Brittberg et al.¹⁰. The cartilage specimens were washed, and adherent bone and synovial tissue were removed. The weights of the samples were recorded (mg), and the samples were then minced and digested in the culture medium. The obtained cells were then filtered through a nylon mesh (pore diameter, 25 μ m) and were counted. The derived

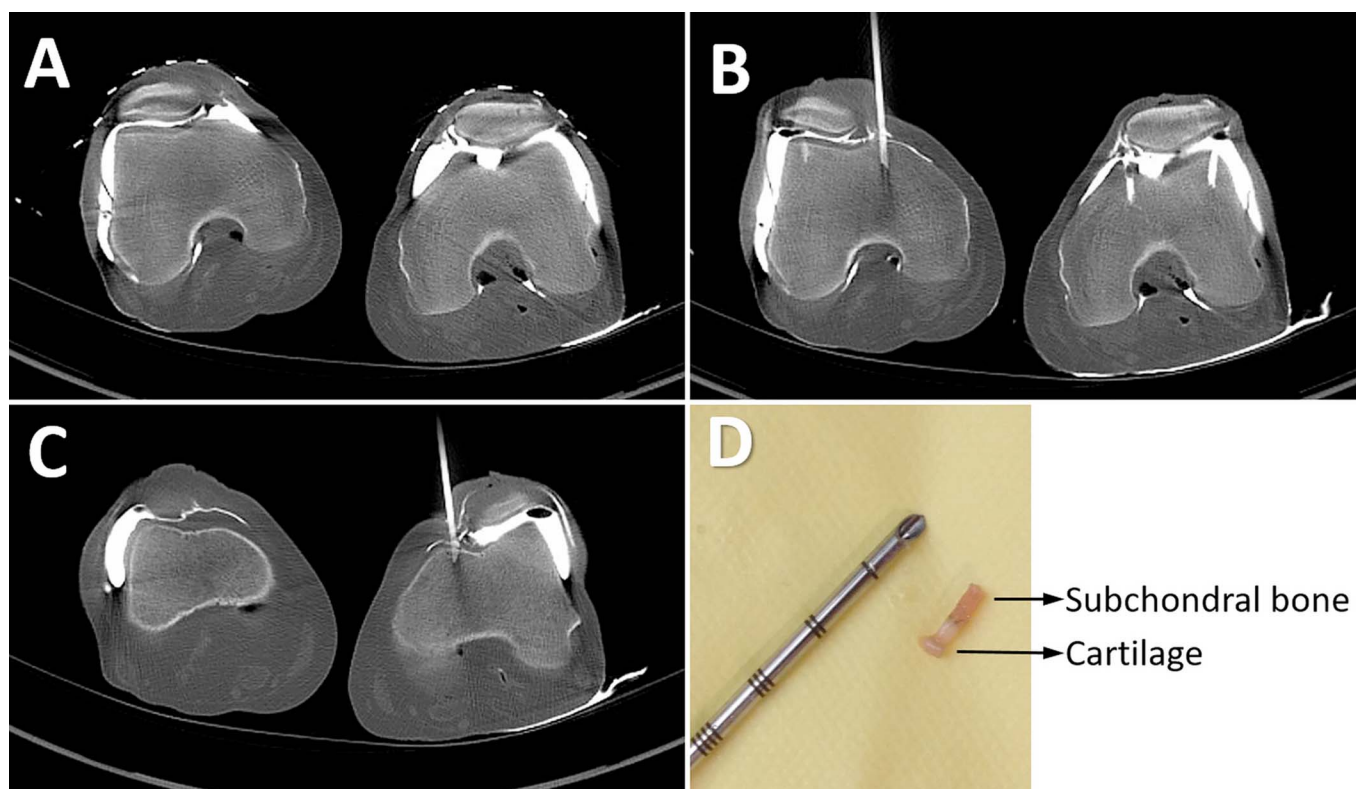


Fig. 2

Figs. 2-A, 2-B, and 2-C Serial axial CTA slices demonstrating the harvesting needle pathway used to obtain cartilage tissue. **Fig. 2-D** Cartilage tissue and accompanying subchondral bone obtained with use of CTA-guided needle harvesting.

TABLE I Absolute Agreement, Consistency, and Accuracy of CTA Measurements in Estimating Full-Thickness Femoral Cartilage Defects*

Defect Site	Defect Height			Defect Width		
	Absolute Agreement (ICC)	Consistency (ICC)	Accuracy†	Absolute Agreement (ICC)	Consistency (ICC)	Accuracy†
Trochlea	0.996‡	0.997‡	0 (2.0)	0.952§	0.946§	0 (3.0)
Medial condyle	0.970‡	0.987‡	2.0 (2.0)	0.848#	0.828#	0 (3.0)
Lateral condyle	0.938§	0.939§	0.5 (3.5)	0.404	0.429	1.0 (3.8)
All	0.981‡	0.983‡	0.5 (2.0)	0.936‡	0.933‡	0 (3.0)

*For interclass correlation coefficients (ICCs), a higher value (closer to 1) was indicative of higher absolute agreement and consistency. For accuracy, which was measured as the Euclidean difference (in millimeters) between the CTA estimates and the direct measurements of the full-thickness lesions, lower values were indicative of higher accuracy. †The values are given as the median, with the interquartile range in parentheses. ‡P < 0.001. §P < 0.01. #P < 0.05.

cells were transferred and cultured, and the number of cells per sample weight (cells/mg), the total number of viable chondrocytes (number of cells), and the cellular growth index (doublings/day) were calculated.

Statistical Analysis

First, in the cadaveric study, the accuracy of CTA in measuring the diameters of the cartilage defects was evaluated. CTA measurements were compared with the direct visual measurements of cartilage lesions, and interclass correlation coefficients (ICCs) were calculated to evaluate the absolute agreement and consistency.

Second, also in the cadaveric study, the accuracy and feasibility of CTA-guided chondrocyte harvesting were determined. The time required to obtain tissue (sec), accuracy (mm), and number of needle readjustments were compared with use of the t test (for normally distributed variables) or the Mann-Whitney U test (for non-normally distributed values) between samplings from the medial and lateral trochlear ridges. Similarly, the variables were compared between the 2 operators.

Third, in the clinical study, the quantity and quality of samples retrieved with use of the needle-harvesting and conventional methods were compared. With use of the paired t test (for normally distributed values) or the paired Wilcoxon signed-rank test (for non-normally distributed values), the weight (total, net, and processed), number of cells, and growth index of samples were compared for each patient.

A 2-tailed p value of <0.05 was considered significant. Analyses were performed with use of the R platform (version 3.2.5; R Foundation for Statistical Computing) and SPSS (version 24; IBM).

Results

CTA measurements of full-thickness cartilage defects had high to perfect absolute agreement and consistency with regard to the direct visual measurements (overall ICC, 0.933 to 0.983). The width of the lateral femoral condyle was an exception in our experiment (ICC, 0.404), possibly due to the low sample size and the exclusion of 1 knee with a completely denuded lateral femoral condyle. CTA also showed high accuracy: the

differences between CTA-derived and direct visual measurements ranged from 0 to 2 mm. Table I summarizes the CTA performance in estimating the full-thickness cartilage defects.

CTA-guided chondrocyte harvesting resulted in successful cartilage retrieval in each case. There were no significant differences between the 2 operators in terms of time, the accuracy of performance, or the number of needle readjustments (p > 0.05). For each operator, sampling from the lateral trochlear ridge was more accurate (p = 0.007 and 0.040) and faster (p = 0.056 and 0.014) when compared with sampling from the medial trochlear ridge. Table II summarizes the performance measures of the 2 operators.

TABLE II Performance Measures for 2 Operators When Obtaining Chondrocytes from Medial and Lateral Trochlear Ridges*

	Operator 1	Operator 2
Time to obtain tissue (sec)		
Medial ridge	106 ± 36	111 ± 35
Lateral ridge	74 ± 34	72 ± 30
P value	0.056	0.014†
Accuracy (mm)		
Medial ridge	3.23 ± 1.72	2.81 ± 1.36
Lateral ridge	1.32 ± 1.01	1.17 ± 0.57
P value	0.007†	0.040†
Needle readjustment attempts		
Medial ridge	1.10 ± 0.99	1.00 (0.81)
Lateral ridge	1.00 (1.00)	1.00 (1.25)
P value	0.315	0.739

*The values are given as the mean and the standard deviation (for normally distributed values) or as the median with the width of the interquartile range in parentheses (for non-normally distributed values). The values for the lateral and medial trochlear ridges were compared with use of the independent 2-samples t test or the non-parametric Mann-Whitney U test. Accuracy was measured as the Euclidean distance from the target (in millimeters); lower values were indicative of higher accuracy. †Significant (p < 0.05).

TABLE III Comparison of Conventional Arthroscopic Harvesting and Needle Harvesting of Chondrocytes in Clinical Study*

	Conventional Arthroscopic Harvesting	Needle Harvesting†	P Value
Total weight prior to bone/synovium removal (mg)	215 (497.5)	101 ± 40.7	0.013‡
Net weight after bone/synovium removal (mg)	170 (272.5)	82 ± 54.5	0.013‡
Processed weight (mg)	176 ± 100	82 ± 52.5	0.011‡
No. of cells/mg	2,749 ± 1,090	1,365 (2,022)	0.093
No. of viable cells	$1.35 \times 10^7 \pm 9.73 \times 10^6$	$5.33 \times 10^6 \pm 1.48 \times 10^6$	0.030‡
Growth index (doublings/day)	0.494 ± 0.089	0.488 ± 0.138	0.897

*The values are given as the mean and the standard deviation (for normally distributed values) or as the median with the width of the interquartile range in parentheses (for non-normally distributed values). The values were compared with use of the paired t test or the paired Wilcoxon signed-rank test. †Needle-harvested chondrocytes were obtained from only 1 core sample from each subject. ‡Significant ($p < 0.05$).

The clinical study showed that a greater amount of tissue (in terms of weight) and a higher number of viable cells were obtained with use of the conventional arthroscopic technique in comparison with needle harvesting (Table III). However, there was no significant difference between 2 methods in terms of the cellular growth index ($p = 0.897$) (Table III).

Discussion

In the present study, we showed that image-guided chondrocyte harvesting might be a feasible method for viable chondrocyte retrieval. We also demonstrated that CTA could be used for accurate assessment of full-thickness cartilage defects. We recognize the current pivotal role of arthroscopic biopsy, as a part of ACI, for chondrocyte harvesting as well as for delineating the nature of the lesion. However, our results suggest that image-guided chondrocyte retrieval may obviate the need for arthroscopic biopsy in some patients in the future.

MACI is indicated and performed for symptomatic patients with isolated 2 to 10-cm² full-thickness cartilage defects of the knee, without any specific age cutoff. In the present study, we tested the hypothesis that an image-guided procedure may be an alternative for arthroscopic chondrocyte retrieval for MACI or ACI, with the possibility of lower overall cost as well as lower rates of complications and morbidity^{15,20}. Image-guided biopsy has been recognized as a minimally invasive, accessible, and feasible technique, with an accuracy comparable with that of open biopsy, which is currently used in clinical practice for the diagnosis of musculoskeletal tumors and infection^{15-21,22}. For the first time, we showed that image-guided chondrocyte harvesting is a feasible and accurate method for cartilage sampling when performed by both a radiologist and an orthopaedic surgeon¹⁴. In the present study, CTA-guided harvesting was performed on the medial and lateral trochlear ridges, which are the recommended sites of cartilage retrieval for ACI^{12,23}. No sample was harvested from the femoral intercondylar notch (the most common site for conventional arthroscopic chondrocyte retrieval), which was not accessible with use of cross-sectional image-guided approaches. We found that all attempts resulted in successful tissue retrieval. In addition, sampling from the lateral trochlear ridge was faster and more accurate in comparison with

sampling from the medial trochlear ridge. We also investigated the adequacy, quality, and viability of the retrieved chondrocytes in a clinical setting. In order to create an MACI membrane, previous investigators have recommended harvesting a specimen containing 200 mg of healthy cartilage^{12,23}. Chondrocytes are then isolated from the harvested sample and are seeded on type-I and III collagen membrane at a density of >500,000 cells/square cm^{12,23}. Despite the lower amount of tissue yielded through our needle-harvest method (with the average weight of harvested samples from a single needle biopsy attempt being 101 mg, which was lower than the required 200 mg), samples obtained with use of the needle showed comparable quality and viability. Our results showed total number of 5,000,000 cells were obtained using needle harvest method which was adequate for creating MACI membrane^{12,23}. Two or more samples using image-guided chondrocyte harvesting may be required for optimal result in subjects with large and/or multiple cartilage defects.

The use of CTA as an accurate imaging modality for the assessment of cartilage defects has been suggested by previous investigators²⁴⁻²⁷. In human cadaveric studies, Vande Berg et al. and Li et al. reported overall correlation coefficients of 0.8 when cartilage defects were evaluated with use of CTA and direct visual measurements^{25,28}. De Filippo et al., in a clinical study, found that CTA had an accuracy of 92% to 95% and perfect interobserver agreement ($\kappa = 0.97$) for the diagnosis of cartilage defects²⁹. Our findings also demonstrated that CTA measurements had excellent accuracy (overall ICC, 0.828 to 0.997). Arthroscopy has been considered to be the gold-standard tool for the assessment of articular damage^{30,31}. Several studies have demonstrated that estimating the exact diameters of cartilage defects is challenging and that imaging modalities may result in underestimation or overestimation of the size of defects when compared with arthroscopy³²⁻³⁵. Gomoll et al. showed that the size of cartilage defects was underestimated by 65% when MRI measurements were compared with direct measurements³⁶. In contrast, the high accuracy of imaging methods for estimating the exact diameters of articular lesions has been demonstrated in a handful of prior studies^{28,32,34,37-39}. Recent advances have led to marked improvement in the

determination of cartilage defect size with use of both high-resolution MRI and CTA^{37,40}.

On the basis of our initial experience in the present study, advanced imaging techniques such as CTA and MRI can be considered as noninvasive alternatives that can obviate the need for arthroscopy for both viable chondrocyte retrieval and the measurement of cartilage defects as part of ACI. However, arthroscopic procedures are valuable for evaluating the size of cartilage defects as well as for chondrocyte harvesting for ACI. Given the current pivotal role of arthroscopy in ACI, it would not be appropriate to perform ACI chondrocyte retrieval on the basis of imaging only. Additional studies are needed to answer the question of whether image-guided chondrocyte retrieval may obviate the need for arthroscopic surgery in some patients. It also should be noted that we only evaluated the role of CTA (not MRI) with a high radiation dose as an alternative method for arthroscopy since we performed both defect size measurements and sampling simultaneously. On the other hand, in comparison with MRI, CTA is a feasible and low-cost method that is widely accessible in most centers. In routine clinical practice, most patients with knee osteoarthritis are evaluated with MRI before undergoing ACI; therefore, we can potentially perform non-enhanced CT-guided tissue harvest and can measure the size of cartilage defects with use of available MRI.

The present study had some limitations. First, it is possible that the use of cadaveric knees had an impact on the results because of differences between the cadaveric and normal knees (e.g., lack of normal articular fluid or subject motion during the intervention). Second, in the clinical portion of the study, CTA-guided chondrocyte harvesting was not conducted and needle harvest was performed during the standard arthroscopic procedure. With regard to these limitations, it should be noted that the current study was the first feasibility study, to our knowledge, that has evaluated the efficacy of image-guided chondrocyte harvesting and that more clinical evidence is needed to establish all aspects of this new method. Third, we only assessed the role of CT, which is associated with a high radiation dose. On the other hand, CTA does not show compositional cartilage abnormalities; therefore, preprocedural high-resolution MRI assessment can be an important step in the evaluation of overall cartilage status in

terms of both defect size and the determination of the optimum target site for chondrocyte harvest. Also, as a result of recent advances, MRI-guided procedures (e.g., magnetic resonance arthrography [MRA]) could be a feasible alternative to CTA-guided procedures for real-time monitoring of the injection of contrast medium and chondrocyte harvest. It also has been suggested that MRI and MRA can precisely determine defect size in a fashion similar to CTA^{26,28}. Thus, we believe that similar studies should be performed to evaluate the accuracy and feasibility of MRI-guided chondrocyte harvesting.

Image-guided chondrocyte harvesting may be a feasible and accurate method for viable chondrocyte retrieval. The current study can provide the platform for a prospective clinical trial to demonstrate the effectiveness of image-guided chondrocyte harvesting in selected patients with use of advanced CT or MRI guidance. ■

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References

- Hafezi-Nejad N, Zikria B, Eng J, Carrino JA, Demehri S. Predictive value of semi-quantitative MRI-based scoring systems for future knee replacement: data from the Osteoarthritis Initiative. *Skeletal Radiol*. 2015 Nov;44(11):1655-62. Epub 2015 Jul 25.
- Messner K, Maletius W. The long-term prognosis for severe damage to weight-bearing cartilage in the knee: a 14-year clinical and radiographic follow-up in 28 young athletes. *Acta Orthop Scand*. 1996 Apr;67(2):165-8.
- Welch T, Mandelbaum B, Tom M. Autologous chondrocyte implantation: past, present, and future. *Sports Med Arthrosc Rev*. 2016 Jun;24(2):85-91.
- Hangody L, Feczko P, Bartha L, Bodó G, Kish G. Mosaicplasty for the treatment of articular defects of the knee and ankle. *Clin Orthop Relat Res*. 2001 Oct;391(Suppl):S328-36.
- Gilbert JE. Current treatment options for the restoration of articular cartilage. *Am J Knee Surg*. 1998 Winter;11(1):42-6.
- Kao YJ, Ho J, Allen CR. Evaluation and management of osteochondral lesions of the knee. *Phys Sportsmed*. 2011 Nov;39(4):60-9.
- Minas T, Gomoll AH, Solhpour S, Rosenberger R, Probst C, Bryant T. Autologous chondrocyte implantation for joint preservation in patients with early osteoarthritis. *Clin Orthop Relat Res*. 2010 Jan;468(1):147-57. Epub 2009 Aug 4.
- Basad E, Ishaque B, Bachmann G, Stürz H, Steinmeyer J. Matrix-induced autologous chondrocyte implantation versus microfracture in the treatment of cartilage defects of the knee: a 2-year randomised study. *Knee Surg Sports Traumatol Arthrosc*. 2010 Apr;18(4):519-27.
- Peterson L, Vasiliadis HS, Brittberg M, Lindahl A. Autologous chondrocyte implantation: a long-term follow-up. *Am J Sports Med*. 2010 Jun;38(6):1117-24. Epub 2010 Feb 24.
- 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 Oct 6;331(14):889-95.
- Harris JD, Siston RA, Pan X, Flanigan DC. Autologous chondrocyte implantation: a systematic review. *J Bone Joint Surg Am*. 2010 Sep 15;92(12):2220-33.
- Mistry H, Connock M, Pink J, Shyangdan D, Clar C, Royle P, Court R, Biant LC, Metcalfe A, Waugh N. Autologous chondrocyte implantation in the knee: systematic review and economic evaluation. *Health Technol Assess*. 2017 Feb;21(6):1-294.
- Harris JD, Siston RA, Brophy RH, Lattermann C, Carey JL, Flanigan DC. Failures, reoperations, and complications after autologous chondrocyte implantation—a systematic review. *Osteoarthritis Cartilage*. 2011 Jul;19(7):779-91. Epub 2011 Feb 17.

14. Allum R. Complications of arthroscopy of the knee. *J Bone Joint Surg Br.* 2002 Sep;84(7):937-45.
15. Rimondi E, Rossi G, Bartalena T, Ciminari R, Alberghini M, Ruggieri P, Errani C, Angelini A, Calabrò T, Abati CN, Balladelli A, Tranfaglia C, Mavrogenis AF, Vanel D, Mercuri M. Percutaneous CT-guided biopsy of the musculoskeletal system: results of 2027 cases. *Eur J Radiol.* 2011 Jan;77(1):34-42. Epub 2010 Sep 15.
16. Mavrogenis AF, Rimondi E, Rossi G, Calabrò T, Ruggieri P. CT-guided biopsy for musculoskeletal lesions. *Orthopedics.* 2013 Jun;36(6):416-8.
17. Fraser-Hill MA, Renfrew DL. Percutaneous needle biopsy of musculoskeletal lesions. 1. Effective accuracy and diagnostic utility. *AJR Am J Roentgenol.* 1992 Apr;158(4):809-12.
18. Fraser-Hill MA, Renfrew DL, Hilsenrath PE. Percutaneous needle biopsy of musculoskeletal lesions. 2. Cost-effectiveness. *AJR Am J Roentgenol.* 1992 Apr;158(4):813-8.
19. Bindelglass DF, Vince KG. Patellar tilt and subluxation following subvastus and parapatellar approach in total knee arthroplasty. Implication for surgical technique. *J Arthroplasty.* 1996 Aug;11(5):507-11.
20. Rimondi E, Busacca M, Moio A, Molinari M, Nigrisoli M, Trentani F, Trentani P, Tigani D. [Computerized tomography guided biopsy in the diagnosis of neoplastic and inflammatory lesions of the pelvis]. *Radiol Med.* 2001 Jan-Feb;101(1-2):60-5. Italian.
21. Altuntas AO, Slavin J, Smith PJ, Schlicht SM, Powell GJ, Ngan S, Toner G, Choong PF. Accuracy of computed tomography guided core needle biopsy of musculoskeletal tumours. *ANZ J Surg.* 2005 Apr;75(4):187-91.
22. Leffler SG, Chew FS. CT-guided percutaneous biopsy of sclerotic bone lesions: diagnostic yield and accuracy. *AJR Am J Roentgenol.* 1999 May;172(5):1389-92.
23. Brittberg M. Cell carriers as the next generation of cell therapy for cartilage repair: a review of the matrix-induced autologous chondrocyte implantation procedure. *Am J Sports Med.* 2010 Jun;38(6):1259-71. Epub 2009 Dec 4.
24. Rand T, Brossmann J, Pedowitz R, Ahn JM, Haghigi P, Resnick D. Analysis of patellar cartilage. Comparison of conventional MR imaging and MR and CT arthrography in cadavers. *Acta Radiol.* 2000 Sep;41(5):492-7.
25. Vande Berg BC, Lecouvet FE, Poilvache P, Jamart J, Materne R, Lengele B, Maldague B, Malghem J. Assessment of knee cartilage in cadavers with dual-detector spiral CT arthrography and MR imaging. *Radiology.* 2002 Feb;222(2):430-6.
26. Vande Berg BC, Lecouvet FE, Malghem J. Frequency and topography of lesions of the femoro-tibial cartilage at spiral CT arthrography of the knee: a study in patients with normal knee radiographs and without history of trauma. *Skeletal Radiol.* 2002 Nov;31(11):643-9. Epub 2002 Sep 14.
27. van Tiel J, Siebelt M, Reijman M, Bos PK, Waarsing JH, Zuurmond AM, Nas-serinejad K, van Osch GJ, Verhaar JA, Krestin GP, Weinans H, Oei EH. Quantitative in vivo CT arthrography of the human osteoarthritic knee to estimate cartilage sulphated glycosaminoglycan content: correlation with ex-vivo reference standards. *Osteoarthritis Cartilage.* 2016 Jun;24(6):1012-20. Epub 2016 Feb 3.
28. Li J, Zheng ZZ, Li X, Yu JK. Three dimensional assessment of knee cartilage in cadavers with high resolution MR-arthrography and MSCT-arthrography. *Acad Radiol.* 2009 Sep;16(9):1049-55. Epub 2009 May 5.
29. De Filippo M, Bertellini A, Pogliacomini F, Sverzellati N, Corradi D, Garlaschi G, Zompatori M. Multidetector computed tomography arthrography of the knee: diagnostic accuracy and indications. *Eur J Radiol.* 2009 May;70(2):342-51. Epub 2008 Mar 10.
30. Duchateau F, Vande Berg BC. MR imaging of the articular cartilage of the knee with arthroscopy as gold standard: assessment of methodological quality of clinical studies. *Eur Radiol.* 2002 Dec;12(12):2977-81. Epub 2002 Aug 2.
31. Oakley SP, Portek I, Szomor Z, Appleyard RC, Ghosh P, Kirkham BW, Murrell GA, Lassere MN. Arthroscopy — a potential “gold standard” for the diagnosis of the chondropathy of early osteoarthritis. *Osteoarthritis Cartilage.* 2005 May;13(5):368-78.
32. Vallotton JA, Meuli RA, Leyvraz PF, Landry M. Comparison between magnetic resonance imaging and arthroscopy in the diagnosis of patellar cartilage lesions: a prospective study. *Knee Surg Sports Traumatol Arthrosc.* 1995;3(3):157-62.
33. Brittberg M, Winalski CS. Evaluation of cartilage injuries and repair. *J Bone Joint Surg Am.* 2003;85(Suppl_2)(Suppl 2):58-69.
34. Campbell AB, Quatman CE, Schmitt LC, Knopp MV, Flanigan DC. Is magnetic resonance imaging assessment of the size of articular cartilage defects accurate? *J Knee Surg.* 2014 Feb;27(1):67-75. Epub 2013 Jul 24.
35. Figueroa D, Calvo R, Vaisman A, Carrasco MA, Moraga C, Delgado I. Knee chondral lesions: incidence and correlation between arthroscopic and magnetic resonance findings. *Arthroscopy.* 2007 Mar;23(3):312-5.
36. Gomoll AH, Yoshioka H, Watanabe A, Dunn JC, Minas T. Preoperative measurement of cartilage defects by MRI underestimates lesion size. *Cartilage.* 2011 Oct;2(4):389-93.
37. Lee SY, Jee WH, Kim SK, Koh IJ, Kim JM. Differentiation between grade 3 and grade 4 articular cartilage defects of the knee: fat-suppressed proton density-weighted versus fat-suppressed three-dimensional gradient-echo MRI. *Acta Radiol.* 2010 May;51(4):455-61.
38. Mohr A. The value of water-excitation 3D FLASH and fat-saturated PDw TSE MR imaging for detecting and grading articular cartilage lesions of the knee. *Skeletal Radiol.* 2003 Jul;32(7):396-402. Epub 2003 Apr 26.
39. Mori R, Ochi M, Sakai Y, Adachi N, Uchio Y. Clinical significance of magnetic resonance imaging (MRI) for focal chondral lesions. *Magn Reson Imaging.* 1999 Oct;17(8):1135-40.
40. Michalik R, Schradling S, Dirrichs T, Prescher A, Kuhl CK, Tingart M, Rath B. New approach for predictive measurement of knee cartilage defects with three-dimensional printing based on CT-arthrography: a feasibility study. *J Orthop.* 2016 Oct 31;14(1):95-103.