

Autologous Chondrocyte Implantation for Bipolar Chondral Lesions in the Tibiofemoral Compartment

Takahiro Ogura,^{*†} MD, Tim Bryant,^{*} BSN, RN, Brian A. Mosier,^{**‡} MD, and Tom Minas,^{*§} MD, MS
Investigation performed at the Cartilage Repair Center, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

Background: Treating bipolar chondral lesions in the tibiofemoral (TF) compartment with cartilage repair procedures is challenging, and a suitable treatment remains unclear.

Purpose: To evaluate clinical outcomes after autologous chondrocyte implantation (ACI) for the treatment of bipolar chondral lesions in the TF compartment.

Study Design: Case series; Level of evidence, 4.

Methods: We evaluated 57 patients who underwent ACI for the treatment of symptomatic bipolar chondral lesions in the TF compartment by a single surgeon between October 1995 and June 2014. One patient did not return for follow-up. Thus, 56 patients (58 knees) were included with a minimum of 2 years' follow-up. A mean of 3.1 lesions per knee were treated, representing a mean total surface area of 16.1 cm² (range, 3.2-44.5 cm²) per knee. Bipolar lesions were present in the medial compartment (32 knees) and in the lateral compartment (26 knees). Patients were evaluated with the modified Cincinnati Knee Rating Scale, visual analog scale for pain, Western Ontario and McMaster Universities Osteoarthritis Index, and Short Form-36. Patients also answered questions regarding self-rated knee function and satisfaction with the procedure. Standard radiographs were evaluated with the Kellgren-Lawrence grading system.

Results: The survival rate was 80% at 5 years and 76% at 10 years. A significantly better survival rate was found in patients with the use of a collagen membrane than periosteum (97% vs 61% at 5 years, respectively; $P = .0014$). Of 46 knees with retained grafts, all functional scores significantly improved postoperatively, with a very high satisfaction rate (91%) at a mean of 8.3 ± 5.1 years (range, 2-20 years) after ACI. At last follow-up, 24 of 46 successful knees were radiographically assessed (mean, 5.5 ± 4.0 years [range, 2.0-18.7 years]) and showed no significant osteoarthritis progression ($P = .3173$). Outcomes for 12 patients were considered as failures at a mean of 4.1 years. Of these, 9 patients were converted to partial or total knee arthroplasty at a mean of 4.4 years. Two patients underwent revision ACI at 5 and 17 months. The other 1 patient did not require revision surgery.

Conclusion: Our study showed that ACI for the treatment of bipolar chondral lesions in the TF compartment provided successful clinical outcomes in patients with retained grafts and possibly prevented or delayed osteoarthritis progression at midterm to long-term follow-up. A collagen membrane is more encouraging than periosteum for bipolar lesions in the TF compartment. While addressing the predisposing factors affecting cartilage repair, ACI could be an adequate salvage procedure for bipolar chondral lesions in the TF compartment for the relatively young arthritic patient who wishes to avoid arthroplasty.

Keywords: autologous chondrocyte implantation; bipolar/"kissing" lesions; tibiofemoral compartment; articular; cartilage; repair

Articular cartilage has a limited innate ability to heal; therefore, chondral defects may proceed to symptomatic osteoarthritis (OA) in the tibiofemoral (TF) compartment if left untreated.⁸ Moreover, there is an increasing number of people who participate in sporting activities in their middle age who have expectations for recovery and are unsuitable for arthroplasty. In these patients, joint replacement is an unsuitable option as high activity demands may lead to early

failure. For those who wish to avoid or delay joint replacement and maintain their biological knees, other surgical treatments are warranted when nonoperative treatment fails. Autologous chondrocyte implantation (ACI), a cell-based regenerative therapy, has been recognized as a promising treatment for large symptomatic articular cartilage defects and shown to result in significant improvement in pain and joint function at long-term follow-up.^{1,6,7,29,39-41,48,49,52} Interest has been expanding in the use of ACI for the treatment of degenerative cartilage defects seen in early OA beyond unipolar focal traumatic chondral lesions. However, controversy exists regarding the efficacy of ACI for the treatment of degenerative cartilage lesions, especially

bipolar or “kissing” lesions. Ding et al¹⁴ demonstrated that baseline cartilage defect scores of the medial and lateral tibiae are predictive of knee cartilage loss over 2 years. Thus, bipolar lesions that include lesions of the tibia intuitively may be recognized as high risk for the development of symptomatic OA. The purpose of this study was therefore to evaluate clinical outcomes after ACI for the treatment of patients who had symptomatic bipolar chondral lesions in the TF compartment. We hypothesized that ACI would be an adequate salvage procedure for patients with bipolar chondral lesions.

METHODS

Patient Cohort

The study was approved by our institutional review board. All patients signed informed consent forms. We performed a retrospective review of prospectively collected data from 57 patients (59 knees) who underwent ACI for bipolar articular cartilage lesions of the TF joint in the knee from October 1995 to June 2014. A single surgeon performed all the surgical procedures. One patient (1 knee) was lost to follow-up. Thus, 56 patients (58 knees) with a minimum of 2 years' follow-up were included in this study. A mean of 3.1 lesions per knee were treated, representing a mean total surface area of 16.1 cm² (range, 3.2-44.5 cm²) per knee (Table 1). Bipolar lesions were located in the medial compartment (32 knees) and in the lateral compartment (26 knees). Apart from the bipolar lesions in the TF compartment, 60 cartilage lesions that included 13 bipolar lesions in the patellofemoral (PF) compartment (26 cartilage lesions) were treated with ACI during the index surgery. A total of 52 patients (93%) had undergone a mean of 2.7 prior surgical procedures (range, 1-8).

Indications

Indications for ACI included ≥ 1 full-thickness articular cartilage defects of the knee, along with symptoms matching the defect location. Surgery was indicated only in patients who had persistent symptoms despite previous other cartilage repair procedures and/or nonoperative treatments, including physical therapy, nonsteroidal anti-inflammatory drugs, injectable therapies, and/or the application of a custom unloader brace. Patients were evaluated through physical examination, radiography, magnetic resonance imaging (MRI), and arthroscopic surgery before treatment with ACI was considered. Contraindications to ACI included inflammatory joint disease, unresolved septic arthritis, and metabolic or crystal arthropathies.

Preoperative Planning and Surgical Technique

ACI was performed as described in detail previously.^{28,33,37} Briefly, after an arthroscopic cartilage biopsy was performed during the initial surgery, chondrocytes were cultured, cryopreserved, and then thawed and secondarily expanded in culture for definitive implantation. The open transplantation procedure required arthrotomy as early as 6 weeks to as late as 2 years after the biopsy. At the time of arthrotomy, access to the tibial lesion and large posterior lesions of the femur was performed by the same technique as previously described.³⁸ The intermeniscal ligament was incised, and a careful subperiosteal dissection was performed, releasing the coronary ligament of the appropriately sided meniscus with a large soft tissue sleeve all the way posterior to the anterior aspect of the deep portion of the medial or lateral collateral ligament. The knee was then hyperflexed with external rotation of the tibia for the medial tibial plateau or internal rotation for the lateral tibial plateau (Figure 1A). The defects were then radically debrided (Figure 1B) and templated, and membranes were prepared, microsutured, and sealed with fibrin glue (Figure 1C). The cells were then delivered into the defects and the openings sutured and sealed. The knee was carefully brought into extension with an opening force (valgus for medial compartment and varus for lateral compartment). The meniscus was carefully reduced and repaired with transosseous 1-0 Vicryl sutures (Ethicon) using a tapered needle and the intermeniscal ligament with 1-0 Vicryl sutures. For surgical procedures performed before May 2007, the periosteum was harvested from the proximal tibia or distal femur. After May 2007, a type I/III bilayer collagen membrane, derived from porcine peritoneum and skin (Bio-Gide; Geistlich Pharma), was used in place of an autologous periosteum. An autologous periosteum was used in 23 knees, and a type I/III collagen membrane (Bio-Gide) was used in the other 35 knees. The periosteum with the cambium layer toward subchondral bone or the collagen membrane with the fluffy layer down was placed on the cartilage defect and secured with multiple 6-0 Vicryl sutures (Ethicon). The suture line was sealed with fibrin glue (Tisseel; Baxter Biosurgery), and autologous cultured chondrocytes were injected underneath the membrane in a watertight cavity.

Articular comorbidities, including malalignment, patellar maltracking, and meniscal deficiency, were corrected at the time of ACI. TF malalignment $>2^\circ$ to 3° was corrected via osteotomy of the tibia or femur, with correction of the mechanical axis to neutral or 0° . PF maltracking was addressed with anteromedialization tibial tubercle osteotomy to centralize patellar tracking^{18,34} and proximal soft tissue balancing (lateral release, vastus medialis obliquus advancement) as necessary to centralize the extensor

[§]Address correspondence to Tom Minas, MD, MS, The Paley Institute, St. Mary's Hospital, 901 45th Street, Kimmel Building, West Palm Beach, FL 33407, USA (email: Tminas@paleyinstitute.org).

*Cartilage Repair Center, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.

†Sports Medicine Center, Funabashi Orthopaedic Hospital, Funabashi, Japan.

‡Allegheny Health Network, Monroeville, Pennsylvania, USA.

One or more of the authors has declared the following potential conflict of interest or source of funding: This study was supported by a grant from the Cartilage Research Foundation. Dr Minas is a consultant for Vericel.

TABLE 1
Patient Characteristics^a

	Value
Age at surgery, mean \pm SD (range), y	37 \pm 11 (14-60)
Sex, male/female, n	34/22
Knee, right/left, n	28/30
Body mass index, mean \pm SD (range), kg/m ²	26.3 \pm 4.3 (17.3-38.6)
Follow-up, mean \pm SD (range), y	8.3 \pm 5.1 (2-20)
No. of defects per knee, mean \pm SD (range)	3.1 \pm 1.1 (2-5)
Total defect surface area, per knee, at index surgery, mean \pm SD (range), cm ²	16.1 \pm 9.5 (3.2-44.5)
Bipolar lesion, n	
Medial TF compartment (concurrent with PF bipolar)	32 knees (6 knees)
Lateral TF compartment (concurrent with PF bipolar)	26 knees (7 knees)
Bipolar lesion size, mean \pm SD (range), cm ²	
Medial TF joint	
MFC	8.3 \pm 3.8 (0.8-16.3)
Medial tibial plateau	3.4 \pm 1.8 (1.0-8.6)
Lateral TF joint	
LFC	5.9 \pm 3.4 (1.0-13.2)
Lateral tibial plateau	3.4 \pm 1.5 (1.0-6.0)
Additional defect location apart from bipolar lesion, n	
LFC	4
MFC	10
Trochlea	26
Patella	20

^aLFC, lateral femoral condyle; MFC, medial femoral condyle; PF, patellofemoral; TF, tibiofemoral.



Figure 1. Intraoperative photographs demonstrating cartilage defects of the lateral femoral condyle and tibial plateau. (A) To access the chondral defects, the intermeniscal ligament is incised, and a careful subperiosteal dissection is performed, releasing the coronary ligament with the lateral meniscus as a large soft tissue sleeve all the way posterior to the anterior aspect of the deep portion of the lateral collateral ligament. The knee is hyperflexed and the tibia internally rotated for both chondral defects. (B) The defects are then radically debrided back to stable full-thickness native cartilage and templated for accurate periosteal harvesting. (C) A periosteal membrane is then microsutured with 6-0 Vicryl sutures and sealed with fibrin glue. Autologous cultured chondrocytes are injected underneath the membrane, and the injection opening is sutured and sealed with fibrin glue.

mechanism. During ACI, 44 patients (79%) underwent concurrent osteotomy surgery (Table 2). A total of 25 patients underwent high tibial osteotomy (HTO) for unloading bipolar lesions in the medial compartment, whereas 5 patients underwent distal femoral osteotomy (DFO) for unloading bipolar lesions in the lateral compartment. Two patients who had bipolar lesions in the medial compartment underwent anterior cruciate ligament (ACL) reconstruction, and 9 patients who had bipolar lesions in the lateral compartment underwent meniscal allograft transplantation (MAT) at the time of ACI.

Postoperative Protocol

Postoperatively, patients were instructed to use a continuous passive motion machine for 6 to 8 hours daily for 6 weeks. Patients remained touch weightbearing for 6 to 8 weeks, with gradual progression to full weightbearing by 10 to 12 weeks. Large bipolar areas were treated with an unloader brace for up to 6 months postoperatively, especially when the tibial surface area was large (>4 cm²). Patients were permitted to return to most activities of daily living after 3 months and to nonimpact functional

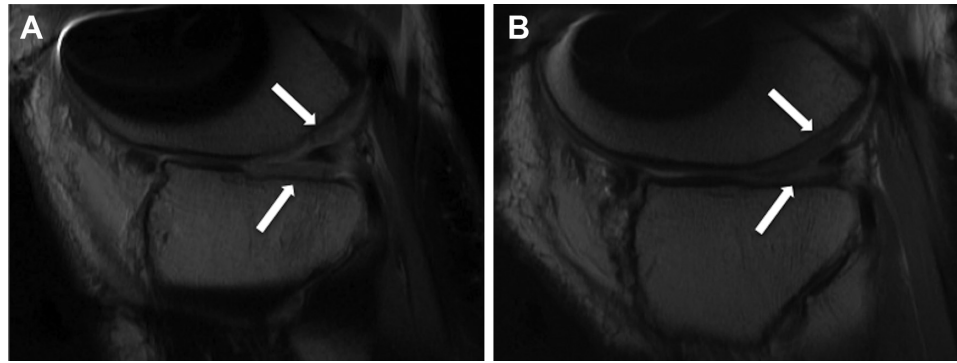


Figure 2. Postoperative sagittal magnetic resonance imaging (proton density fat saturated) of the involved compartment. This patient's previous surgical procedures included microfracture, drilling to the lateral femoral condyle (LFC), and removal of a loose body. Autologous chondrocyte implantation (ACI) to the LFC, lateral tibial plateau (LTP), and trochlea (lesion sizes: 600 mm², 225 mm², and 225 mm², respectively) was performed with concomitant distal femoral osteotomy and tibial tubercle osteotomy. (A) Four months after ACI, the implantation site is completely covered by tissue that shows intermediate to high signal in the LFC and LTP (arrows). (B) One year after ACI, the implantation site is completely covered by tissue that shows more homogeneity in signal intensity with a congruent articular surface (arrows). No subjacent marrow edema is detected.

TABLE 2
Concurrent Osteotomy
at Autologous Chondrocyte Implantation^a

Procedure	Medial Compartment, n	Lateral Compartment, n
HTO	12	2
TTO	2	7
HTO + TTO	13	2
DFO + TTO	1	5
Total	28	16

^aDFO, distal femoral osteotomy; HTO, high tibial osteotomy; TTO, tibial tubercle osteotomy.

activities including the use of a stationary bicycle, treadmill walking, and progression to an elliptical trainer and swimming, without cutting movements, after 4 to 6 months. After 16 to 18 months, inline jogging was permitted if on clinical examination there was no tenderness or swelling and no complaints of pain. Figure 2 shows progressive healing, with defects filled with repair tissue appearing similar to the adjacent native cartilage with the resolution of bone marrow edema at 4 months and 1 year after ACI. Pivoting activities were then permitted from 18 to 24 months postoperatively. The postoperative recovery protocol was individually adjusted according to defect location and size, concurrent procedures, degree of graft maturation noted on MRI, previous activity level, and realistic desired future activity level.³⁵

Failure Definition

Graft failure was defined as persistent or recurrent clinical symptoms in conjunction with MRI and/or arthroscopic evidence of graft delamination or surgical removal of more than 25% of the graft area, revision cartilage repair, or conversion to arthroplasty.

Radiographic Assessment

Standing (bipedal) long axial alignment radiographs and anteroposterior, posteroanterior (Rosenberg), and lateral radiographs of the TF compartment were scored according to the Kellgren-Lawrence (K-L) system²⁷ to evaluate the preoperative OA grade as a baseline and the progression of OA grade before and after the index surgery. K-L grades were scored by one of the authors (T.O.), who was a fully trained orthopaedic surgeon apart from the senior author (T.M.).

Survival Analysis and Clinical Outcome Assessment

The survival rate was evaluated with the Kaplan-Meier method, with failure of the graft as the endpoint measure. Patients were evaluated with the modified Cincinnati Knee Rating Scale,^{10,32} Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC),⁵ visual analog scale (VAS) for pain, and Short Form-36 (SF-36).⁹ The original Cincinnati Knee Rating Scale was based on a 0-to-100 continuous scale,⁴⁵ whereas the modified Cincinnati Knee Rating Scale uses a 1-to-10 categorized scale, with a 2-point change being considered clinically meaningful (Figure 3).^{10,32} Patients also answered questions regarding self-rated knee function and satisfaction with the procedure. Scores were collected preoperatively and at yearly intervals postoperatively during consultations or via a mailed questionnaire. Subanalyses were performed according to age (<40 vs ≥40 years), sex, bipolar lesion size (<11 vs ≥11 cm², based on the median size in our cohorts), body mass index (BMI; <30 vs ≥30 kg/m², technically considered a definition of obesity according to World Health Organization recommendations⁴⁶), whether bipolar lesions were present in the medial or lateral compartment, presence of concurrent unloading osteotomy, membrane cover (periosteum vs collagen [Bio-Gide]), baseline K-L grade (grade 0-1 vs grade 2-3), presence of PF bipolar lesions, and presence of additional cartilage lesions treated.

<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10		
POOR FAIR GOOD VERY GOOD EXCELLENT		
Poor	(1-2)	I have significant limitations that affect activities of daily living.
Fair	(3-4)	I have moderate limitations that affect activities of daily living. No sports possible.
Good	(5-6)	I have some limitations with sports but I can participate; I compensate.
Very Good	(7-8)	I have only a few limitations with sports.
Excellent	(9-10)	I am able to do whatever I wish (any sport) with no problem.

Figure 3. Modified Cincinnati Knee Rating Scale.

Statistical Analysis

All statistical analyses were performed with Stata (version 13; StataCorp). The level of significance was set a priori at $P < .05$. Kaplan-Meier curves were used for survival analyses. The Wilcoxon signed-rank test was performed to compare differences in functional scores between the 2 time points (preoperatively and at the different follow-up time points). Mann-Whitney U tests were performed to compare the scores at the latest follow-up between different groups.

RESULTS

Radiographic Assessment

Some baseline preoperative radiographs were not available to review because many radiographs were destroyed after the conversion to digital radiographs. Preoperative radiographs were available in all but 3 patients, which showed a mean K-L grade of 2.0 ± 0.5 (range, 0-3). Of 46 knees with retained grafts, 24 knees were available to review with a minimum of 2 years postoperatively. We found no significant increase in the OA grade at a mean of 5.5 ± 4.0 years (range, 2.0-18.7 years) postoperatively (K-L grade, 1.9 ± 0.6 preoperatively vs 1.9 ± 0.7 postoperatively; $P = .3173$). Of 24 knees evaluated, the K-L grade showed no increase in 23 knees, while the other 1 knee had a 1-point increase from grade 3 to 4 at 13.5 years.

Survival Analysis

Outcomes for 12 patients were considered as failures. The survival rate was 80% (95% CI, 66%-89%) at 5 years and 76% (95% CI, 60%-86%) at 10 years (Figure 4). In survival subanalyses, there was no significant difference according to age, sex, bipolar lesion size, BMI, whether bipolar lesions were present in the medial or lateral compartment, presence of concurrent unloading osteotomy, baseline K-L grade, presence of PF bipolar lesions, and presence of additional cartilage lesions treated. However, we found a significantly better survival rate in patients with the use of a collagen membrane than periosteum (97% vs 61% at 5 years, respectively; $P = .0014$) (Figure 5). Additionally, female patients demonstrated a worse survival rate (67% vs 87% at 5 years,

respectively; $P = .0577$) than male patients but failed to reach statistical significance. ACI with HTO in the medial compartment showed a higher survival rate of 94% at 5 years and 82% at 10 years than ACI without HTO (60% at 5 and 10 years) but failed to reach statistical significance ($P = .0855$), whereas no difference was observed between ACI with DFO and without DFO in the lateral compartment (Table 3).

Functional Scores and Patient Satisfaction

All patient-reported outcomes for the patients with retained grafts showed a significant improvement at 2 years, 5 years, and at the time of latest follow-up (mean, 8.3 ± 5.1 years [range, 2-20 years]) postoperatively compared with preoperative scores (Table 4). In subanalyses, there was no significant difference in the functional scores at the latest follow-up according to age, sex, bipolar lesion size, whether bipolar lesions were present in the medial or lateral compartment, presence of concurrent unloading osteotomy, baseline K-L grade, presence of PF bipolar lesions, and presence of additional cartilage lesions treated. However, there was a significant difference in the modified Cincinnati score at the latest follow-up according to BMI (5.8 ± 1.6 for BMI $<30 \text{ kg/m}^2$ vs 4.5 ± 0.5 for BMI $\geq 30 \text{ kg/m}^2$; $P = .0146$).

Of 46 knees with retained grafts, 91% were satisfied with ACI, 85% reported their knee as better with surgery, and 83% rated their outcome as good/excellent. Of 12 knees that had failed grafts, 50% were satisfied with ACI and rated their knee as better; notably, 92% would choose to undergo ACI if they could go back in time (Table 5).

Subsequent Surgical Procedures (SSPs)

Thirty-eight (66%) knees required a mean of 1.5 SSPs (total $n = 57$; range, 1-4). Among them, 33 SSPs were performed arthroscopically primarily because of the graft ($n = 23$) (hypertrophy) and arthrofibrosis ($n = 10$). Of the 23 that were graft related, 16 (70%) were with a periosteum, and 7 (30%) were with a collagen membrane. Open surgery included removal of painful hardware ($n = 10$), cartilage repair of a newly developed lesion ($n = 2$), compartment syndrome ($n = 1$), ACL reconstruction because of an injury

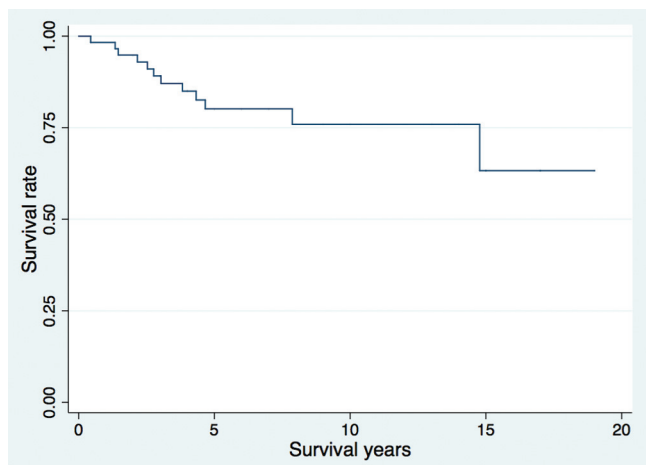


Figure 4. Overall Kaplan-Meier survival curves. The endpoint was defined as failure of the graft.

(n = 1), MAT (n = 1), and open debridement for cellulitis that required hardware removal (n = 1).

Failure Cases

Overall, outcomes for 12 patients were considered as failures at a mean 4.1 ± 3.9 years (range, 0.4-14.8 years). Of these, 9 patients proceeded to conversion to partial or total knee arthroplasty at a mean of 4.4 ± 4.0 years (range, 1.3-14.8 years). Two patients underwent revision ACI at 5 and 17 months postoperatively. One patient did not require revision surgery (Table 6).

DISCUSSION

Our study demonstrated that the survival rate of ACI for patients who had bipolar cartilage lesions in the TF compartment was 80% at 5 years and 76% at 10 years. A total of 84% of patients were able to avoid joint replacement and maintain their biological knees by the final follow-up of this study (mean, 8.3 years [range, 2-20 years]). All functional scores of patients with retained grafts improved after a mean of 7.2 years after the index surgery with clinically and statistically meaningful outcomes and had a very high rate of satisfaction. No significant increase in the OA grade was observed within the patients available to review with retained grafts after a mean of 5.5 years postoperatively.

Controversy still exists regarding the clinical results and treatment option of ACI for bipolar lesions, which usually represent degenerative change. Peterson et al⁵² reported that patients who had bipolar lesions had a worse final outcome than patients with multiple unipolar lesions at an average of 12.8 years' follow-up. In contrast, Minas et al³⁶ previously reported a 93% survival rate and good clinical outcomes in patients with early OA including 27% of patients who had bipolar lesions at an average of 5 years'

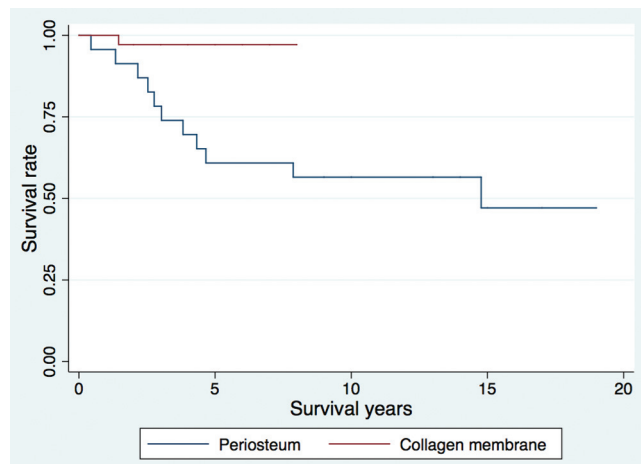


Figure 5. Kaplan-Meier survival curves based on the cover membrane type: periosteum (n = 23) versus collagen membrane (n = 35). The endpoint was defined as failure of the graft.

follow-up (PF: n = 30; medial TF: n = 6; lateral TF: n = 6). Ossendorf et al⁵⁰ reported that patients who had kissing cartilage lesions had similar results as those who had single large cartilage lesions at an average of 2.5 years' follow-up, although it was a relatively small case series (bipolar lesions: n = 9). Our findings demonstrated good clinical outcomes, in line with those studies,^{36,50} focusing on bipolar lesions in the TF compartment, with a mean follow-up of 8.3 years. Moreover, our radiographic assessment showed no significant increase in the K-L grade postoperatively, which previous studies failed to report.

Several other cartilage repair procedures have been reported to address cartilage lesions in patients with early OA, often including bipolar lesions. Bae et al² reported good results with microfracture for the treatment of unicompartamental OA in elderly patients with relatively small lesions (average size, 3.9 cm²) at short-term follow-up (2.3 years). As this procedure has been known to result in deterioration over time as a result of the poor biomechanical properties of the fibrous repair tissue produced,⁵¹ it becomes more concerning particularly when treating bipolar lesions with microfracture because of poor durability on both the femoral and tibial sides. Meric et al³¹ evaluated the results of osteochondral allograft transplantation for patients (average age, 40 years) who had bipolar lesions in 48 knees (lateral TF: n = 20; medial TF: n = 14; PF: n = 14). They reported a high failure rate of 46% during an average follow-up period of 7 years and a survival rate of 64% at 5 years and 39% at 10 years. A possible reason for the high failure rate may include the low rate of concomitant unloading osteotomy performed in their cohort (4%) and the high rate of bipolar lesions in the PF compartment treated (29%). They also showed that larger lesions had a significantly higher failure rate, whereas our results showed no significant difference in the survival rate as it relates to lesion size. In addition, when ACI is performed, the surface alone is treated, preserving healthy subchondral bone,

TABLE 3
Survival Rate With/Without Unloading Osteotomy^a

Procedure	Medial Compartment		Procedure	Lateral Compartment	
	5 y, % (95% CI)	10 y, % (95% CI)		5 y, % (95% CI)	10 y, % (95% CI)
With HTO (n = 24)	94 (63-99)	82 (42-96)	With DFO (n = 7)	71 (26-92)	71 (26-92)
Without HTO (n = 8)	60 (13-88)	60 (13-88)	Without DFO (n = 19)	71 (44-87)	71 (44-87)
P value	.0855		P value	.8483	

^aDFO, distal femoral osteotomy; HTO, high tibial osteotomy.

TABLE 4
Preoperative and Postoperative Clinical Scores in Patients With Retained Grafts (46 Knees)^a

Knee Scoring System	Preoperatively (n = 46)	2 y (n = 46)	5 y (n = 38)	Latest Follow-up (n = 46)
Modified Cincinnati	3.2 ± 1.0	4.8 ± 1.5 ^c	5.5 ± 1.5 ^c	5.5 ± 1.6 ^c
VAS	7.0 ± 0.9	2.8 ± 1.6 ^c	2.2 ± 1.6 ^c	2.1 ± 1.6 ^c
WOMAC				
Total	44.2 ± 16.7	27.2 ± 14.7 ^c	19.7 ± 13.7 ^c	20.4 ± 14.9 ^c
Pain	10.2 ± 4.1	6.1 ± 3.7 ^c	4.3 ± 3.4 ^c	4.5 ± 3.6 ^c
Stiffness	4.0 ± 1.7	3.6 ± 7.9 ^c	2.1 ± 1.5 ^c	2.4 ± 1.6 ^c
Function	29.9 ± 12.1	18.5 ± 10.3 ^c	13.3 ± 9.6 ^c	13.3 ± 10.3 ^c
SF-36				
PCS	42.3 ± 8.1	49.2 ± 7.2 ^c	50.5 ± 7.2 ^c	51.6 ± 6.5 ^c
MCS	47.9 ± 9.5	52.2 ± 6.1 ^b	54.0 ± 5.2 ^c	54.2 ± 5.0 ^c

^aData are presented as mean ± SD. MCS, mental component summary; PCS, physical component summary; SF-36, Short Form-36; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

^bP < .01 (compared with preoperative scores).

^cP < .001 (compared with preoperative scores).

TABLE 5
Satisfaction With Surgery as of Final Follow-up (56 Patients, 58 Knees)^a

Question	Operative Success (n = 46)	Operative Failure (n = 12)	Total (n = 58)
Compared with before each surgery, how would you rate your operated joint now?			
Better	39 (85)	6 (50)	45 (78)
About the same	7 (15)	6 (50)	13 (22)
Worse	0 (0)	0 (0)	0 (0)
What is your overall satisfaction level with the joint surgery?			
Satisfied	42 (91)	6 (50)	48 (83)
Neutral	4 (9)	2 (17)	6 (10)
Dissatisfied	0 (0)	4 (33)	4 (7)
If you could go back in time and make the decision again, would you choose to have your joint surgery?			
Yes	45 (98)	11 (92)	56 (97)
Uncertain	1 (2)	1 (8)	2 (3)
No	0 (0)	0 (0)	0 (0)
How would you rate the results of your joint surgery?			
Good/excellent	38 (83)	2 (17)	40 (69)
Fair	6 (13)	9 (75)	15 (26)
Poor	2 (4)	1 (8)	3 (5)

^aData are presented as n (%).

whereas allograft transplantation removes healthy subchondral bone and usually fails by bone collapse from creeping substitution of bone with subchondral resorption and

fractures in large lesions.⁴² Other studies also reported less favorable outcomes after osteochondral allograft transplantation for patients who had bipolar lesions.^{3,12} Hangody

TABLE 6
Outcomes in Failure Cases^a

Patient	Age, Sex	Bipolar Location (Femoral/Tibial), Size, cm ²	Additional Cartilage Lesion Size, cm ²	Cover Membrane Type/ Concurrent Surgery	Preoperative K-L Grade	Revision Surgery
1	41, M	Medial, 5.3/1.7	No	Periosteum/HTO	2	UKA at 4.3 y
2	19, F	Medial, 12.0/4.0	No	Periosteum/HTO	2	Failed at 7.9 y, no revision surgery needed
3	38, F	Medial, 6.8/1.5	No	Periosteum/no	3	UKA at 2.5 y
4	39, F	Medial, 5.3/4.0	Trochlea, 6.3	Periosteum/no	N/A	TKA at 2.8 y
5	33, F	Lateral, 3.0/1.8	No	Periosteum/no	N/A	TKA at 2.2 y
6	36, M	Lateral, 9.4/6.0	No	Periosteum/no	2	TKA at 3.8 y
7	43, M	Lateral, 6.0/5.3	No	Periosteum/MAT	2	TKA at 14 y
8	30, F	Lateral, 5.1/3.6	No	Periosteum/MAT	1	Revision ACI at 5 mo
9	39, M	Lateral, 4.0/3.2	MFC, 6.3; trochlea, 4.5	Periosteum/TTO	2	Bicompartmental knee arthroplasty at 3 y
10	36, F	Lateral, 4.0/2.3	No	Periosteum/MAT	2	TKA at 4.7 y
11	48, M	Lateral, 8.8/5.0	Trochlea, 2.3	Collagen membrane/MAT, TTO, DFO	2	Revision ACI and MAT at 17 mo
12	43, F	Lateral, 1.7/2.9	MFC, 11; patella, 6.2; trochlea, 4.4	Periosteum/HTO, TTO	2	TKA at 1.3 y

^aACI, autologous chondrocyte implantation; DFO, distal femoral osteotomy; F, female; HTO, high tibial osteotomy; K-L, Kellgren-Lawrence; M, male; MAT, meniscal allograft transplantation; MFC, medial femoral condyle; N/A, not available; TKA, total knee arthroplasty; TTO, tibial tubercle osteotomy; UKA, uni-compartment knee arthroplasty.

et al²² reported a good success rate of autologous osteochondral mosaicplasty for the treatment of lesions sized 1.0 to 4.0 cm² in an athletic group, including 27% of patients who had OA changes. However, this procedure is not suitable for larger lesions including bipolar lesions because of the limited area for harvesting osteochondral grafts from the same joint. Hangody et al²² have also stated that mosaicplasty is not suitable for the tibia as obtaining an orthogonal position at implantation, which is critical to success, is technically difficult or not possible. Imade et al²⁵ reported that osteochondral autograft transplantation showed limited results in treating cartilage defects based on patient age and OA grade (K-L grade), although bipolar lesions were excluded in their study. It was difficult to make a direct comparison with other procedures in previous studies because of variations with indication criteria, lesion size, location, and definition of early OA, among others. In addition, strong evidence is still lacking regarding any superiority of any specific cartilage repair technique,⁶⁰ which demonstrates that careful indications for each technique are necessary. Nevertheless, our study showed that ACI could be a suitable option for bipolar chondral lesions in the TF joint.

Survival subanalyses revealed a significantly better survival rate in patients with a collagen membrane (Bio-Gide) than periosteum. The better quality of repair tissue and good clinical outcomes with collagen membrane-covered ACI have been shown than with periosteum-covered ACI.^{30,43} The observed difference is likely because of the material and biological properties of the periosteum versus collagen membrane. The surgeon followed the same principles of complete exposure of bipolar lesions, debridement, suturing, and sealing membranes watertight before delivering the cells. However, the periosteum was noted to have variable and poor tensile properties and was prone to tearing, requiring repair. In addition, the periosteum

frequently underwent hypertrophy after implantation, whereas the collagen membrane was easy to handle, did not tear, had excellent tensile properties, and had a smooth surface that did not undergo hypertrophy but underwent biological resorption within 6 to 9 months after implantation. A longer follow-up of patients with a collagen membrane will be necessary to confirm this observation. Female patients had a worse survival rate than male patients but this failed to reach statistical significance. This finding was consistent with previous studies that reported a higher failure rate of cartilage repair in the female sex.^{17,19,39,59} On the other hand, older age (≥ 40 years) did not significantly affect the survival rate. Additionally, subanalyses for the functional scores revealed significantly better scores for the modified Cincinnati Knee Rating Scale in patients whose BMI was < 30 kg/m² than ≥ 30 kg/m². The negative effect of a higher BMI on clinical outcomes after ACI has been reported in previous studies,^{26,44} although controversy still exists.⁴ The negative effect of a higher BMI observed in our study may suggest the importance of avoiding high contact forces to the ACI graft, particularly for bipolar lesions in the TF compartment. Preoperative intervention to reduce body weight will be of interest to investigate whether it improves post-operative knee function after ACI.

Our observed high success rate in ACI with HTO for unloading the medial compartment (94% and 82% at 5 and 10 years, respectively) was consistent with a previous study that included a larger cohort.³⁹ Although there was no significant difference in the survival rate between isolated ACI and ACI combined with unloading osteotomy in the present study, a small sample size might have hindered the detection of a statistical significance as there was a 34% difference in survival at 5 years and a 22% difference at 10 years. To date, there is no strong evidence

regarding the benefit of a combination of cartilage repair and realignment procedures. A recent meta-analysis observed higher survival rates at 5 years of follow-up for combined HTO and cartilage repair procedures compared with isolated HTO but not at 10 years and later.²³ However, the cartilage procedures in the analysis included different techniques (microfracture, osteochondral autograft/allograft transplantation, and ACI), which we believe hindered the assessment of the difference in survival rates at long-term follow-up. Regarding radiographic findings based on the K-L grade, Ekland et al¹⁵ reported that the OA grade at baseline was maintained within 2 years but significantly increased at 5 years after isolated open-wedge tibial osteotomy for medial OA. In contrast to their observation, our study showed no significant increase in the OA grade during the study period (mean, 5.5 years), which indicates that ACI may have some additional chondroprotective and preventative effects on ongoing degenerative changes in the knee. According to several studies, the results of isolated HTO showed a good survival rate within 10 years but deteriorated after 15 years,^{21,24,54,56} whereas our study showed that the survival rate in patients with ACI and HTO was maintained to 15 years. Moreover, a study showed that cartilage defects in the tibia predict poor outcomes after isolated HTO.⁵⁷ Taken together, ACI to treat bipolar lesions in the TF compartment may have some advantageous effects in addition to unloading osteotomy, as seen with the clinical outcomes in our study. However, only a comparative study of HTO alone compared with HTO and ACI will determine the true benefit of ACI when combined with HTO.

Another benefit of ACI over HTO alone is the contraindication to varus or valgus osteotomy with a cartilage defect in the contralateral compartment. Osteotomy combined with ACI can potentially overcome this contraindication by corrective osteotomy to the midline axis to maintain long-term joint preservation. In our study, 3 patients who had bipolar lesions in the medial compartment and also had additional cartilage lesions in the lateral compartment were successfully treated with ACI and HTO. In addition, we included 4 patients who had lateral bipolar lesions but underwent corrective valgus HTO to the midline for addressing varus malalignment and 1 patient who had medial bipolar lesions but underwent corrective varus DFO to the midline for addressing valgus malalignment. All but 1 patient were successfully treated.

The SSPs observed in this study were consistent with a previous study (61%) that showed clinical outcomes for the treatment of chondral lesions in patients with early OA.³⁶ A systematic review showed that patients with older age and chondral lesions greater than 4.5 cm² had a higher reoperation rate. When considering the older cohort presented here with a mean age of 37 years and larger lesions at ACI, the rate of SSPs (66%) is not surprising. Given that 70% of graft-related procedures were related to the periosteum-covered grafts, the use of a collagen membrane has proven to be superior regarding reoperation rates and outcomes when treating bipolar lesions. A previous multicenter study has already shown that a collagen membrane decreased reoperations after ACI.²⁰

There are several concerns with ACI treatment for patients who have bipolar lesions from biomechanical and biological points of view. Bipolar lesions in the TF compartment include large chondral lesions and a kissing contact area that requires repair maturation and durability because of high contact forces on the weightbearing surfaces of the joint. To this end, hyaline cartilage is preferable to fibrocartilage. Additionally, although the cartilage tissue was harvested from healthy-appearing sites in the nonweightbearing portion of the knee, the ability of chondrocytes to proliferate in the context of OA and their response to healing are unknown. However, several in vitro studies have shown good proliferation of OA chondrocytes.^{11,13,58} Optimizing the use of ACI in early OA will rely on further appropriate refined criteria of identifying early OA via advanced imaging and biomarkers and their use for follow-up after ACI.

The strengths of our study include a single-surgeon series with the same indications, same postoperative course, and high follow-up rate. The limitations of this study include the fact that this was a case series and did not include a control group; however, it would be difficult to find a control group in light of multiple previous surgeries and disabling baseline preoperative symptoms in this relatively young population that is referred to us for surgical management. Isolated osteotomy without ACI would be a reasonable alternative control group; however, other lesions treated with ACI (31 patients) would make this sample very small (27 patients total) for what took 2 decades to obtain the patients treated. Our cohort also included many patients who underwent concomitant procedures including osteotomy, ACL reconstruction, and MAT at the time of ACI. Because the majority of our patients underwent ACI with HTO, it was not possible to separate out the effects of HTO and ACI in these patients. However, the same philosophy was used consistently throughout the series that predisposing factors leading to cartilage damage should be addressed during a single reconstruction procedure. Others have reported comparable outcomes when ACI was performed with those concomitant procedures.^{16,47,53,55} Finally, we were not able to review all radiographs despite our efforts.

In conclusion, ACI is a promising treatment for bipolar lesions in the TF compartment. A total of 46 of 58 (79%) knees treated with retained grafts significantly improved in pain and function over a mean of 8.3 years' follow-up, with 76% survivorship at 10 years. Eighty-four percent of patients were able to avoid arthroplasty and maintained their biological knees with a very high rate of satisfaction (91%). ACI for bipolar chondral lesions is an adequate salvage treatment in relatively young arthritic patients to maintain their biological knee and an active lifestyle.

REFERENCES

1. Aldrian S, Zak L, Wondrasch B, et al. Clinical and radiological long-term outcomes after matrix-induced autologous chondrocyte transplantation: a prospective follow-up at a minimum of 10 years. *Am J Sports Med.* 2014;42(11):2680-2688.

2. Bae DK, Yoon KH, Song SJ. Cartilage healing after microfracture in osteoarthritic knees. *Arthroscopy*. 2006;22(4):367-374.
3. Beaver RJ, Mahomed M, Backstein D, Davis A, Zukor DJ, Gross AE. Fresh osteochondral allografts for post-traumatic defects in the knee: a survivorship analysis. *J Bone Joint Surg Br*. 1992;74(1):105-110.
4. Behery OA, Harris JD, Karnes JM, Siston RA, Flanigan DC. Factors influencing the outcome of autologous chondrocyte implantation: a systematic review. *J Knee Surg*. 2013;26(3):203-211.
5. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol*. 1988;15(12):1833-1840.
6. Bentley G, Biant LC, Vijayan S, Macmull S, Skinner JA, Carrington RW. Minimum ten-year results of a prospective randomised study of autologous chondrocyte implantation versus mosaicplasty for symptomatic articular cartilage lesions of the knee. *J Bone Joint Surg Br*. 2012;94(4):504-509.
7. Biant LC, Bentley G, Vijayan S, Skinner JA, Carrington RW. Long-term results of autologous chondrocyte implantation in the knee for chronic chondral and osteochondral defects. *Am J Sports Med*. 2014;42(9):2178-2183.
8. Biswal S, Hastie T, Andriacchi TP, Bergman GA, Dillingham MF, Lang P. Risk factors for progressive cartilage loss in the knee: a longitudinal magnetic resonance imaging study in forty-three patients. *Arthritis Rheum*. 2002;46(11):2884-2892.
9. Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ*. 1992;305(6846):160-164.
10. Browne JE, Anderson AF, Arciero R, et al. Clinical outcome of autologous chondrocyte implantation at 5 years in US subjects. *Clin Orthop Relat Res*. 2005;436:237-245.
11. Cavallo C, Desando G, Facchini A, Grigolo B. Chondrocytes from patients with osteoarthritis express typical extracellular matrix molecules once grown onto a three-dimensional hyaluronan-based scaffold. *J Biomed Mater Res A*. 2010;93(1):86-95.
12. Chui K, Jeys L, Snow M. Knee salvage procedures: the indications, techniques and outcomes of large osteochondral allografts. *World J Orthop*. 2015;6(3):340-350.
13. Dehne T, Karlsson C, Ringe J, Sittinger M, Lindahl A. Chondrogenic differentiation potential of osteoarthritic chondrocytes and their possible use in matrix-associated autologous chondrocyte transplantation. *Arthritis Res Ther*. 2009;11(5):R133.
14. Ding C, Cicuttini F, Scott F, Boon C, Jones G. Association of prevalent and incident knee cartilage defects with loss of tibial and patellar cartilage: a longitudinal study. *Arthritis Rheum*. 2005;52(12):3918-3927.
15. Ekland A, Nerhus TK, Dimmen S, Thornes E, Heir S. Good functional results following high tibial opening-wedge osteotomy of knees with medial osteoarthritis: a prospective study with a mean of 8.3 years of follow-up. *Knee*. 2017;24(2):380-389.
16. Farr J, Rawal A, Marberry KM. Concomitant meniscal allograft transplantation and autologous chondrocyte implantation: minimum 2-year follow-up. *Am J Sports Med*. 2007;35(9):1459-1466.
17. Filardo G, Kon E, Di Martino A, et al. Second-generation arthroscopic autologous chondrocyte implantation for the treatment of degenerative cartilage lesions. *Knee Surg Sports Traumatol Arthrosc*. 2012;20(9):1704-1713.
18. Fulkerson JP. Anteromedialization of the tibial tuberosity for patellofemoral malalignment. *Clin Orthop Relat Res*. 1983;177:176-181.
19. Gille J, Schuseil E, Wimmer J, Gellissen J, Schulz AP, Behrens P. Mid-term results of autologous matrix-induced chondrogenesis for treatment of focal cartilage defects in the knee. *Knee Surg Sports Traumatol Arthrosc*. 2010;18(11):1456-1464.
20. Gomoll AH, Probst C, Farr J, Cole BJ, Minas T. Use of a type I/III bilayer collagen membrane decreases reoperation rates for symptomatic hypertrophy after autologous chondrocyte implantation. *Am J Sports Med*. 2009;37 Suppl 1:20S-23S.
21. Gstottner M, Pedross F, Liebensteiner M, Bach C. Long-term outcome after high tibial osteotomy. *Arch Orthop Trauma Surg*. 2008;128(1):111-115.
22. Hangody L, Dobos J, Balo E, Panics G, Hangody LR, Berkes I. Clinical experiences with autologous osteochondral mosaicplasty in an athletic population: a 17-year prospective multicenter study. *Am J Sports Med*. 2010;38(6):1125-1133.
23. Harris JD, McNeilan R, Siston RA, Flanigan DC. Survival and clinical outcome of isolated high tibial osteotomy and combined biological knee reconstruction. *Knee*. 2013;20(3):154-161.
24. Hui C, Salmon LJ, Kok A, et al. Long-term survival of high tibial osteotomy for medial compartment osteoarthritis of the knee. *Am J Sports Med*. 2011;39(1):64-70.
25. Imade S, Kumahashi N, Kuwata S, Iwasa J, Uchio Y. Effectiveness and limitations of autologous osteochondral grafting for the treatment of articular cartilage defects in the knee. *Knee Surg Sports Traumatol Arthrosc*. 2012;20(1):160-165.
26. Jaiswal PK, Bentley G, Carrington RW, Skinner JA, Briggs TW. The adverse effect of elevated body mass index on outcome after autologous chondrocyte implantation. *J Bone Joint Surg Br*. 2012;94(10):1377-1381.
27. Kellgren JH, Lawrence JS. Radiological assessment of rheumatoid arthritis. *Ann Rheum Dis*. 1957;16(4):485-493.
28. King PJ, Bryant T, Minas T. Autologous chondrocyte implantation for chondral defects of the knee: indications and technique. *J Knee Surg*. 2002;15(3):177-184.
29. Martincic D, Radosavljevic D, Drobnic M. Ten-year clinical and radiographic outcomes after autologous chondrocyte implantation of femoral condyles. *Knee Surg Sports Traumatol Arthrosc*. 2014;22(6):1277-1283.
30. McCarthy HS, Roberts S. A histological comparison of the repair tissue formed when using either Chondrogide(R) or periosteum during autologous chondrocyte implantation. *Osteoarthritis Cartilage*. 2013;21(12):2048-2057.
31. Meric G, Gracitelli GC, Gortz S, De Young AJ, Bugbee WD. Fresh osteochondral allograft transplantation for bipolar reciprocal osteochondral lesions of the knee. *Am J Sports Med*. 2015;43(3):709-714.
32. Micheli LJ, Browne JE, Ergelet C, et al. Autologous chondrocyte implantation of the knee: multicenter experience and minimum 3-year follow-up. *Clin J Sport Med*. 2001;11(4):223-228.
33. Minas T. The role of cartilage repair techniques, including chondrocyte transplantation, in focal chondral knee damage. *Instr Course Lect*. 1999;48:629-643.
34. Minas T, Bryant T. The role of autologous chondrocyte implantation in the patellofemoral joint. *Clin Orthop Relat Res*. 2005;436:30-39.
35. Minas T, Chiu R. Autologous chondrocyte implantation. *Am J Knee Surg*. 2000;13(1):41-50.
36. 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;468(1):147-157.
37. Minas T, Ogura T, Bryant T. Autologous chondrocyte implantation. *JBJS Essent Surg Tech*. 2016;6(2):e24.
38. Minas T, Peterson L. Advanced techniques in autologous chondrocyte transplantation. *Clin Sports Med*. 1999;18(1):13-44, v-vi.
39. Minas T, Von Keudell A, Bryant T, Gomoll AH. The John Insall Award: a minimum 10-year outcome study of autologous chondrocyte implantation. *Clin Orthop Relat Res*. 2014;472(1):41-51.
40. Moradi B, Schonit E, Nierhoff C, et al. First-generation autologous chondrocyte implantation in patients with cartilage defects of the knee: 7 to 14 years' clinical and magnetic resonance imaging follow-up evaluation. *Arthroscopy*. 2012;28(12):1851-1861.
41. Moseley JB Jr, Anderson AF, Browne JE, et al. Long-term durability of autologous chondrocyte implantation: a multicenter, observational study in US patients. *Am J Sports Med*. 2010;38(2):238-246.
42. Muscolo DL, Ayerza MA, Aponte-Tinao LA. Survivorship and radiographic analysis of knee osteoarticular allografts. *Clin Orthop Relat Res*. 2000;373:73-79.

43. Niemeyer P, Salzman G, Feucht M, et al. First-generation versus second-generation autologous chondrocyte implantation for treatment of cartilage defects of the knee: a matched-pair analysis on long-term clinical outcome. *Int Orthop*. 2014;38(10):2065-2070.
44. Niemeyer P, Salzman GM, Hirschmuller A, Sudkamp NP. [Factors that influence clinical outcome following autologous chondrocyte implantation for cartilage defects of the knee]. *Z Orthop Unfall*. 2012;150(1):83-88.
45. Noyes FR, Barber SD, Moar LA. A rationale for assessing sports activity levels and limitations in knee disorders. *Clin Orthop Relat Res*. 1989;246:238-249.
46. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser*. 2000;894: i-xii, 1-253.
47. Ogura T, Bryant T, Minas T. Biological knee reconstruction with concomitant autologous chondrocyte implantation and meniscal allograft transplantation: mid- to long-term outcomes. *Orthop J Sports Med*. 2016;4(10):2325967116668490.
48. Ogura T, Bryant T, Minas T. Long-term outcomes of autologous chondrocyte implantation in adolescent patients. *Am J Sports Med*. 2017;45(5):1066-1074.
49. Ogura T, Mosier BA, Bryant T, Minas T. A 20-year follow-up after first-generation autologous chondrocyte implantation. *Am J Sports Med*. 2017;45(12):2751-2761.
50. Ossendorf C, Steinwachs MR, Kreuz PC, et al. Autologous chondrocyte implantation (ACI) for the treatment of large and complex cartilage lesions of the knee. *Sports Med Arthrosc Rehabil Ther Technol*. 2011;3:11.
51. Peterson L, Brittberg M, Kiviranta I, Akerlund EL, Lindahl A. Autologous chondrocyte transplantation: biomechanics and long-term durability. *Am J Sports Med*. 2002;30(1):2-12.
52. Peterson L, Vasiliadis HS, Brittberg M, Lindahl A. Autologous chondrocyte implantation: a long-term follow-up. *Am J Sports Med*. 2010;38(6):1117-1124.
53. Pike AN, Bryant T, Ogura T, Minas T. Intermediate-to long-term results of combined anterior cruciate ligament reconstruction and autologous chondrocyte implantation. *Orthop J Sports Med*. 2017;5(2):2325967117693591.
54. Polat G, Balci HI, Cakmak MF, Demirel M, Sen C, Asik M. Long-term results and comparison of the three different high tibial osteotomy and fixation techniques in medial compartment arthrosis. *J Orthop Surg Res*. 2017;12(1):44.
55. Rue JP, Yanke AB, Busam ML, McNickle AG, Cole BJ. Prospective evaluation of concurrent meniscus transplantation and articular cartilage repair: minimum 2-year follow-up. *Am J Sports Med*. 2008;36(9):1770-1778.
56. Sabzevari S, Ebrahimpour A, Roudi MK, Kachooei AR. High tibial osteotomy: a systematic review and current concept. *Arch Bone Joint Surg*. 2016;4(3):204-212.
57. Spahn G, Kirschbaum S, Kahl E. Factors that influence high tibial osteotomy results in patients with medial gonarthrosis: a score to predict the results. *Osteoarthritis Cartilage*. 2006;14(2):190-195.
58. Tallheden T, Bengtsson C, Brantsing C, et al. Proliferation and differentiation potential of chondrocytes from osteoarthritic patients. *Arthritis Res Ther*. 2005;7(3):R560-R568.
59. 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(12):2566-2574.
60. Vasiliadis HS, Wasiak J. Autologous chondrocyte implantation for full thickness articular cartilage defects of the knee. *Cochrane Database Syst Rev*. 2010;(10):CD003323.