A 20-Year Follow-up After First-Generation Autologous Chondrocyte Implantation

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Background: Treating articular cartilage defects is a demanding problem. Although several studies have reported durable and improved clinical outcomes after autologous chondrocyte implantation (ACI) over a long-term period, there is no report with over 20 years’ follow-up.

Purpose: To evaluate clinical outcomes after first-generation ACI for the treatment of knees with disabling, large single and multiple cartilage defects for which patients wished to avoid prosthetic arthroplasty, with a minimum of 20 years’ follow-up.

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

Methods: The authors reviewed prospectively collected data from 23 patients (24 knees; mean age, 35.4 years [range, 13-52 years]) undergoing ACI for the treatment of symptomatic, full-thickness articular cartilage lesions. A mean of 2.1 lesions per knee were treated over a mean total surface area of 11.8 cm² (range, 2.4-30.5 cm²) per knee. Kaplan-Meier survival analysis and functional outcome scores, including the modified Cincinnati Knee Rating System, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and Short Form–36 (SF-36), were used. Patients also self-reported an improvement in pain with a visual analog scale and a satisfaction survey.

Results: The 20-year survival rate was 63% (95% CI, 40%-78%). The evaluation of the 15 knees with retained grafts demonstrated that all clinical scores except the WOMAC subscore for stiffness and SF-36 mental component summary score improved significantly and were sustained to 20 years postoperatively. Ninety-three percent of these patients rated knee-specific outcomes as good or excellent. The outcomes for 9 of 24 knees were considered failures, including 5 undergoing revision ACI and 4 being converted to arthroplasty at a mean of 1.7 and 5.9 years, respectively. Only 1 of 5 knees that underwent revision ACI was converted to arthroplasty at 1.9 years after the index surgery, and the other 4 patients were able to maintain their biological knee. Overall, 20 years later, 79% of patients maintained their native knee, for which they initially sought treatment, and were satisfied when evaluated.

Conclusion: First-generation ACI provided satisfactory survival rates and significant clinical improvements over a 20-year follow-up, which offers an important standard for comparison with newer-generation ACI technologies of the future.

Keywords: autologous chondrocyte implantation; long-term follow-up; articular; cartilage; repair
simple, small lesions to compare in clinical trials,\textsuperscript{2,21,49} this series sought to treat patients with large, painful disabling articular lesions that we see commonly in our clinic in patients who wish to avoid a prosthesis and maintain their biological knees. Therefore, the purpose of this study was to evaluate the long-term clinical outcomes of ACI in this patient population with a minimum of 20 years’ follow-up.

\section*{METHODS}

\subsection*{Patient Demographics}

This study was approved by our institutional review board. Data were collected in a prospective manner, and informed consent was obtained from all patients at the time they were entered into the database. Between June 1995 and July 1996, a total of 23 patients (24 knees) were treated with ACI for symptomatic, full-thickness chondral defects of the knee by a single surgeon. Twenty-three patients (24 knees) were included in this study because all had successfully completed 20 years of follow-up at the time of data analysis. There were 16 men and 7 women with a mean (±SD) age of 35.4 ± 10.4 years (range, 13-52 years) at the time of the index surgery. Patients were followed up after surgery for a minimum of 20 years (range, 20-21 years). The mean number of treated lesions per knee was 2.1 ± 1.0 (range, 1-4), with a mean total surface area of 11.8 ± 8.0 cm\textsuperscript{2} (range, 2.4-30.5 cm\textsuperscript{2}) per knee. Moreover, we divided patients into 3 cartilage defect classifications: simple (single unipolar Outerbridge\textsuperscript{41} grade III/IV lesions on the femur or grade ≤II on the tibia or patella), complex (multifocal unipolar Outerbridge grade III/IV chondral lesions on the femur, concurrent [closing wedge] high tibial osteotomy/Maquet tibial tubercle osteotomy,\textsuperscript{35} osteochondritis dissecans, unipolar lesions on the tibia or patella), and salvage (bipolar focal chondral lesions, generalized chondromalacia Outerbridge grade ≥II). There were 2 simple, 12 complex, and 10 salvage types (Table 1).

Before ACI, 46 previous surgical procedures were performed among 20 patients, representing 87.0\% of the 23 patients. Some patients had undergone more than one procedure. The most common procedures were arthroscopic debridement (48\%), followed by arthroscopic meniscectomy (15\%) and marrow stimulation techniques (MSTs; 9\% including abrasion and drilling). This is a longer-term follow-up study of our initial 23 patients from a previously reported study.\textsuperscript{33}

\subsection*{Patient Evaluation}

Patients who underwent ACI were evaluated prospectively. Indications for surgery included ≥1 full-thickness articular cartilage lesions of the knee with symptoms matching the defect location. Patients were frequently referred to obtain a second opinion to avoid joint replacement. Surgery was indicated in patients who had persistent symptoms despite previous cartilage repair procedures with other techniques and/or nonoperative treatments, including physical therapy, nonsteroidal anti-inflammatory drugs, injectable therapies, and/or the application of a custom unloader brace. These were generally motivated patients who wished to avoid joint replacement at a young age. Patients were evaluated by a physical examination, radiography, magnetic resonance imaging (MRI), and arthroscopic surgery before treatment with ACI. Contraindications to treatment included inflammatory joint disease, unresolved septic arthritis, and metabolic or crystalline arthropathy.

At the onset of the study, smokers were included, as were patients with a body mass index (BMI) >35 kg/m\textsuperscript{2}. As our own results, as well as those of others,\textsuperscript{18,19} showed adverse outcomes of smoking and a BMI >35 kg/m\textsuperscript{2}, these became exclusion criteria for ACI and osteotomy. Exclusion criteria for ACI started to become clear in the late 1990s when we noted failures in patients who were

\begin{table}
\centering
\caption{Patient Demographics (N = 23 Patients, 24 Knees)}
\begin{tabular}{|l|l|}
\hline
Variable & Value \\
\hline
Age at surgery, mean ± SD (range), y & 35.4 ± 10.4 (13-52) \\
Sex, male/female, n & 16/7 \\
Knee, right/left, n & 14/10 \\
Body mass index, mean ± SD (range), kg/m\textsuperscript{2} & 24.4 ± 4.3 (18.34-36.4) \\
Follow-up, mean ± SD, y & 20.6 ± 0.3 \\
No. of cartilage lesions, n & \\
1 & 8 \\
2 & 8 \\
3 & 5 \\
4 & 3 \\
Workers’ compensation, n (%) & 8 (33) \\
Smoker, n & 1 \\
Narcotic abuser, n & 2 \\
Cause of lesion, n & \\
Trauma & 23 \\
Osteochondritis dissecans & 1 \\
No. of defects per knee, mean ± SD (range) & 2.1 ± 1.0 (1-4) \\
Total surface area of defect, per knee, at index surgery, mean ± SD (range), cm\textsuperscript{2} & 11.8 ± 8.0 (2.4-30.5) \\
Total No. of defects & 50 \\
Defect location, n & \\
Lateral femoral condyle & 9 \\
Medial femoral condyle & 17 \\
Trochlea & 13 \\
Patella & 7 \\
Lateral tibial plateau & 4 \\
Medial tibial plateau & 0 \\
Unipolar/bipolar lesion, n & 17/7 \\
Bipolar lesion, medial/lateral/patellofemoral, n & 0/2/5 \\
Type of lesion, n & \\
Simple & 2 \\
Complex & 12 \\
Salvage & 10 \\
\hline
\end{tabular}
\end{table}
noncompliant with physical therapy and obese patients (BMI >35 kg/m²). Some patients on baseline narcotics and who were cigarette smokers demonstrated addictive, noncompliant, and manipulative behavior patterns. These patients were difficult to manage postoperatively with pain management, frequently became stiff, or were noncompliant with physical therapy, and ultimately failed owing to a traumatic injury or poor biological growth of the ACI graft (cigarette smoking).

Presurgical Planning and Surgical Technique

ACI was performed as described in detail previously.30 After arthroscopic cartilage biopsy was performed during the initial surgery, 200 to 300 mg of healthy, nonweightbearing articular cartilage from the intercondylar notch was sent for culture and cryopreservation (Vericel). After insurance approval, the cryopreserved chondrocytes were then thawed and expanded for definitive cell implantation. The second open surgical arthroscopy, and defect(s) implantation were performed on an elective basis from 6 weeks to 2 years after chondrocyte cryopreservation. The defect(s) was radically debrided with a knife and ring curette back to healthy intact cartilage, preserving the integrity of the subchondral bone, and the defect(s) was carefully templated with sterile tracing paper. The periosteum was harvested using the template(s) from the proximal tibia or distal femur, placed on the cartilage defect, and secured flush to the articular surface with multiple interrupted 6-0 Vicryl sutures (Ethicon). The suture line was then waterproofed with autologous fibrin glue prepared preoperatively in the hospital blood bank, the autologous cultured chondrocytes were injected underneath the membrane, and the opening injection site was then sutured and sealed with fibrin glue (commercially available fibrin glue was not available in the United States during this study period).

Predisposing factors for articular damage such as malalignment and patellar maltracking were addressed at the time of surgery. Tibiofemoral malalignment >2° to 3° was corrected via osteotomy of the tibia or femur (all osteotomies during this study period were closing wedge), with correction of the mechanical axis to neutral or 0°. Patellofemoral maltracking was addressed with tibial tubercle osteotomy (Maquet technique25 or Elmslie-Trillat procedure50 during this study period) for patellar tracking and proximal soft tissue balancing (lateral release, vastus medialis obliques advancement) as necessary to centralize the extensor mechanism. Nine of 24 knees (37.5%) underwent the index surgery with ACI and a concomitant procedure (Table 2).

Definition of Failure

Failure of the graft was defined as revision cartilage repair or conversion to arthroplasty for persistent or recurrent symptoms in conjunction with MRI and/or arthroscopic evidence of graft delamination, inadequate fill, or degeneration requiring additional surgical treatment. Arthroscopic removal of periosteal hypertrophy was not considered a failure but a subsequent surgical procedure (SSP) that has almost disappeared with the use of collagen membranes in 2007. The reason for failure after ACI was defined as follows based on the intraoperative and/or MRI radiographic findings: (1) failure due to the ACI graft alone (graft failure including delamination or biological failure to form adequate, hard cartilaginous tissue); (2) failure due to the progression of disease in the native, non-transplanted articular cartilage (progression); and (3) failure due to a traumatic event to the native articular cartilage or transplanted ACI graft (trauma).

Survival Analysis

The survival rate was evaluated with the Kaplan-Meier method, with failure of the graft as the endpoint measure. Subanalysis for the survival rate was performed according to sex, age, cartilage defect size (<4.5 cm² vs ≥4.5 cm²), type of cartilage lesion (simple + complex vs salvage), presence of concomitant osteotomy, history of MSTs, and presence of workers’ compensation.

Clinical Outcome Assessment

Patients were prospectively evaluated with validated outcome measures including the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC),3 visual analog scale (VAS) for pain, and Short Form–36 (SF-36).7 Activity-based outcomes were assessed by a nonvalidated categorical scale, the modified Cincinnati Knee Rating System.9 The original Cincinnati Knee Rating System was based on a 0-to-100 continuous scale, whereas the modified Cincinnati Knee Rating System uses a 1-to-10 categorized scale, with a 2-point change being considered clinically meaningful (Figure 1).9,27 The VAS is based on a 0-to-10 scale, with 10 being worst pain. Patients also answered questions regarding self-rated knee function and satisfaction with the procedure. Scores were gathered preoperatively and at 2, 5, 10, and 20 years postoperatively during consultations or via a mailed questionnaire. Preoperative scores were collected from all of the patients in the office. Postoperative scores were collected from 65% of the patients via mail and 35% in the office.

Postoperative Course

Postoperatively, patients were instructed to use a continuous passive motion machine for 6 to 8 hours daily for 6 weeks. Patients remained flatfoot touch weightbearing
for 6 weeks, with gradual progression to full weightbearing between 7 and 12 weeks. Patients were allowed to return to most activities of daily living after 3 months and to noncontact, inline sporting activities without cutting movements after 4 to 6 months, such as bicycling, treadmill walking, elliptical training, swimming, rollerblading, and hiking. After 12 to 14 months, jogging was permitted if there was no swelling or pain evident. Pivoting activities were permitted from 14 to 18 months postoperatively. The postoperative recovery protocol was individually adjusted according to the defect location, concurrent procedures, degree of graft maturation, and previous activity level.31

### Statistical Analysis

Kaplan-Meier curves were used for survival analyses, followed by a log-rank analysis. The Wilcoxon signed-rank test was used to compare differences in functional scores (obtained from the modified Cincinnati, VAS, WOMAC, and SF-36) between the 2 time points (preoperatively and at each follow-up). The outcome scores of patients who were considered failures within the time periods of follow-up were not included in the calculations. In addition, the Wilcoxon signed-rank test was used to compare differences in the change in functional scores from preoperatively to 2 years’ follow-up between patients with treatment success and those with treatment failure within the study period. The level of significance was set a priori at \( P < .05 \). All statistical analyses were performed with Stata (version 13; StataCorp).

### RESULTS

#### Survival Analysis

Overall, the survival rate was 63% (95% CI, 40%-78%) at both 10 and 20 years (Figure 2). Nine knees were considered to be a failure during follow-up. Subanalysis for the survival rate did not find a significant difference according to sex, age, cartilage defect size (\(<4.5 \text{ cm}^2 \) vs \( \geq 4.5 \text{ cm}^2 \)), type of cartilage lesion (simple + complex vs salvage), presence of concomitant osteotomy, previous MSTs, and presence of workers’ compensation (Table 3). One patient who was a smoker at the time of ACI underwent revision ACI at 10 months.

#### Functional Outcomes

All patient-reported outcomes for the knees with retained grafts showed a significant improvement at 2, 5, and 20 years.
years postoperatively compared with preoperative scores (Figures 3-7 and Table 4). Only the WOMAC stiffness subscore and SF-36 mental component summary (MCS) score did not demonstrate significant improvement. The greatest improvements in clinical scores were observed during the first 2 years. There were declines in the mean VAS score and the mean modified Cincinnati score after 5 years; however, these scores remained significantly improved compared with preoperative values. In contrast, no decline was seen in the WOMAC total score after 5 years.

Between knees with treatment success and knees that eventually failed within the study period, there was a significant difference in the change in the modified Cincinnati score from preoperatively to 2 years' follow-up ($P = .0370$). Except for the modified Cincinnati score, no significant difference was found in the other functional scores (Table 5). Three knees failed before 2 years' follow-up and were excluded.

**Patient Satisfaction**

Of 15 successful knees, 14 patients rated knee function as better after surgery, indicated they would undergo the same surgery again, and rated knee-specific outcomes as good ($n = 4$) or excellent ($n = 10$). All were satisfied with the procedure (Table 6). Among 15 patients who rated their knee as good ($n = 5$) or excellent ($n = 10$) at 2 years postoperatively, 11 patients rated their knee as good ($n = 2$) or excellent ($n = 9$) at 20 years postoperatively. The other 4 patients were considered a failure during the study period. Of 4 patients who rated their knee as fair at 2 years postoperatively, 2 patients rated their knee as good ($n = 1$) or excellent ($n = 1$) at 20 years. Additionally, of 2 patients
who rated their knee as poor at 2 years, 1 rated it as good at 20 years. Of 9 failed knees, all patients answered the questions at a mean of 4 months before they failed. Four of these 9 patients rated their operated knee as better than preoperatively. In these 4 patients, their pain level evaluated with the VAS was improved clinically meaningfully, although the improvement of the modified Cincinnati score was poor. Thus, their activity level was not significantly improved, which resulted in proceeding to joint replacement or revision cartilage surgery.

Subsequent Surgical Procedures

Twenty of 24 knees required a total of 30 SSPs. Twenty-seven of 30 procedures occurred within 5 years postoperatively. The majority of SSPs were managed arthroscopically. The most common reason for an SSP was ACI graft related in 15 (including 9 periosteal hypertrophy and 7 partial graft delamination), followed by arthrofibrosis in 3 knees, painful hardware in 3 knees, arthroscopic assessment in 3 knees, removal of a loose body in 2 knees, arthroscopic lateral release in 1 knee, infection of hardware in 1 knee, and saphenous neuroma in 1 knee. Eight of these 20 knees proceeded to become failures.

Treatment Failures

Nine of 24 knees were considered failures in this study period (Table 7). Two knees failed after a traumatic event. Overall, the mean time to failure after the index surgery was 3.6 years (range, 0.4-10 years). Five of 9 knees who rated their knee as poor at 2 years, 1 rated it as good at 20 years.

Of 9 failed knees, all patients answered the questions at a mean of 4 months before they failed. Four of these 9 patients rated their operated knee as better than preoperatively. In these 4 patients, their pain level evaluated with the VAS was improved clinically meaningfully, although the improvement of the modified Cincinnati score was poor. Thus, their activity level was not significantly improved, which resulted in proceeding to joint replacement or revision cartilage surgery.

**TABLE 4**

Preoperative and Postoperative WOMAC Scores in Knees With Retained Grafts

<table>
<thead>
<tr>
<th>WOMAC</th>
<th>Preoperative (n = 24)</th>
<th>2 Years (n = 21)</th>
<th>5 Years (n = 17)</th>
<th>10 Years (n = 16)</th>
<th>20 Years (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>38.8 ± 16</td>
<td>24.3 ± 14.5b</td>
<td>17.6 ± 16.3c</td>
<td>12.0 ± 13.9c</td>
<td>12.7 ± 7.4c</td>
</tr>
<tr>
<td>Pain</td>
<td>9.3 ± 4.1</td>
<td>5.6 ± 3.8b</td>
<td>4.3 ± 4.1b</td>
<td>2.8 ± 3.3c</td>
<td>2.6 ± 2.5c</td>
</tr>
<tr>
<td>Stiffness</td>
<td>3.3 ± 1.7</td>
<td>2.7 ± 1.8</td>
<td>2.1 ± 1.6</td>
<td>1.7 ± 1.3c</td>
<td>2.2 ± 1.0</td>
</tr>
<tr>
<td>Function</td>
<td>26.2 ± 10.9</td>
<td>16.1 ± 10b</td>
<td>11.2 ± 11.4c</td>
<td>7.6 ± 10.0c</td>
<td>7.7 ± 4.8c</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

*P < .01 (compared with preoperative scores).

**P < .001 (compared with preoperative scores).

_**P < .05 (compared with preoperative scores).
underwent revision ACI at a mean of 1.7 years (range, 0.4-4.1 years) postoperatively. Among these 5 knees, 4 were treated with revision ACI, of which 1 failed because of a traumatic injury (motor vehicle accident) after revision ACI and was treated with re-revision ACI. The remaining 1 of 5 knees was converted to arthroplasty at 1.9 years after revision ACI. The other 4 of 9 knees were converted to arthroplasty at a mean of 5.9 years (range, 2.2-9.8 years) postoperatively primarily because of the progression of disease. The mean age at the time of arthroplasty was 39 years (range, 34-45 years).

**DISCUSSION**

In this review of a prospectively collected data set, we analyzed data from 23 patients (24 knees) who underwent first-generation ACI for symptomatic articular cartilage lesions of the knee joint with a minimum of 20 years’ follow-up. Our results demonstrated a 63% survival rate at both 10 and 20 years after first-generation ACI and significant improvements in all clinical outcomes except for the WOMAC subscore for stiffness and SF-36 MCS score. Notably, the greatest improvements in clinical outcomes were observed at 2 years postoperatively and were sustained for up to 20 years postoperatively. This cohort of patients had large, disabling cartilage lesions after failed prior surgeries and wished to maintain their biological knees, which was possible in 19 of 24 knees, corresponding to a high patient satisfaction rate of 79% during the follow-up. To the best of our knowledge, our study is the longest follow-up study of cartilage repair describing clinical outcomes after first-generation ACI with a minimum of 20 years’ follow-up.

Our results were consistent with those of previous studies that have shown significant long-term clinical improvements in patients after ACI. A recent systematic review showed successful outcomes in 82% of patients at a mean follow-up of 11.4 years.48 However, no studies are available with respect to the follow-up exceeding 20 years postoperatively. The results of our study showed that the survival rate was 63% at both 10 and 20 years postoperatively in our initial cohort of patients. Previous studies reported that the failure rate was 7% to 26% at a mean of 11.2 years’ follow-up. Our failure rate of 33% at 10 years postoperatively was comparable.33 Additionally, given the fact that a recent systematic review also showed that larger lesions had an increased risk of reoperations and failure,43 our study, including notably larger cartilage lesions than those in previous studies, showed that ACI provided a sufficient survival rate for the treatment of large cartilage lesions with over 20 years’ follow-up.

**Subanalysis for the survival rate did not find a significant difference; however, the best survival rate (100%) at 20 years postoperatively was found for a defect size < 4.5 cm², and the worst rate (25%) was found in patients who had a history of MSTs. This observation was in line with previous studies that have shown an increased failure rate of lesion sizes > 4.5 cm² and subsequent ACI after MSTs.**

**TABLE 5**

<table>
<thead>
<tr>
<th>Rating System</th>
<th>Success (n = 15)</th>
<th>Failure (n = 6)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>△Modified Cincinnati</td>
<td>3.4 ± 2.6</td>
<td>1.0 ± 1.1</td>
<td>.0370</td>
</tr>
<tr>
<td>△VAS</td>
<td>–3.4 ± 2.4</td>
<td>–1.8 ± 0.8</td>
<td>.0825</td>
</tr>
<tr>
<td>△WOMAC total</td>
<td>–17.4 ± 17.6</td>
<td>–23 ± 20.1</td>
<td>.0939</td>
</tr>
<tr>
<td>△WOMAC pain</td>
<td>–4.5 ± 4.5</td>
<td>–0.5 ± 3.6</td>
<td>.1009</td>
</tr>
<tr>
<td>△WOMAC stiffness</td>
<td>–0.7 ± 2.1</td>
<td>0.0 ± 1.4</td>
<td>.3624</td>
</tr>
<tr>
<td>△WOMAC function</td>
<td>–12.3 ± 12.1</td>
<td>–16.6 ± 16.4</td>
<td>.1016</td>
</tr>
<tr>
<td>△SF-36 PCS</td>
<td>6.8 ± 10.9</td>
<td>4.8 ± 8.9</td>
<td>.5853</td>
</tr>
<tr>
<td>△SF-36 MCS</td>
<td>0.2 ± 6.5</td>
<td>3.5 ± 8.3</td>
<td>.3500</td>
</tr>
</tbody>
</table>

*Values are expressed 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.*

*Values are expressed as n (%).
The greatest improvement in functional scores was observed in the first 2 years in our study. This finding was consistent with those of previous studies. Peterson et al.\textsuperscript{14} showed that clinical outcomes at 2 years were maintained at the final follow-up at a mean of 6.5 years. Our results were obtained over a much longer follow-up period with a minimum of 20 years postoperatively. Moseley et al.\textsuperscript{36} reported that 87% of patients who showed improvement (modified Cincinnati overall condition score $>1$-point increase) at 1 to 5 years of follow-up also demonstrated improvement at the longer 6- to 10-year follow-up period. Similarly, our study showed that 11 of 14 patients (79%) who reported improvement (modified Cincinnati overall condition score $>2$-point increase) at 2 years postoperatively also demonstrated improvement at 10 and 20 years' follow-up. Moreover, there was a significant difference in the change in the modified Cincinnati score from preoperatively to 2 years postoperatively between knees that were successfully treated over 20 years and knees that eventually failed ($P = .0370$). Therefore, these results indicate that the improvement at 2 years postoperatively, especially determined by the modified Cincinnati score greater than 2 points, was a predictor for a successful outcome up to 20 years.

The study by Brun et al.\textsuperscript{10} showed that 45% of patients demonstrated hyaline-like cartilage more than 18 months after ACI compared with 24% at earlier time points. Additionally, the presence of hyaline tissue containing type II collagen after ACI repair correlated with good to excellent clinical results.\textsuperscript{10,20,45} Another basic research study\textsuperscript{47} showed that procollagen IIA, which indicates an immature chondroprogenitor phenotype instead of mature chondrocytes, increased from $<2\%$ in the first 2 years postoperatively to 30\% at 3 to 5 years after surgery. This study suggested that cartilage repair tissue produced after ACI probably takes more than 2 years to mature. Thus, this ongoing time-dependent maturity of cartilage tissue in previous studies could explain the time-dependent clinical improvements observed in our study.

While all outcomes except the WOMAC stiffness subscore and SF-36 MCS score at each follow-up significantly improved compared with preoperatively, we found a slight decline in VAS and modified Cincinnati scores after 5 years. When considering that a 2-point change in VAS scores and modified Cincinnati scores is considered clinically meaningful,\textsuperscript{13,14} however, the decline observed in VAS and modified Cincinnati scores after 5 years was less than 2 points and not considered clinically meaningful. This interpretation could be supported by the fact that no decline was seen in all WOMAC scores after 5 years. Even though there is no doubt that the effects of aging decrease physical function, ACI surgery provided sufficient durability and a very high patient satisfaction rate. Regarding WOMAC stiffness subscores except at 10 years' follow-up, relatively high preoperative scores might not have allowed for the significant improvement. Although the SF-36 physical component summary score improved significantly, the SF-36 MCS score did not reach significant improvement compared with preoperatively except at 10 years' follow-up. This observation was consistent with a previous study that showed the SF-36 MCS was the least responsive outcome score after cartilage repair.\textsuperscript{11}

Regarding patient-reported satisfaction, all patients with retained grafts over 20 years were satisfied with ACI. Among 9 knees that failed during follow-up, notably, 4 patients rated their knee as better compared with preoperatively, and they were also satisfied with the surgical procedure even though they failed. The reason for their satisfaction might be explained by the fact that their pain level was improved significantly, although their activity level remained poor. In addition, 3 of these 4 patients were able to avoid arthroplasty and maintain their biological knees up to a mean of 4.6 years (range, 2.2-6.3 years) postoperatively. The remaining knee had 4 cartilage defects implanted, and 2 of 4 grafts failed. Thus, the retained grafts might have contributed to the improvements in pain, function, and satisfaction for this patient.

Half of the SSPs in our study were primarily performed because of a periosteum-related issue (periosteum hypertrophy and delamination), the majority of which were

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, Sex</th>
<th>Cartilage Lesion</th>
<th>Size, cm$^2$</th>
<th>Reason for Failure</th>
<th>Revision Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45, Male</td>
<td>MFC, trochlea</td>
<td>6.8</td>
<td>Trauma</td>
<td>Revision ACI at 4.1 y, followed by third ACI at 14 y (because of trauma-MVA)</td>
</tr>
<tr>
<td>2</td>
<td>33, Female</td>
<td>LFC, LTP</td>
<td>4.8</td>
<td>Progression</td>
<td>TKA at 2.2 y</td>
</tr>
<tr>
<td>3</td>
<td>31, Male</td>
<td>LFC, patella, trochlea</td>
<td>30.5</td>
<td>Progression</td>
<td>TKA at 6.3 y</td>
</tr>
<tr>
<td>4</td>
<td>31, Female</td>
<td>MFC, LFC, patella, trochlea</td>
<td>20.3</td>
<td>Graft failure (patella, LFC)</td>
<td>Revision ACI at 5 mo</td>
</tr>
<tr>
<td>5</td>
<td>35, Male</td>
<td>MFC, LFC, patella, trochlea</td>
<td>19.5</td>
<td>Progression</td>
<td>TKA at 9.8 y</td>
</tr>
<tr>
<td>6</td>
<td>34, Male</td>
<td>MFC</td>
<td>10.5</td>
<td>Graft failure</td>
<td>Revision ACI at 2.3 y</td>
</tr>
<tr>
<td>7</td>
<td>38, Female</td>
<td>MFC</td>
<td>5.0</td>
<td>Trauma</td>
<td>Revision ACI at 10 mo</td>
</tr>
<tr>
<td>8</td>
<td>36, Male</td>
<td>LFC, LTP</td>
<td>15.4</td>
<td>Graft failure (LFC)</td>
<td>TKA at 5.4 y</td>
</tr>
<tr>
<td>9</td>
<td>52, Female</td>
<td>MFC, LFC, trochlea</td>
<td>10.0</td>
<td>Progression</td>
<td>Revision ACI at 11 mo, followed by TKA at 23 mo</td>
</tr>
</tbody>
</table>

\textsuperscript{a}ACI, autologous chondrocyte implantation; LFC, lateral femoral condyle; LTP, lateral tibial plateau; MFC, medial femoral condyle; MVA, motor vehicle accident; TKA, total knee arthroplasty.
arthroscopically treated. Twenty-nine of 30 procedures occurred within 5 years postoperatively, which is consistent with the previous study.36

Our study of first-generation periosteal ACI reports on the results of the first year or “learning curve” of the senior surgeon’s experience and is a small sample (23 patients, 24 knees over 20 years of follow-up) with disabling cartilage injuries. Since first described in 1994, ACI has evolved in its indications and techniques to address the concomitant “background factors” for chondral defects and replacement of the periosteal membrane. The use of periosteum is time-consuming, adding to the operative time, is technically difficult to harvest and handle, is painful to patients because of the need for an additional incision for harvesting the periarticular area, and increases the risk of arthrofibrosis when taken from the femur. Periosteal hypertrophy seen after implantation was the cause for a significant number of SSPs in our cohort of patients, which is not seen with the use of a collagen membrane.17 If periosteum is used, the considerable rate of SSPs possibly required should be discussed with patients before proceeding to ACI. Thankfully, the use of periosteum was abandoned in 2007 for the use of a collagen membrane, which made the procedure more predictable for the patient and surgeon alike, diminishing the need for SSPs up to 50%. This follow-up of first-generation ACI is therefore of historical interest and speaks to the durability of the repair tissue formed by the procedure.

Techniques to address the underlying diseased subchondral bone altered after MSTs to lessen the risk of failure in conjunction with ACI are being developed, including the removal of sclerotic bone and the ACI “sandwich” technique,29,51 which may have improved survival rates and functional outcomes in this cohort of patients. The senior author (T.M.) also comments that some of the patients treated in this series may not meet a more refined contemporary set of indications for ACI because of the breadth of disease or other underlying factors not necessarily recognized when the ACI technique was first introduced. For instance, the effect of cigarette smoking, prior failed MSTs, and the use of baseline narcotics before ACI were all noted to have an adverse effect on clinical outcomes,19,32 which was not known at the time of the study onset. Nonetheless, we believe that the results of our study will serve as an important baseline for comparison to newer cartilage repair techniques regarding safety, durability, clinical outcomes, and patient satisfaction over a 20-year follow-up.

Additionally, the cost of this procedure should be taken into consideration because it has been noted that ACI is a more costly procedure than other cartilage repair procedures. However, several studies have demonstrated the cost-effectiveness of ACI because of the lasting improvements in outcomes over the long term.23,28,34

The strength of our study is that it is a single-surgeon series with consistent surgical indications, surgical technique, rehabilitation, outcome measures, and 100% follow-up exceeding 20 years. However, limitations should be noted. This was a small sample, and a 20- to 25-year follow-up with greater than 100 patients may give a more realistic outcome with the first-generation technique. There was no control or alternative treatment group, and we did not include radiographic outcomes that could have provided useful information with respect to the risk of progression to osteoarthritis with graft failure, despite stable clinical improvement. However, we were unable to obtain the radiographs of patients who underwent the index surgery 20 years ago, as many of the films were destroyed after the conversion to digital radiography, and many of the 20-year follow-ups were with questionnaires without radiographs. Knutsen et al25 15-year long-term study demonstrated that osteoarthritis could not be avoided by cartilage repair whether it be ACI or microfracture; 57% versus 48% (not significantly different), respectively, had a Kellgren and Lawrence grade of ≥2. However, they also lacked a nonoperative control group. This study questioned whether cell cultivation was at all worthwhile as the clinical outcomes between ACI and microfracture also were not different. However, the patient cohort in their study was different from ours, which included many patients with complex salvage knees who can benefit more from ACI than microfracture. In our 20-year database of over 800 patients treated, we had only 37 patients (simple type) with a neutrally aligned, stable knee, with an intact meniscus and a single mean defect size of 4.5 cm², the ideal case looked for in randomized controlled trials. Two of the knees in this series had simple lesions, and both maintained an excellent clinical outcome and survivorship with ACI. The vast majority of patients have more than one defect, including all surfaces of the knee that respond well to ACI. Especially for the patellofemoral joint, microfracture fares poorly,22 whereas ACI does well.12,15,16,24,39 We also did not include an MRI evaluation. Our series on patellar ACI demonstrated high correlation between the magnetic resonance observation of cartilage repair tissue (MOCART) score and good clinical outcomes.52 However, the correlation between the MOCART score and clinical outcomes in other studies after cartilage repair has not been established.6,38

In conclusion, this small study of patients performed 20 years ago shows that first-generation periosteal ACI provides reliable and durable clinical improvements over 20 years, with the greatest increase in function and pain relief within the first 2 years. Biological knees were maintained in 79% of patients who were 35.4 years old, on average, at the onset of the study with a large area of cartilage damage of 11.8 cm², on average, per knee. Additionally, very high patient satisfaction (19/24, 79%) during the follow-up period was predictable. We believe that our study serves as an important benchmark for comparison with cartilage repair techniques to follow.

REFERENCES
3. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring


