TITLE

A prospective clinical and radiological evaluation to 5 years following arthroscopic matrix-induced autologous chondrocyte implantation (MACI).

ABSTRACT

Background: While mid-term outcomes after matrix-induced autologous chondrocyte implantation (MACI) are encouraging, the procedure permits an arthroscopic approach which may reduce the morbidity of arthrotomy and permit accelerated rehabilitation.

Hypothesis: A significant improvement in clinical and radiological outcomes following arthroscopic MACI will exist through to 5 years post-surgery.

Study Design: Prospective case series.

Methods: We prospectively evaluated the first 31 patients (15 males, 16 females) that underwent MACI performed via arthroscopic implantation to address symptomatic tibiofemoral chondral lesions. MACI was followed by a structured rehabilitation program in all patients. Clinical scores were administered pre-operatively and at 3 and 6 months, as well as 1, 2 and 5 years post-surgery. These included the KOOS, Lysholm Knee Score (LKS), Tegner Activity Scale (TAS), visual analogue pain scale, SF-36, active knee motion and six minute walk test. Isokinetic dynamometry assessed peak knee extension and flexion strength and limb symmetry indices (LSIs) between the operated and non-operated limbs. High resolution magnetic resonance imaging (MRI) was undertaken at 3 months and 1, 2 and 5 years, to evaluate graft repair as well as an MRI composite score.

Results: There was a significant improvement (p<0.05) in all KOOS subscales, the LKS and TAS, the SF-36 physical component subscale, pain frequency and severity, active knee flexion and extension, and six-minute walk distance. Isokinetic knee extensor strength significantly improved and all knee extensor and flexor LSIs were above 90% (apart from peak knee extension strength at 1 year). At 5 years, 93% of patients were satisfied with MACI to relieve their pain, 90% with improving their ability to undertake daily activities and 80% with the improvement in participating in sport. Graft infill (p=0.033) and the MRI composite score (p=0.028) significantly improved over time, with 87% of patients demonstrating good-excellent tissue infill at 5 years. There were two graft failures at 5 years post-surgery.

Conclusion: This arthroscopically performed MACI technique demonstrated good clinical and radiological outcomes to 5 years, with high levels of patient satisfaction.

Keywords: arthroscopy, matrix-induced autologous chondrocyte implantation (MACI), clinical outcomes, magnetic resonance imaging (MRI), rehabilitation.

What is known about this subject: Matrix-induced autologous chondrocyte implantation (MACI) has demonstrated encouraging clinical outcomes in the repair of full thickness articular cartilage defects in the knee. However, MACI traditionally required an open arthrotomy to undertake the second-stage implantation of the cell-based scaffold. The surgical technique does permit an arthroscopic approach, which reduces the associated morbidity of arthrotomy, including the reduced risk of complications such as adhesions, post-operative joint stiffness, excessive pain and impressive scarring, and may permit accelerated rehabilitation. A number of arthroscopic techniques have, therefore, now been proposed, with an array of associated technical difficulties and results reported. The majority of these reported techniques are technical notes, small case series and/or present early post-operative clinical outcomes.

What this study adds to existing knowledge: As mentioned above, while a range of arthroscopic MACI techniques have been published, the majority of these reported papers are technical notes, small case series and/or present early post-operative clinical outcomes. There are only a few published studies that present data investigating outcomes in patients following arthroscopically performed MACI to 5 years or beyond. Therefore, this study presents a comprehensive clinical, functional and radiological follow up in patients to 5 years after arthroscopic MACI.

INTRODUCTION

Matrix-induced autologous chondrocyte implantation (MACI) is a two-stage surgical technique employed to address full thickness, symptomatic knee chondral lesions. Initially, it involves a cartilage biopsy, isolation and expansion of chondrocytes *ex-vivo*, seeding of cells directly onto a collagen membrane, and subsequent re-implantation into the knee. Whilst encouraging clinical outcomes have been reported for MACI,[5, 13, 20, 21, 30, 43, 55] traditionally the second-stage implantation required an open arthrotomy, though the surgical technique does permit an arthroscopic approach. Arthroscopic implantation reduces the associated morbidity of arthrotomy, including the reduced risk of complications such as adhesions, post-operative joint stiffness, excessive pain and impressive scarring,[17] and may permit accelerated rehabilitation.

A number of arthroscopic techniques have now been proposed, with an array of associated technical difficulties and results reported.[7, 9, 17-19, 27, 30-32, 36, 37, 48, 52] To the best of our knowledge, there remains limited data investigating outcomes in patients following arthroscopically performed MACI to five years or beyond.[19, 30-32] In 2012, we presented outcomes in a pilot series of patients who underwent a new arthroscopic technique for performing MACI, to determine the early safety and efficacy of this procedure in treating articular cartilage defects in the knee.[10] This study presents an extension of this patient cohort, with a comprehensive clinical and radiological follow up in patients to 5 years post-surgery. We hypothesized that a significant improvement in clinical and radiological outcomes following this arthroscopic MACI technique would exist throughout the post-operative timeline to 5 years post-surgery, with high levels of patient satisfaction.

MATERIALS AND METHODS

Participants

Between June 2006 and April 2010, 31 patients (15 males, 16 females) were prospectively recruited and evaluated before undergoing MACI via an arthroscopic surgical technique. Initially, a *priori* power calculation was performed using G-Power (Dusseldorf, Germany) for the primary outcome variable; pre- to post-surgical change in the pain subscale of the Knee Injury and Osteoarthritis Outcome Score (KOOS), demonstrating that 19 patients were required to reveal differences at the 5% significance level, with 90% power and employing a large effect size (0.8). Given the early success and steady flow of patients undergoing the arthroscopic surgical procedure, we continued recruitment to allow for attrition.

All patients exhibited persistent pain and symptoms associated with grade III or IV chondral lesions, assessed with the International Cartilage Repair Society (ICRS) chondral defect classification system.[6] Patients were MACI candidates if they were 15-65 years of age, appeared able and willing to follow a structured rehabilitation program and presented with isolated, full thickness chondral defects. This was confirmed in all cases via magnetic resonance imaging (MRI) assessment, which was also used to assess the location, size and severity of the defect, as well as other soft tissue damage incorporating the menscii or ligamentous structures. Patients were excluded if they had a body mass index (BMI) > 35, ligamentous instability, had undergone a prior extensive meniscectomy, had ongoing progressive inflammatory arthritis or had varus/valgus lower limb mal-alignment (as indicated by > 3° tibiofemoral anatomic angle). The orthopaedic specialist evaluated the patient for joint mal-alignment initially. Should further investigation be warranted then the patient would be sent for Maquet views, though this was not required in any of these patients.

Should the patient be suitable for MACI, the defect location and surrounding environment dictated whether they were a candidate for the arthroscopic approach. This was initially evaluated via MRI, and confirmed at the time of first-stage arthroscopic biopsy. All patients over the time period that were planned for arthroscopic MACI based on the aforementioned criteria underwent the technique successfully. Isolated lesions on the weight bearing surface of the femoral or tibial condyle were considered, unless the lesion was at the external periphery of the condyle. These may be problematic with the arthroscopic technique due to the potential interference of the meniscii with the inflatable portion of the indwelling catheter as per this arthroscopic method, and described below. Patients with patella, trochlea or multiple lesions were not considered as they were beyond the current capabilities of this technique.

Therefore, over the recruitment period (June 2006 to April 2010), a total of 73 patients underwent MACI grafting (31 of these arthroscopic). The arthroscopic technique permits easy conversion to a mini-open technique at any stage during the operation if required. However, none of the patients that were planned for the arthroscopic method (n=31) required conversion to an open technique during the course of the surgery. A flowchart of study recruitment and assessment is demonstrated in Figure 1. All patients provided their written informed consent prior to study enrollment and pre-operative evaluation, and ethics approval was obtained from the relevant hospital ethics committee. This study conformed to the STROBE (Strengthening the reporting of observational studies in epidemiology) checklist.

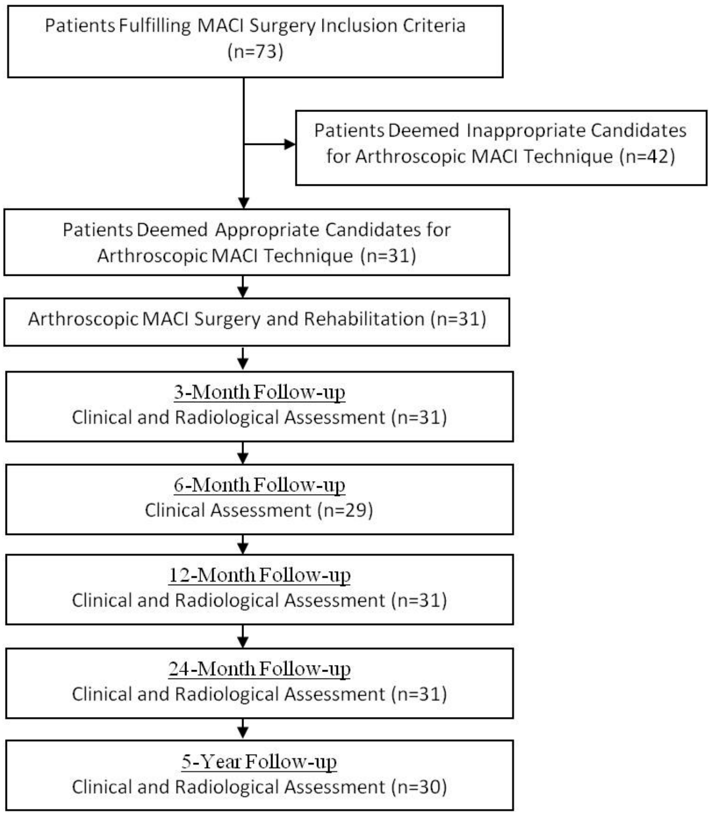


Figure 1. Study flowchart demonstrating recruitment and evaluation over the 5 year period.

The MACI Surgical Technique

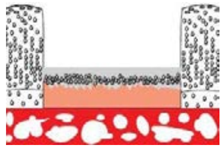
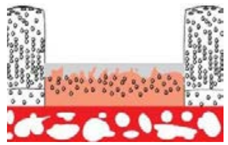
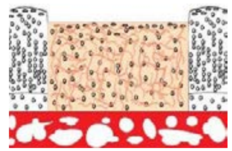
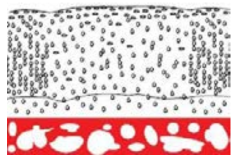
The arthroscopic biopsy and subsequent implantation of the matrix has been previously described,[10] with this study presenting an extension of this cohort with mid-term clinical and radiological follow up. Briefly, an arthroscopic surgery was initially undertaken to harvest healthy articular cartilage from the non weight bearing trochlear notch or the medial/lateral femoral condylar ridge for cell culturing. The geometry and containment of the defect, suitability for second-stage arthroscopic implantation and meniscal and ligamentous integrity, was also assessed at this time. The biopsy was then sent to the laboratory (Genzyme, Perth, Western Australia), whereby chondrocytes were isolated from the cartilage tissue, cultured for approximately 4-8 weeks and seeded onto a type I/III collagen membrane (ACI-Maix Matricel GmbH, Germany) three days prior to second-stage re-implantation.

At second-stage arthroscopic graft implantation, standard antero-medial and antero-lateral portals were employed. The joint was irrigated using Ringer's lactate solution. The lesion was prepared by debriding the walls to ensure a well-defined and contained defect, and removing all damaged cartilage down to the subchondral plate. The defect was then 'mapped' in several planes using the end of a graduated arthroscopy probe and, based on these measurements, the matrix was over-sized and cut. The knee was converted to a 'dry' arthroscopy by draining all fluid and drying the defect bed. The graft was introduced via a large bore arthroscopic cannula, with an 8mm inner diameter, with no valves (Conmed Linvatec, Largo FL.), and positioned within the defect. Graft size was re-assessed and further trimming was performed if required. Once satisfied with matrix size and orientation, the graft was folded away from the defect to introduce fibrin glue via a 19-gauge needle (Becton and Dickinson, Franklin Lakes NJ), before re-positioning of the graft. A Silastic Foley Catheter (Cook Urological, Inc., Indiana, USA) was introduced and the balloon inflated with saline to distribute 30 seconds of even pressure. Visualisation of the matrix was permitted via the opposite portal, with the transparent silastic allowing graft visualisation underneath. The knee was put through several cycles of knee flexion and extension under visualisation to ensure graft stability.

Post-operative Rehabilitation

All patients underwent a coordinated post-operative rehabilitation program of progressive exercise and graduated weight bearing over 3 months, while further education and advice was provided up until the 12 month time-point (Table 2) and beyond if required.[15]

Table 1. Structured rehabilitation program undertaken by patients following arthroscopic MACI.

Timeline	Rehabilitation Guidelines	Repair Tissue Maturation
Week 1-2	• WB: ≤ 20% BW • Ambulatory Aids: 2 crutches used at all times • Knee ROM: passive & active ROM from 0-30° • Knee Bracing: 0-30° • Rehabilitation: isometric contractions & circulation exercises, CPM & cryotherapy	Implantation & Protection (0-6 wks) 
Week 3-6	• WB : 30% BW (week 3) to 60% BW (week 6) • Ambulatory Aids : 1-2 crutches dictated by WB status • Knee ROM: active ROM from 0-90° (week 3) to 0-125° (week 6) • Knee Bracing: 0-45° (week 3) to full knee flexion (week 6) • Rehabilitation: isometric/straight leg & passive/active knee flexion exercises, remedial massage, patella mobilisation, CPM, cryotherapy & hydrotherapy	
Week 7-12	• WB: 60% BW (week 6) to full WB as tolerated (week 8) • Ambulatory Aids: 1 crutch as required until full WB achieved • Knee ROM: Full active ROM (week 7) • Knee Bracing Full knee flexion • Rehabilitation: introduce cycling, walking, proprioceptive/balance, resistance & CKC exercises	Transition & Proliferation (6-12 wks) 
3-6 months	• Rehabilitation: introduction of more demanding OKC (terminal leg extension) & CKC (inner range quadriceps and modified leg press), upright cycling, rowing ergometry & elliptical trainers	Remodeling (3-6 months) 
6-9 months	• Rehabilitation: increase difficulty of proprioceptive/balance, OKC & CKC exercises (ie. step ups/downs, squats), introduce controlled mini trampoline jogging	Maturation (6 months onwards) 
9-12 months	• Rehabilitation: increase difficulty of CKC exercises (ie. Lunge/squat activities on unstable surfaces), introduction of agility drills relevant to patient's sport, return to competitive activity after 12 months	

ROM = range of motion; BW = body weight; WB = weight bearing; CPM = continuous passive motion; CKC = closed kinetic chain; OKC = open kinetic chain.

Clinical Evaluation

Patients were evaluated pre-operatively and at 3 months, 6 months, 1, 2 and 5 years post-surgery, using: 1) the Knee Injury and Osteoarthritis Outcome Score (KOOS)[53] to assess knee pain, symptoms, activities of daily living (ADL), sport and recreation and knee related quality of life (QOL), 2) the Lysholm Knee Score (LKS), 3) a Visual Analogue Scale (VAS) to evaluate the frequency (VAS-F) and severity (VAS-S) of knee pain on a scale of 0-10, 4) the Tegner Activity Scale (TAS) to evaluate the patient’s activity level on a 0-10 point scale, ranging from sick leave or disability (0 points) through to elite competitive (soccer) sports (10 points)[56] and 5) the Short Form Health Survey (SF-36) which produced a mental (MCS) and physical component score (PCS).[4] A Patient Satisfaction Questionnaire was employed at 5 years post-surgery to investigate each patients overall level of satisfaction, as well as their satisfaction with MACI in relieving knee pain, improving the ability to perform normal daily activities and their ability to participate in sport.

Objectively, maximal active knee flexion and extension were evaluated pre-surgery and at all post-operative time points, as was the six minute walk test[12, 50] to assess the maximum comfortable distance the patient could walk in a six minute period. Isokinetic strength of the quadriceps and hamstrings muscle groups was assessed at 1, 2 and 5 years post-surgery using an isokinetic dynamometer (Isosport International, Gepps Cross, South Australia). Concentric knee extension and flexion strength was measured through a range of 0-90˚ of knee flexion, at a single isokinetic angular velocity of 90°/s. Each trial consisted of four repetitions: three low intensity repetitions of knee extension and flexion, immediately followed by one maximal test effort. Two trials on each lower limb were undertaken, alternating between the operated and non-operated limbs. During each maximal effort, patients were asked to perform to their maximal muscle strength, while standardized verbal encouragement was provided. For all efforts, the peak torque value (Nm) and hamstring/quadriceps (H/Q) ratio were obtained, measured by dividing the peak concentric hamstrings torque by the peak concentric quadriceps torque. A limb symmetry index (LSI) was calculated for all strength measures by dividing the peak values on the operated limb by that recorded on the non-operated limb.

Radiological Evaluation

High resolution MRI was undertaken at 3 months, as well as 1, 2 and 5 years post-surgery, using a 3 T clinical scanner (Siemens, Erlangen, Germany; Philips, Best, the Netherlands; General Electric, Milwaukee, WI, USA). Standardized proton density and T2-weighted fat-saturated images were obtained in coronal and sagittal planes (slice thickness 3 mm, field of view 14-15 cm, 512 matrix in at least one axis for proton density images with a minimum 256 matrix in one axis for T2-weighted images). Additional axial proton density fat-saturated images were obtained (slice thickness 3-4 mm, field of view 14-15 cm, minimum 224 matrix in at least one axis).

We sought to evaluate eight pertinent parameters of graft repair (graft infill, signal intensity, border integration, surface contour, tissue structure, effusion, subchondral lamina and bone),[39] following the magnetic resonance observation of cartilage repair tissue (MOCART) scoring system.[38, 50, 60, 61] The eight defined parameters were each scored from 1-4 (1=poor; 2=fair; 3=good; 4=excellent) in comparison to the adjacent native cartilage, though ‘graft infill’ could also be scored with a fifth level (3.5, very good) corresponding with ‘graft hypertrophy’.[39, 60] An MRI composite score was also calculated by multiplying each individual score by a weighting factor,[50] and adding the scores together. MRI evaluation was performed by an independent, experienced musculo-skeletal radiologist, blinded to the clinical details and clinical outcome assessment.

Statistical Analysis

To investigate the progression of clinical and MRI-based outcomes over time, a one-way repeated measures analysis of variance (ANOVA) was used. Repeated measures ANOVA were also used to investigate the change in strength outcomes (knee extension and flexion torque, H/Q ratio) throughout the post-operative timeline, between the operated and non-operated limbs. The number and percentage of grafts evaluated as good or excellent for each of the eight parameters of graft repair and the MRI composite score, was presented at 3 months and 1, 2 and 5 years post-surgery. The kappa coefficient was used to assess intra-observer reliability for the eight pertinent morphological MRI scores, while the intra-class correlation coefficient was used for the continuous MRI composite score. This was achieved by re-scoring 20 randomly selected MRI images filtered through a second time to the radiologist. Statistical analysis was performed using SPSS software (SPSS, Version 17.0, SPSS Inc., USA), while statistical significance was determined at $p<0.05$.

RESULTS

The 31 patients that underwent arthroscopic MACI included 25 on the femoral condyles (18 medial, 7 lateral) and 6 on the tibial condyles (2 medial, 4 lateral) (Table 2). The mean defect size was 2.52 cm^2 (range: 1.00-5.00), pre-operative duration of symptoms was 7.6 years (range: 1-25) and 18 (58%) had been treated previously with one or more knee surgical procedures, including: arthroscopy with chondral debridement with or without the removal of a loose body (n=12), partial meniscectomy (n=7), anterior cruciate ligament (ACL) reconstruction (n=4), and prior MACI through an open arthrotomy (n=1).

Table 2. Patient demographics and injury/surgery history for the 31 patients who underwent arthroscopic matrix-induced autologous chondrocyte implantation.

Variable	Mean (range)
Age (years)	35.3 (16 - 57)
Height (m)	1.71 (1.55 - 1.97)
Weight (kg)	77.9 (46.0 - 127.9)
Body Mass Index (BMI)	26.2 (18.4 - 34.8)
Defect Size (cm^2)	2.52 (1.00 - 5.00)
Prior Procedures	1.2 (0.0 - 4.0)
Duration of Symptoms (y)	7.6 (1.0 - 25.0)
Gender (male/female)	15 / 16
Knee (left/right)	10 / 21
Defect Location (MFC/LFC/MTP/LTP)	18 / 7 / 2 / 4

MFC = medial femoral condyle; LFC = lateral femoral condyle; MTP = medial tibial plateau; LTP = lateral tibial plateau.

Apart from two patients who missed their six month clinical evaluation (an intention to treat analysis was performed using the “last value carried forward” technique for these two time points) and one patient who was pregnant and could not undergo MR imaging at 5 years post-surgery (and was also not evaluated clinically at 5 years), clinical and MRI evaluation in all other patients (and at all time points) was completed.

Clinical Evaluation

There was a significant improvement ($p<0.05$) throughout the pre- and post-operative timeline for all patient-reported outcome scores, apart from the SF-36 MCS (Table 3). Of all 30 patients who completed the Patient Satisfaction Questionnaire at 5 years post-surgery, 93% (n=28) were satisfied with the ability of MACI to relieve their knee pain, 90% (n=27) were satisfied with the improvement in their ability to undertake daily activities and 80% (n=24) were satisfied with the improvement in their ability to participate in sport. Overall, 90% (n=27) of patients were satisfied with the results of their MACI surgery.

Table 3. Analysis of Variance (ANOVA) results summary for clinical outcomes. Shown are means (SE).

Variable	Pre-surgery	3 months	6 months	1 year	2 years	5 years	P value
KOOS (Pain)	59.6 (3.9)	76.1 (2.4)	81.8 (2.1)	84.3 (1.9)	89.3 (1.5)	91.2 (1.8)	<0.0001
KOOS (Symptoms)	62.3 (3.4)	80.9 (1.9)	85.0 (1.9)	87.0 (1.5)	87.2 (1.5)	85.6 (2.1)	<0.0001
KOOS (ADL)	75.8 (3.6)	85.1 (1.8)	88.3 (1.8)	91.5 (2.1)	95.1 (1.0)	94.1 (1.6)	<0.0001
KOOS (Sport)	32.4 (4.4)	22.5 (4.5)	37.9 (5.1)	59.5 (4.4)	68.4 (4.1)	71.5 (4.7)	<0.0001
KOOS (QOL)	29.1 (3.1)	42.8 (3.5)	50.9 (3.3)	57.7 (3.5)	64.4 (3.9)	67.5 (4.6)	<0.0001
Lysholm Knee Score	53.8 (6.9)	65.5 (7.5)	70.5 (4.5)	76.3 (4.7)	82.3 (4.0)	86.8	<0.0001
Tegner Activity Scale	2.7 (0.3)	2.9 (0.4)	3.0 (0.3)	3.4 (0.3)	4.5 (0.5)	5.5 (0.5)	<0.0001
SF-36 (PCS)	39.1 (1.9)	40.7 (1.9)	44.7 (1.5)	48.6 (1.2)	51.0 (1.0)	51.0 (1.4)	<0.0001
SF-36 (MCS)	50.9 (1.5)	53.6 (2.0)	55.6 (1.4)	55.3 (1.4)	54.5 (1.3)	54.6 (1.4)	0.272
VAS (Frequency)	6.8 (0.5)	3.0 (0.4)	2.2 (0.3)	2.0 (0.3)	2.1 (0.4)	1.9 (0.4)	<0.0001
VAS (Severity)	5.7 (0.4)	2.8 (0.4)	2.1 (0.4)	2.2 (0.3)	1.7 (0.2)	1.7 (0.3)	<0.0001
Six minute Walk Test (m)	501.6 (13.1)	496.7 (12.4)	568.0 (13.1)	612.7 (11.6)	624.3 (14.3)	640.9 (13.2)	<0.0001
Knee Flexion ROM (deg)	139.5 (1.7)	139.4 (1.2)	142.3 (1.0)	142.4 (0.9)	143.0 (0.9)	143.5 (1.2)	0.021
Knee Extension ROM (deg)	0.0 (0.3)	-0.5 (0.2)	-1.3 (0.3)	-1.6 (0.3)	-1.9 (0.3)	-1.9 (0.3)	0.009

ADL = Activities of Daily Living; QOL = Quality of Life; PCS = Physical Component Score; MCS = Mental Component Score; VAS = Visual Analogue Scale; ROM = Range of Motion.

Active knee ROM (flexion and extension) and six-minute walk distance significantly improved ($p<0.05$) throughout the post-operative time line (Table 3). While peak knee extension torque ($p=0.042$) and the H/Q ratio ($p=0.045$) significantly improved over time, there was no change ($p=0.113$) in peak knee flexion torque (Table 4). There were no group or interaction effects in any of the strength measures, and all knee extensor and flexor LSIs were above 90% (apart from peak knee extension strength at 1 year), when comparing the operated and non-operated limbs (Table 4).

Table 4. Strength scores for the operated and non-operated limbs at 1, 2 and 5 years post-surgery. Shown are means (SE).

Variable	Limb	1 year	2 years	5 years	Time Effect (*p* value)	Group Effect (*p* value)	Interaction Effect (*p* value)
Peak Knee Extension Torque (Nm)	Operated	164.4 (16.5)	185.3 (18.3)	188.9 (14.7)	0.042	0.400	0.671
	Non-operated	183.8 (16.5)	198.3 (18.3)	193.0 (14.7)			
Peak Knee Flexion Torque (Nm)	Operated	124.7 (12.1)	128.4 (13.8)	126.6 (10.6)	0.113	0.440	0.312
	Non-operated	127.7 (12.2)	133.4 (13.8)	126.9 (10.6)			
H/Q Ratio	Operated	0.87 (0.05)	0.78 (0.04)	0.71 (0.03)	0.045	0.471	0.376
	Non-operated	0.76 (0.05)	0.71 (0.04)	0.68 (0.03)			
LSI	Knee Extension	0.88	0.91	0.91		N/A	
	Knee Flexion	0.99	0.97	0.97			

H/Q = hamstring/quadriceps; LSI = limb symmetry index.

Radiological Evaluation

Evaluation of intra-observer reliability indicated perfect agreement for six of the eight individual MRI parameters (graft infill = 1.00; signal intensity = 1.00; border integration = 0.93; surface contour = 1.00; structure = 0.92; subchondral lamina = 1.00; subchondral bone = 1.00 and; effusion = 1.00), and an intra-class correlation coefficient for the MRI composite score of 0.996 (95%CI: 0.991 – 0.999), for the 20 randomly selected image pairs.

The MRI composite score significantly improved (p=0.028) from 3 months to 5 years post-surgery (Table 5). With respect to individual parameters, significant improvement was observed over time for graft infill (p=0.033), signal intensity (p<0.0001) and subchondral lamina (p<0.0001), though there were no significant time effects (p>0.05) for the remaining variables (Table 5). Of the 30 patients evaluated with MRI at 5 years post-surgery, 87% (n=27) demonstrated good-excellent tissue infill (Table 6), with 80% (n=24) demonstrating either complete tissue infill or hypertrophy, in comparison to the adjacent native cartilage. Furthermore, 80% (n=24) of grafts scored good-excellent on the MRI composite score (Table 6). Figure 2 shows the development of a post-operative MACI graft located on the medial femoral condyle for one patient, as assessed via MRI, throughout the post-operative timeline.

Table 5. MRI assessment of grafts in comparison to the adjacent native cartilage. Shown are means (SE).

Post-operative Time Point	Graft Infill	Signal Intensity	Border Integration	Surface Contour	Structure	Subchondral Lamina	Subchondral Bone	Effusion	MRI Composite score
3 months	2.85 (0.15)	2.03 (0.11)	2.71 (0.20)	2.90 (0.20)	3.06 (0.20)	3.00 (0.10)	2.77 (0.14)	3.58 (0.09)	2.74 (0.10)
1 year	3.34 (0.14)	2.77 (0.15)	3.00 (0.20)	2.84 (0.22)	3.23 (0.16)	3.71 (0.10)	2.65 (0.21)	3.55 (0.10)	3.11 (0.12)
2 years	3.39 (0.14)	2.97 (0.14)	3.16 (0.20)	2.97 (0.21)	3.13 (0.18)	3.77 (0.08)	2.58 (0.22)	3.61 (0.11)	3.22 (0.13)
5 years	3.39 (0.16)	2.84 (0.15)	3.10 (0.19)	2.87 (0.21)	3.16 (0.19)	3.65 (0.09)	2.81 (0.20)	3.84 (0.07)	3.14 (0.14)
p value	0.033	<0.0001	0.380	0.975	0.939	<0.0001	0.822	0.522	0.028

Table 6. The number (%) of grafts at 3 months and 1, 2 and 5 years post-surgery rated as good-excellent or poor-fair, for the MRI composite score and the eight individual magnetic resonance imaging (MRI) parameters, compared to the adjacent native cartilage.

Post-operative Time-point	Rating	Graft Infill	Signal Intensity	Border Integration	Surface Contour	Structure	Subchondral Lamina	Subchondral Bone	Effusion	MRI Composite score
3 months (n=31)	Good-Excellent	22 (71%)	12 (39%)	19 (61%)	21 (68%)	23 (74%)	26 (84%)	23 (74%)	30 (97%)	14 (45%)
	Poor-Fair	9 (29%)	19 (61%)	12 (39%)	10 (32%)	8 (26%)	5 (16%)	8 (26%)	1 (3%)	17 (55%)
1 year (n=31)	Good-Excellent	28 (90%)	22 (71%)	21 (68%)	21 (68%)	26 (84%)	31 (100%)	21 (68%)	30 (97%)	24 (77%)
	Poor-Fair	3 (10%)	9 (29%)	10 (32%)	10 (32%)	5 (16%)	0 (0%)	10 (32%)	1 (3%)	7 (23%)
2 years (n=31)	Good-Excellent	28 (90%)	26 (84%)	26 (84%)	23 (74%)	26 (84%)	28 (90%)	22 (71%)	29 (94%)	25 (81%)
	Poor-Fair	3 (10%)	5 (16%)	5 (16%)	8 (26%)	5 (16%)	3 (10%)	9 (29%)	2 (6%)	6 (19%)
5 years (n=30)	Good-Excellent	27 (87%)	26 (84%)	26 (87%)	21 (70%)	24 (80%)	27 (90%)	21 (70%)	29 (97%)	24 (80%)
	Poor-Fair	4 (13%)	5 (16%)	4 (13%)	9 (30%)	6 (20%)	3 (10%)	9 (30%)	1 (3%)	6 (20%)

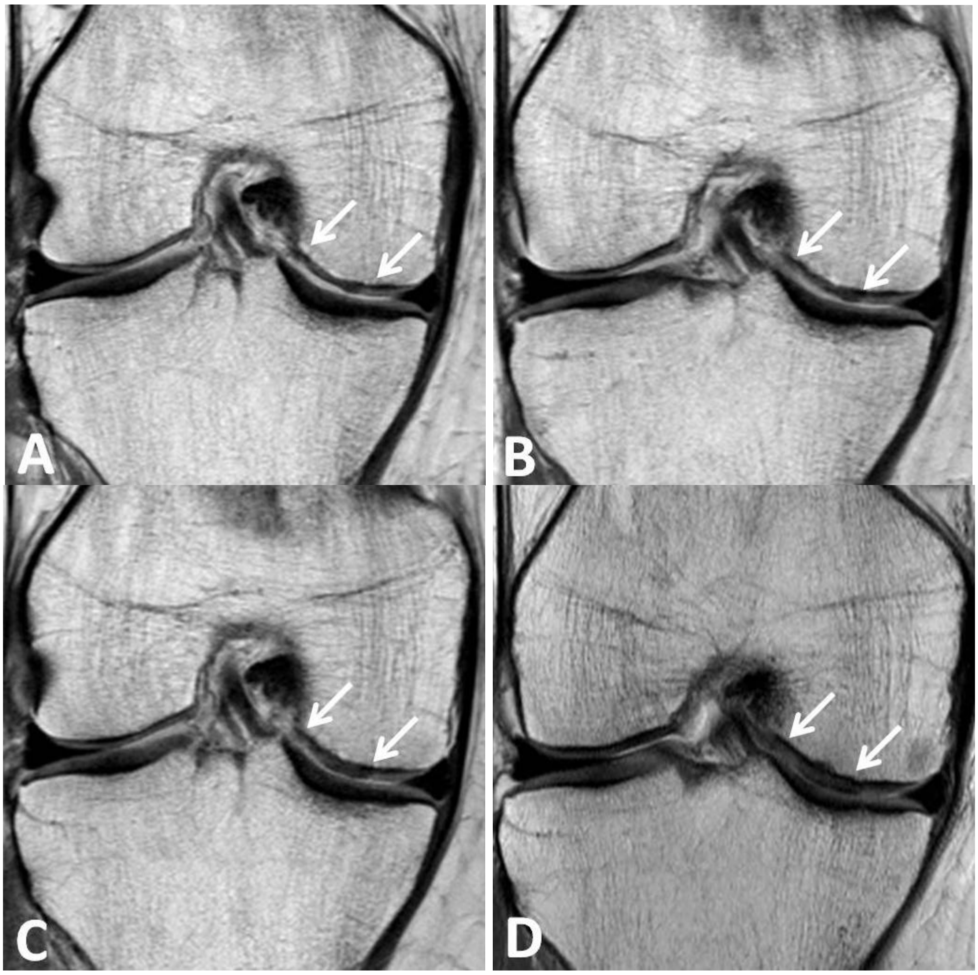


Figure 2. Proton density fast spin echo magnetic resonance images of a MACI graft (between white arrows) to the medial femoral condyle of the same patient at: A) 3 months post-surgery, B) 1 year post-surgery, C) 2 years post-surgery and D) 5 years post-surgery.

Complications and Failures

No early post-operative complications were observed, such as wound infections, hematomas or deep vein thrombosis (DVT). In total, three (10%) patients demonstrated a hypertrophic graft at 3 months post-surgery, of which two remained hypertrophic out to 5 years. A further five patients (16%) had reduced or full tissue infill at 3 months (compared to the native cartilage), though had become hypertrophic on MRI at 12 months. In total, seven patients (23%) exhibited hypertrophic grafts on MRI at 5 years, of which none were associated with pain or mechanical symptoms. The distribution of these was: medial femoral condyle (n=5), lateral femoral condyle (n=1) and lateral tibial plateau (n=1). One graft failure was previously reported and evident in a compliant, 29 year old male, with a pre-operative BMI of 26.0 and no pre-existing conditions that would warrant surgical exclusion.[10] This patient had also failed MACI performed via an open arthrotomy to the same defect location six years prior to this surgery. In addition, one further failure was observed at 5 years post-surgery, in a patient that demonstrated good tissue infill at earlier post-operative time points (Figure 3).

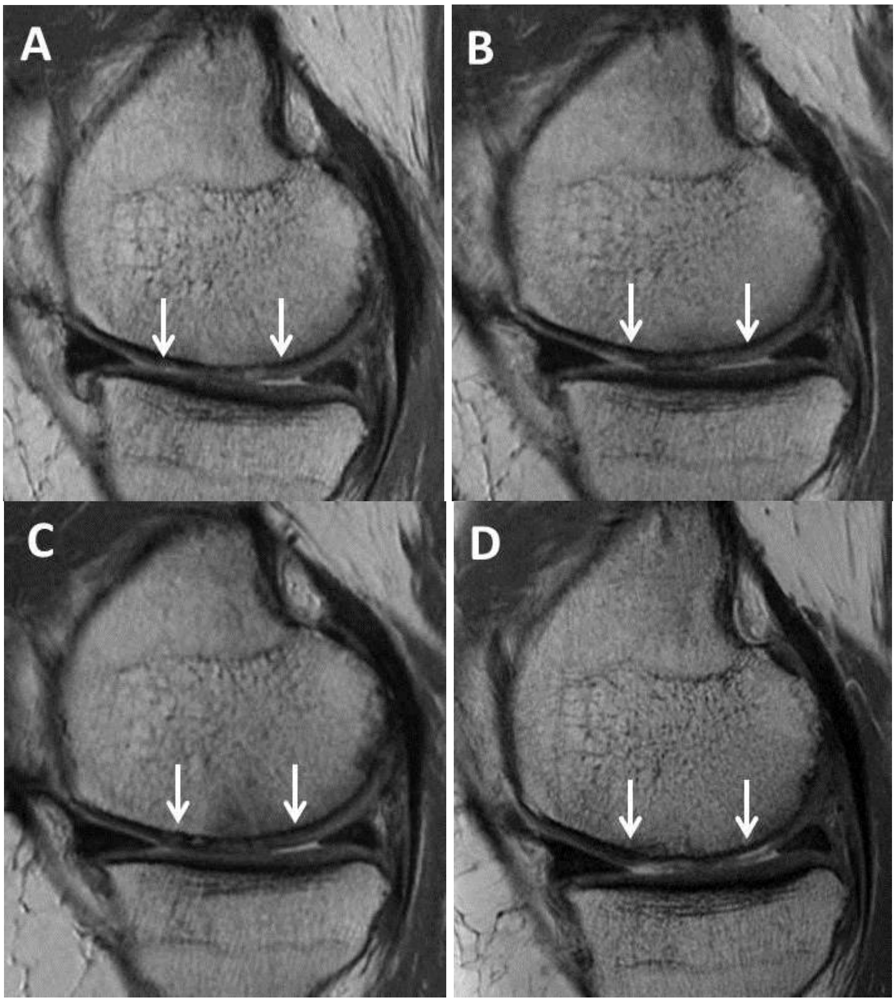


Figure 3. Proton density fast spin echo magnetic resonance images of a MACI graft on the medial femoral condyle, demonstrating D) graft failure at 5 years, despite encouraging progress at A) 3 months, B) 1 year and C) 2 years post-surgery.

DISCUSSION

Whilst encouraging clinical outcomes have been reported for MACI,[5, 13, 20, 21, 30, 43, 55] the open arthrotomy traditionally required for the second-stage implantation presents a range of associated potential complications such as arthrofibrosis, decreased ROM, pain and scarring. Therefore, a number of arthroscopic techniques have now been proposed.[7, 9, 17-19, 27, 30-32, 36, 37, 48, 52] We hypothesized that a significant improvement in clinical and radiological outcomes would be observed to 5 years following arthroscopically performed MACI. In this study, significant and sustained improvement was observed in patient reported outcome and functional measures, as well as MRI-based morphological graft scores, along with high levels of patient reported satisfaction.

We observed significant post-operative improvement in the majority of clinical measures employed, including all KOOS subscales, the LKS, the TAS, the SF-36 PCS, reported knee pain frequency and severity, active knee flexion and extension, and six-minute walk distance. Apart from the KOOS sport domain and the six minute walk test which fell between pre-operative and 3 month post-operative evaluation, largely due to the physical limitations imposed on patients in this early post-operative period,[25, 51] all scores appeared better as early as 3 months and continued to improve throughout the post-operative time line. While the specific use of our chosen patient-reported outcome tools could not be located in existing 5 year reports using arthroscopic MACI implantation, it would appear these outcomes are comparable to MACI performed through an open arthrotomy at 5 years.[11, 13] Furthermore, the objective measures (knee ROM and six minute walk distance) are at least comparable, if not better, then these prior publications.[11, 13]

We observed no significant differences between the operated and non-operated limbs in maximal isokinetic knee strength (extension or flexion) throughout the post-operative time line. Prior research investigating isokinetic knee strength after MACI performed via open arthrotomy demonstrated significant peak knee extensor torque deficit on the operated limb at all pre- and post-operative time points to 5 years.[14] It may be that arthroscopic MACI permits a more accelerated rehabilitation process with reduced soft tissue trauma and pain, muscular inhibition and associated maintenance of strength. Post-operatively, restoration of lower limb muscle function including isokinetic knee strength is considered important for a successful return to physical activity.[1, 2, 28, 35, 57] While several LSI cut-offs have been reported in evaluating strength and functional performance with respect to ACL reconstruction,[3] both < 90%[29, 49, 57] and < 85%[40, 44] have been regarded as unsatisfactory, abnormal and may suggest that an individual is unsafe to return to regular sports activity. In this study, apart from the peak knee extension LSI at 1 year post-surgery (88%), all other knee extensor and flexor LSIs at the remaining time points were above 90%.

Overall, the significant clinical and functional improvement throughout the post-operative time line correlated with the high level of satisfaction reported by patients in this study. At 5 years post-surgery, 93% of patients were satisfied with the ability of MACI to relieve their knee pain and 90% with the improvement in their ability to undertake daily activities. Furthermore, while specific sports were not explored, the significant post-operative improvement in the TAS as well as the sport and recreation subscale of the KOOS, likely contributed to 80% of patients reporting satisfaction with the improvement in their ability to participate in sport.

The MRI composite score and graft infill significantly improved over time, with 5 year scores at least comparable to prior research employing an identical scoring tool in patients 5 years after MACI performed via open arthrotomy.[11, 13] On MRI, it was evident that tissue infill continued through to 2 years post-surgery, maintained to 5 years. While individual parameters of signal intensity, tissue structure, subchondral bone and effusion appeared to improve to 5 years, border integration, surface contour and subchondral lamina, and the combined MRI composite score, all improved to 2 years before a mild decline to 5 years post-surgery. While this was not significant, it may well have been created by a graft failure reflected on MRI at 5 years, in patient who demonstrated good tissue infill at 3 months, 1 and 2 years post-surgery.

At 5 years, 87% of grafts demonstrated good-excellent tissue infill in comparison to the native cartilage, with 80% demonstrating either complete tissue infill or graft hypertrophy. The MRI composite score was also rated good-excellent in 80% of cases at 5 years. Prior research presenting the incidence of complete tissue infill at 2-5 years after MACI is varied, ranging from 40-92% of cases.[11, 13, 20, 30, 61] We observed seven patients (23%) with graft hypertrophy on MRI at 5 years post-surgery, predominantly on the medial femoral condyle. While this remains slightly higher than some reported literature at 5 years after MACI including 12%[13] and 13%,[20] 20-24%[11] has also been reported at 5 years, with one study also reporting graft hypertrophy in 25% of cases at 3 year follow up.[55] Nevertheless, it should be noted that none of the seven cases in this study with hypertrophy on MRI at 5 years were symptomatic.

We observed seven cases of asymptomatic graft hypertrophy at 5 years post-surgery, though documented two graft failures in this cohort at (or before) 5 years post-surgery. One of these had been previously reported in a compliant 29 year old male, with a pre-operative BMI of 26.0 and who had previously failed MACI performed with an open arthrotomy six years prior.[10] Despite encouraging tissue repair at 3 months, 1 and 2 years post-surgery, a second failure developed as defined on MRI at 5 years. We were unable to ascertain any reason for this failed case. While it has been reported that graft de-lamination generally presents within the first 6 months,[41] these failures were documented on MRI at 1 year and 5 years for the first and second case, respectively. Prior 5 year follow up studies after MACI have reported failure rates of 3%,[13] 5%[30] and 9%,[11] with a 2-7 year follow up also documenting 7%.[43]

While 5 year clinical and MRI-based scores in this study appear comparable (or better) than those reported for MACI previously,[11, 13, 20, 30, 43, 61] other cartilage repair methods may provide suitable treatment methods. Firstly, a recent review by Goyal et al.[22] reported that evidence was lacking showing any superiority of MACI over first (periosteal-covered) and second (collagen-covered) generation chondrocyte implantation techniques.[22] Though they also stated these findings were limited by a short duration of follow up, small and younger patient cohorts, and the evaluation of medium-sized defects.[22] Samsudin et al.[54] reiterated these findings in their review reporting no superiority and a trend towards similar outcomes when comparing ACI generations with other cartilage repair techniques. However, they reported similar limitations in synthesizing the literature, also stating issues such as heterogeneous patient demographics, interventions and outcomes employed.

The role of microfracture in treating cartilage defects was reviewed by Goyal et al.[24] and, while they reported it to be of benefit for small lesions in patients with low post-operative demands at short-term follow-up, failure could be expected beyond five years regardless of lesion size. Oussedik et al.[47] reported the benefit of MACI over microfracture in their review. In this current study, we showed that clinical outcomes, MRI-based graft status and patient satisfaction all remained stable at 5 years, though longer term follow up will continue with time. The benefits of MACI over osteochondral autograft transfer (OAT) techniques remain less clear and, while a recent review demonstrated superiority of OAT over microfracture,[23] of the four studies that were included comparing OAT and periosteal and/or collagen-covered ACI, no difference could be demonstrated. However, there have been no studies comparing MACI with osteochondral grafting methods. Finally, based on the studies included in a recent review comparing marrow stimulation, ACI and OAT techniques,[42] no significant difference in pain and functional improvement could be demonstrated at intermediate-term follow up. Again, sound comparison of techniques remains limited by the lack of long term comparative follow up, and heterogeneity in the clinical and MRI-based outcome measures employed.

We acknowledge some limitations in this study. Firstly, this prospective case series lacks any comparative cohort, though the 31 patients presented reflect the first 31 that were planned for, and subsequently underwent, this arthroscopic MACI technique. Therefore, the non-comparative design was reflective of the pilot nature of such a surgical technique, thereby investigating the safety, efficacy and comparative outcomes to existing published MACI research, before embarking on comparative studies of arthroscopic and mini-open techniques of MACI. Secondly, we acknowledge that due to the non-comparative nature of this pilot study, employing only a single pre-operative patient clinical evaluation, there is always uncertainty in exactly how much of the observed clinical effect is attributable to the treatment, even given the encouraging MRI outcomes and apparent regeneration of tissue.

Thirdly, evolving MRI evaluation methods investigating the biochemical characteristics of the repair tissue are emerging, including dGEMRIC (delayed gadolinium-enhanced MRI of cartilage) and T2 mapping.[33, 58, 59] These may provide more information on the ‘ultra-structure’ of the repair tissue,[8] compared to the morphological graft scoring system we have employed. Finally, we chose to employ patient-reported outcome measures (KOOS, SF-36, VAS) used routinely for chondrocyte implantation,[4, 12, 38, 46, 50] though a specific cartilage repair outcome measure is currently lacking.[26] Furthermore, a number of other clinical scoring tools do exist and have been used in other research, which may make the comparison of outcomes amongst these studies difficult.

It has been stated that an arthroscopic implantation technique may minimize adhesions, pain and scarring, as well as improve active knee ROM, whilst accelerating post-operative rehabilitation due to reduced pain and muscular deficits.[18] However, while the advantage of an arthroscopic over an open surgical technique has been demonstrated for other knee procedures,[34, 45] a comparison of arthroscopic and min-open surgical techniques with MACI is yet to be undertaken. Edwards et al.[16] demonstrated improved active knee ROM and strength, as well as a reduced hospital stay and less post-operative complications, in a retrospective study comparing open and arthroscopically performed MACI. Certainly, our study reported no post-operative complications that may be observed more commonly in more invasive techniques such as wound infections, hematomas or DVT. However, despite the perceived benefits of arthroscopic surgery, no further research exists specifically evaluating the aforementioned variables following MACI performed via an open or arthroscopic method.

This arthroscopically performed MACI technique demonstrated good clinical and radiological outcomes to 5 years, with high levels of patient satisfaction. This current research would support prior published work suggesting MACI does provide a suitable mid-term treatment option for articular cartilage defects in the knee. Long-term follow-up of these patients will continue to confirm the durability of repair tissue and longevity of improved patient clinical outcome and quality of life, while future research should look to compare different techniques (arthroscopic and open) to investigate whether less invasive methods reduce the morbidity of arthrotomy and permit accelerated rehabilitation.

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