Prospective clinical study of autologous chondrocyte implantation and correlation with MRI at three and 12 months

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In order to determine the usefulness of MRI in assessing autologous chondrocyte implantation (ACI) the first 57 patients (81 chondral lesions) with a 12-month review were evaluated clinically and with specialised MRI at three and 12 months.

Improvement 12 months after operation was found subjectively (37.6 to 51.9) and in knee function levels (from 85% International Cartilage Repair Society (ICRS) III/IV to 61% I/II). The International Knee Documentation Committee (IKDC) scores showed an initial deterioration at three months (56% IKDC A/B) but marked improvement at 12 months (88% A/B).

The MRI at three months showed 82% of patients with at least 50% defect fill, 59% with a normal or nearly normal signal at repair sites, 71% with a mild or no effusion and 80% with a mild or no underlying bone-marrow oedema. These improved at 12 months to 93%, 93%, 94% and 91%, respectively.

The overall MR score at 12 months suggested production of normal or nearly normal cartilage in 82%, corresponding to a subjective improvement in 81% of patients and 88% IKDC A/B scores. Second-look surgery and biopsies in 15 patients (22 lesions) showed a moderate correlation of MRI with visual scoring; 70% of biopsies showed hyaline and hyaline-like cartilage. Thus, MRI at 12 months is a reasonable non-invasive means of assessment of ACI.

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Autologous chondrocyte implantation (ACI) has emerged as a viable treatment option for chondral defects in the knee. The short-term clinical results are reported to be good or excellent in 71% to 90% of cases[1-4] and rates of patient satisfaction with improved function and pain levels range from 72% to 100%.[5-10] The long-term durability of the clinical outcome has recently been shown by Peterson et al,[11] who reported good or excellent results in 84% of 61 patients with a follow-up of up to 11 years. These superior results are attributed to the capacity of ACI to produce hyaline articular cartilage. Confirmation of the production of normal hyaline articular cartilage can only be definitely assessed by second-look surgery and biopsy of the repair. Therefore a non-invasive method of assessment of graft survival and cartilage maturation after ACI would be useful for following up ACI-treated lesions, both for predicting outcome and directing post-operative rehabilitation. MRI appears to be the most likely procedure of choice. The high accuracy of MRI for assessment of the morphology of articular cartilage in the knee has been reported,[12-17] but there is little information about the correlation of this imaging morphology with the biochemical, biomechanical, histological or clinical findings after ACI. In this prospective study we aimed to determine the usefulness of MRI in assessing the repair tissue after ACI and to correlate the MRI findings with the clinical outcome.

Material and Methods

Since October 2001, patients with focal chondral defects (grade 3 or 4 by modified Outerbridge scoring)[18] of the knee who fulfilled the standard indications have been treated by ACI by the senior author (IH). The process involves two procedures, and is a modification of that described by Peterson et al.[2] At the initial arthroscopy, cells were harvested from the intercondylar notch, or the margin of the lesion, since we had previously demonstrated that debrided tissue from the lesion contains culture-viable cells.[19] The volume of the lesion was estimated to determine the appropriate cell density during culture. During the cell implantation, the volume of the lesion was measured. The cells, which were originally delivered in 1 ml of media as a centrifuged pellet, were resuspended in a volume of medium equivalent to the volume of the lesion. The

rehabilitation protocol consisted of continuous passive motion which started 24 hours post-operatively, static quadriceps exercises and prone knee curls. For condylar lesions, patients were allowed toe-touch-weight-bearing for the first six weeks in an extension splint, then progressive weight-bearing in a varus/valgus unloading brace. The brace was discarded after three months. For patellofemoral lesions, patients were allowed weight-bearing as tolerated in an extension splint; crutches were discarded at three weeks if there was good static quadriceps control. The protective splint was used for 12 weeks.

We have included in this study a consecutive series of the first 57 patients who have been reviewed at 12 months after ACI. A total of 81 lesions was grafted in 58 knees; one patient had both knees treated on separate occasions and there were 30 right and 28 left knees. There were 45 men and 12 women with a mean age of 40.5 years (21 to 64). Only 19 knees had no other surgery apart from the ACI; 38 knees had one or more procedures performed either before or concomitant with the cell-harvest procedure. These other operations included debridement/chondroplasty (17 knees), microfracture (seven), medial (17) and lateral (12) meniscectomy, reconstruction of the ACL (five), high tibial osteotomy (three), release of the lateral retinaculum (two) and surgery on the patellar tendon (three).

In 38 knees, there was a single lesion, 17 had two lesions and three had three lesions. The mean size of the lesion was 3.7 cm^2 (1 to 7). They were located in the medial (34) and lateral (12) femoral condyles, as well as the patella (six) and trochlea (29). Thus, 59% were condylar and 41% patellofemoral defects.

Clinical and MRI evaluation. Our follow-up protocol for ACI follows the International Cartilage Repair Society (ICRS) evaluation for cartilage with objective International Knee Documentation Committee (IKDC) clinical scoring performed by a clinical fellow before and at three and 12 months after operation. All patients completed subjective evaluation and knee functional status forms, before and at one year after operation. MRI was carried out at three and 12 months after operation. All 58 consecutive knees with follow-up at one year had MRI at this time, but for logistical reasons only 56 knees had scans at three months. MRI was carried out using a 1.5 MR unit (Signa LX; General Electric Systems, Milwaukee, Wisconsin) with a send-receive phased-array dedicated knee coil to optimise the signal and image quality. The MR technique included the following sequences:

1) Sagittal T1-weighted imaging (TR/TE 600/12, FOV 16 cm slice thickness 4.0 mm with 0.5 mm gap).

2) Sagittal T1 GE fat-suppressed imaging according to Disler et al.[16,17]

3) Coronal T2 fat-suppressed imaging (TR/TE 4500/80, FOV 14 cm slice thickness 3.5 mm with no gap).

4) Coronal and axial PD (TR/TE 4000/30) imaging. We selected this in order to make the native joint fluid bright, thus providing good differential contrast against the grey chondral and graft surfaces. This technique has previously been shown to be reliable for identifying and grading chondral injuries by Potter et al.[12] We favoured a targeted approach whereby high-resolution images in two planes were performed tangential to the site of the graft: sagittal and transverse for trochlear and patellar lesions, and coronal and sagittal for condylar lesions.

An experienced musculoskeletal radiology consultant (DC) and a senior musculoskeletal imaging fellow (FM) assessed the MR scans for fill, signal, associated bone-marrow oedema of the site of repair and joint effusion. In order to improve data collection and processing, a scale of 1 to 4 was used for these criteria, with 1 indicating the best and 4 the worst result. The fill of the repair site was graded as complete (1), >50% of the defect (2), <50% (3), or a full-thickness defect (4). The signal at the repair site was graded as normal (1, identical to adjacent articular cartilage), nearly normal (2, slight areas of hyperintensity), abnormal (3, larger areas of hyperintensity) or absent (4). Bone-marrow oedema and effusion were both graded as absent (1), mild (2), moderate (3) or severe (4). Additionally, an overall MR score was given, corresponding to the worst score in the four categories. Interobserver agreement was very good (kappa = 0.94) for the MRI ratings of the first 40 patients and subsequent readings were made by the radiology consultant alone. Other noteworthy features relating to the graft, such as graft hypertrophy or fissuring, were recorded.

Second-look surgery and biopsy. Fifteen knees underwent second-look surgery at a mean of 11.3 months (6 to 17) from ACI. The ICRS assessment form for repair of cartilage was used to score the repair sites visually; these were compared with the MR scores at 12 months. In the first seven patients, we were unable to take biopsy specimens for lack of an adequate biopsy instrument. Later, we procured a Giebel needle (Karl Storz, Tuttlingen, Germany) which allowed us to take 2 mm core biopsies which included the subchondral bone, a feature which we felt was essential to a meaningful biopsy. Specimens were fixed with Ruthenium Red/osmium and embedded in Epon-Araldite; 2 μm sections were made and stained with Toluidine Blue.

Statistical analysis. Student's *t*-test (at $p < 0.05$) was used to compare the pre-operative, and 3- and 12-month IKDC scores and also the 3- and 12-month MR scans and the pre-operative and 12-month subjective scores. The Pearson correlation coefficient (r^2) was computed to determine a linear correlation between the IKDC and MR scores, both at three and 12 months.

Results

Subjective evaluation and functional status. There was a significant improvement in the patients' subjective knee rating from a mean of 37.6 points before to 51.9 points at 12 months after operation ($p < 0.001$); 81% of the 58 knees were reported as being subjectively improved by the.

Table I. Details of the clinical scores

Objective IKDC score	Pre-op (%)	At three months (%)*	At 12 months (%)
A (normal)	30 *(51.7)*	7 *(12.1)*	35 *(60.3)*
B (nearly normal)	22 *(37.9)*	25 *(43.1)*	16 *(27.6)*
C (abnormal)	4 *(6.9)*	21 *(36.2)*	6 *(10.4)*
D (severely abnormal)	2 *(3.5)*	5 *(8.6)*	1 *(1.7)*
Subjective evaluation scores			
Mean	37.6	-	51.9
ICRS knee functional status†			
I (I can do everything I want with my joint)	1 *(2.1)*	-	4 *(9)*
II (I can do nearly everything I want to do with my joint)	6 *(12.2)*	-	23 *(52)*
III (I am restricted and many things I want to do with my joint are not possible)	32 *(65.3)*	-	14 *(32)*
IV (I am very restricted and I can do almost nothing with my joint without severe pain and disability)	10 *(20.4)*	-	3 *(7)*

*not scored at this time
†n = 49 for pre-op and n = 44 for post-op; not all patients answered this item in the questionnaires

Table II. Clinical outcome by type of lesion

	Objective IKDC at 12 months				Functional status at 12 months*				Subjective evaluation	
Location of lesion	A	B	C	D	I	II	III	IV	Pre-op	12 months
Single patellofemoral lesion (n = 17)	8	6	3	0	2	7	5	0	36.5	54.3
Single condylar lesion (n = 21)	13	6	2	0	2	5	5	3	33.3	46.5
Multiple lesions (n = 20)	14	4	1	1	0	11	4	0	43.1	55.6

*n = 49 for pre-op and n = 44 for post-op; not all patients answered this item in the questionnaires

Table III. Percentage distribution of MR scores at three and 12 months, by number and *percentage*

	Fill		Signal		Effusion		Bone-marrow oedema		Overall score	
MR score	3 months	12 months	3 months	12 months	3 months	12 months	3 months	12 months	3 months	12 months
1	44 *(56.4)*	64 *(79.0)*	3 *(3.9)*	51 *(63.0)*	19 *(24.4)*	48 *(59.2)*	30 *(38.5)*	48 *(59.2)*	1 *(1.3)*	21 *(26.0)*
2	20 *(25.6)*	11 *(13.6)*	43 *(55.1)*	24 *(29.6)*	36 *(46.2)*	28 *(34.6)*	32 *(41.0)*	26 *(32.2)*	31 *(39.7)*	45 *(55.6)*
3	5 *(6.5)*	2 *(2.5)*	22 *(28.2)*	2 *(2.5)*	21 *(26.9)*	4 *(4.9)*	15 *(19.2)*	7 *(8.6)*	36 *(46.2)*	10 *(12.3)*
4	9 *(11.5)*	4 *(4.9)*	10 *(12.8)*	4 *(4.9)*	2 *(2.5)*	1 *(1.3)*	1 *(1.3)*	0 *(0.0)*	10 *(12.8)*	5 *(6.1)*

patients. Patients were asked to categorise their level of knee function based on the ICRS 4-level scale (Table I). Before operation, 14% classified their knee function as level I or II, 65.3% as level III, and 20% as level IV. At 12 months, there was a significant improvement ($p < 0.001$) with 61% having level-I or level-II knee function, 32% level III, and 7% level IV.

IKDC clinical score. Using the objective IKDC scoring criteria (Table I), 89.6% of knees were classified as A or B before operation, but at three months, only 55.5% were rated A or B, representing a significant early clinical deterioration ($p < 0.001$). However, when comparing the 3- and 12-month scores, there was also a significant clinical recovery, with 87.9% of knees rated A or B ($p < 0.001$). Comparison of the pre-operative and one-year results showed no statistically significant difference ($p < 0.27$). Of the six knees rated as C or D before operation, four remained as C or D at one year, while two improved to A or B. Although no apparent clinical improvement was recorded by the IKDC criteria, all six were reported by the patients to be subjectively improved by a mean of 25 points. When analysed according to location of the lesion, we found no significant difference ($p < 0.05$) in the objective and subjective scores and functional levels between patients with a single patellofemoral lesion, a single condylar lesion, or multiple lesions (Table II).

MRI rating and clinical correlation. MR scans were available for 78 lesions at three months (Table III): 82% of lesions had 50% to 100% fill, 59% had normal or nearly normal signals at the repair site, 71% had mild or no effusion and 80% had mild or no underlying bone-marrow oedema. The overall MR score showed 41% of the lesions to be normal or nearly normal at three months. By 12 months, these scores had improved significantly ($p < 0.05$) such that 92.6% had 50% to 100% fill, 92.6% had normal or nearly normal signals at the repair site, 93.8% had mild to no effusion and 91.4% had mild to no underlying bone-marrow oedema. Overall, the MR score at 12 months showed 81.6% to be normal or nearly normal. The improvement in the MR scores paralleled the improvement in the IKDC scores. However, for each of the four MR criteria and the overall score, no significant correlation was established

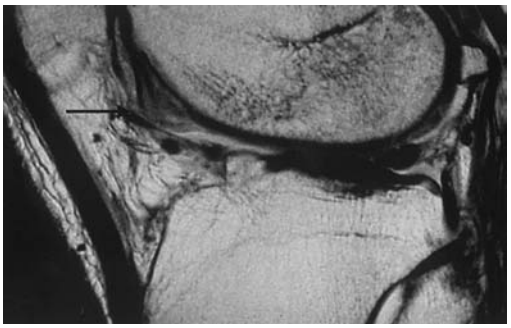

Fig. 1a

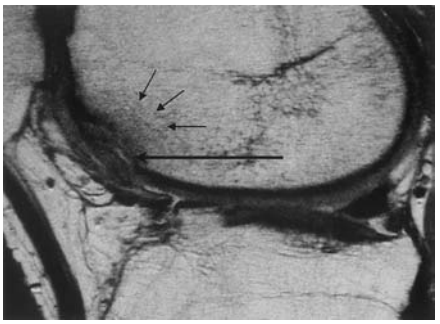

Fig. 1b

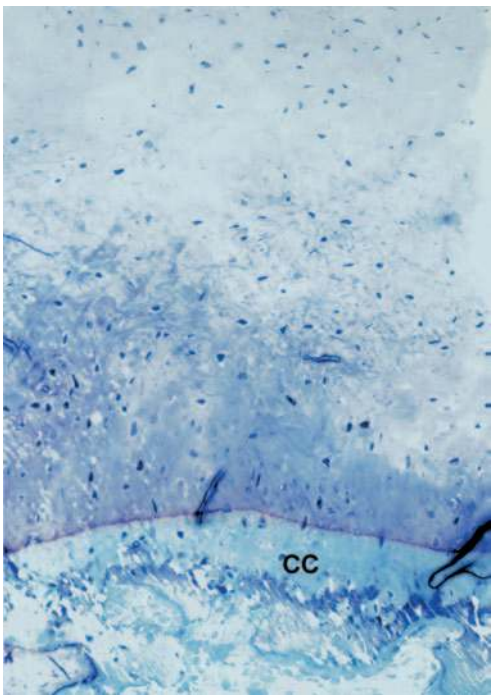

Fig. 1c

Trochlear lesion after ACI. Figure 1a – Sagittal MRI at three months, showing graft hypertrophy with an abnormal signal (arrow). Figure 1b – Sagittal MRI at 12 months showing graft hypertrophy, a normal signal, with mild subchondral bone-marrow oedema (short arrows), and a cleft undermining the graft (long arrow). Figure 1c – Photomicrograph of the appearance of a central core biopsy at 13 months showing fibrocartilage and a layer of calcified cartilage (CC).

with the IKDC clinical score or the subjective score ($r^2 < 0.2$), both at three and 12 months. Of the 46 lesions rated as 3 or 4 (abnormal or severely abnormal) by overall MR score at three months, 89% were still found in IKDC A or B knees at 12 months, and of the 32 lesions rated as 1 or 2 (normal or nearly normal) by the overall MR score, 88% were found in IKDC A or B knees at 12 months.

Notable MRI morphological findings. Additional findings at three months (Figs 1a and 2a) included clefts in the graft (three), displaced grafts (two), a fibrillated graft surface (six), fluid undermining the graft (four), and graft hypertrophy (eight). However, these findings did not seem to affect the results adversely since these lesions were found mainly in IKDC A or B knees at that time, and appeared to have resolved on the 12-month MR scans. At 12 months (Figs 1b and 2b), notable findings included clefts (five), a defect at the margins of the graft (one), surface fissures and/or fraying (three), subcortical cysts (three), and graft hypertrophy (six). Most of these lesions were again found in IKDC A or B knees at 12 months.

Second-look surgery and biopsy. There were 22 lesions assessed at a mean of 11.5 months using the ICRS visual cartilage repair scoring, which evaluates depth of repair, integration to border zone and macroscopic appearance. By visual scoring, 20 lesions were scored as normal, and two as nearly normal (Table IV). On MRI at 12 months, 16 lesions were scored as normal or nearly normal, five as abnormal and one as severely abnormal. The visual scores had a moderate correlation with the overall MR score at 12 months ($r^2 = 0.4$). Core biopsies of 13 grafts showed the presence of hyaline articular cartilage in five and hyaline-like cartilage in four. These specimens had excellent integration into subchondral bone, a definite layer of calcified cartilage and a zonation pattern typical of normal articular cartilage (Fig. 2c). Most specimens showed vestigial elements of the periosteal patch. The deeper zones had a homogenous hya-

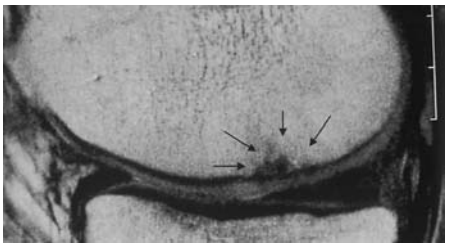

Fig. 2a

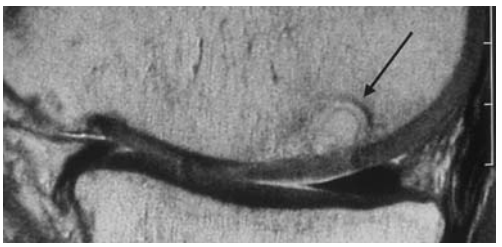

Fig. 2b

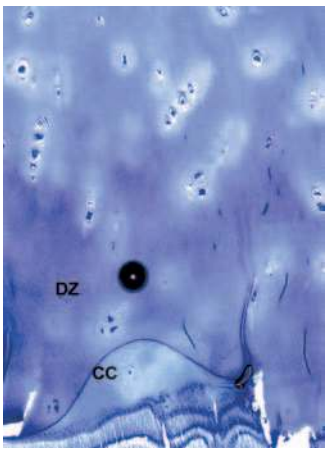

Fig. 2c

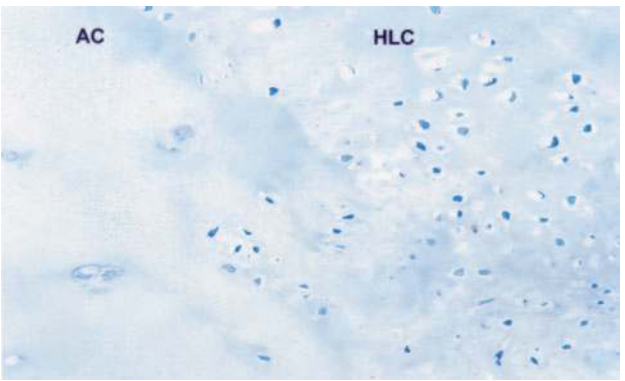

Fig. 2d

Medial femoral condyle lesion after ACI. Figure 2a – Sagittal MRI at three months showing good fill and mild subchondral bone oedema. Figure 2b – Sagittal MRI at 12 months showing good fill. There is a small subcortical cyst (arrow). Figure 2c – Photomicrograph of the appearance of a central core biopsy after ten months, showing hyaline-like cartilage (DZ, deep zone; CC, calcified cartilage zone). Figure 2d – Photomicrograph of the appearance of a marginal core biopsy showing seamless integration of new hyaline-like cartilage (HLC) with adjacent articular cartilage (AC).

Table IV. ICRS visual cartilage repair scores, 12-month MR scores, and core biopsy results

Case	Location of the lesion*	Timing of 2nd-look from ACI (mths)	Overall MR score at 12 months†	ICRS visual repair category†	Objective IKDC score at 12 months	Core biopsy result‡
1	MFC	17	2	2	A	Hyaline-like
2	MFC	10	1	2	A	Fibrohyaline
	Trochlea	10	1	2	A	Fibrohyaline
3	MFC	12	2	2	A	-
	Trochlea	12	2	2	A	-
4	LFC	12	3	2	B	-
	Trochlea	12	3	2	B	Fibrocartilage
5	MFC	9	1	2	B	-
6	MFC	10	3	2	A	Hyaline articular cartilage
7	Trochlea	10	2	2	B	-
8	MFC	16	4	2	B	Hyaline articular cartilage
9	Trochlea	13	2	2	A	Fibrocartilage
	MFC	13	1	1	A	Hyaline-like
	LFC	13	1	1	A	Hyaline articular cartilage
10	MFC	6	2	2	A	-
11	LFC	12	2	2	A	Hyaline articular cartilage
	MFC	12	2	2	A	Hyaline articular cartilage
12	Trochlea	10	3	2	C	-
13	MFC	9	1	2	A	-
14	MFC	10	3	2	A	Hyaline-like
	Trochlea	10	2	2	A	Hyaline-like
15	Trochlea	10	2	2	C	-

*MFC, medial femoral condyle; LFC, lateral femoral condyle
†grade 1, normal; 2, nearly normal; 3, abnormal; 4, severely abnormal
‡(-), indicates no core biopsy

line-like matrix with chondrocytes nested in typical lacunae. The differentiation between hyaline and hyaline-like was based on the greater cell density noted in the latter at the deeper zones; the matrices were similar. Two grafts had fibrocartilaginous superficial and mid-zones, but hyaline-like characteristics in the deeper zones (mixed fibrohyaline), while two grafts showed fibrocartilage. However, these specimens also showed excellent subchondral integration of bone and an intermediate layer of calcified cartilage (Fig. 1c). Moreover, in biopsies taken from the margins of the graft with adjacent normal cartilage, we found a seamless integration of the neocartilage to the adjacent cartilage (Fig. 2d). Second-look surgery did not appear to affect the outcome at 12 months adversely since most of these were IKDC A or B at one year. Of the four fibrohyaline or fibrocartilage grafts, only one had an abnormal MR score.

Discussion

One objective of our study was to report the clinical outcome at one year. We used the IKDC 2000 knee examination form as our clinical outcome tool since it is has been adopted by the ICRS as part of its evaluation of cartilage, although other ACI studies have used other systems as well, such as the Lysholm, modified and overall Cincinnati, Tegner, HSS and Knee Society scores.[2-5,7,8,11]

The results at one year indicate that 88% of the knees were normal or nearly normal, but with no significant difference from pre-operative scores. It would seem that the pre-operative status of our patients, based on an objective IKDC rating, is actually good, with 89.6% being normal or nearly normal. Most of these patients had disabling symptoms pre-operatively as was reflected in their subjective evaluations which assessed pain, limitation of activity and mechanical knee symptoms. They also had considerable functional impairment pre-operatively with 86% being restricted or very restricted. The IKDC objective score is based only on seven domains, of which only three are actually part of the final score, namely, effusion, passive motion deficit, and ligament examination. Perhaps only effusion, however, has a direct contribution from focal cartilage defects; passive motion and ligament examination are probably affected more by co-existing pathology. Hence, although an objective knee examination may not show much difference between before and one year after operation, the value of this procedure to our patients in the short term is best reflected in the considerable improvement in subjective symptoms (81% of knees improved) and in the level of knee function (61% unrestricted or mildly restricted at 12 months). We also noted that of the six knees objectively rated as abnormal or severely abnormal pre-operatively, two had improved to normal or nearly normal at one year. Of the four remaining, two had a loss of flexion of more than 25°; one had anterior translation of less than 6 mm and a pivot-shift clunk and one had a moderate effusion. These pre-operative conditions were not improved at one year although repair of the articular cartilage would not be expected to alter these. It would seem, therefore, that the IKDC objective scoring may not be the most ideal system for repair procedures of articular cartilage.

It has been previously reported that patellar lesions do not fare as well as condylar lesions[20] and, subsequently, attention to correction of patellofemoral maltracking was emphasised[21] as a means of improving outcome. Our clinical results at one year suggest that there is no significant difference in clinical outcome between patellofemoral and condylar lesions. This may be because only two patients in our series had patellofemoral maltracking which required a lateral release.

The other goals of our study were to determine whether MRI could be useful in assessing graft maturation and if some of the MRI parameters correlated with the clinical outcome. We felt that the amount of fill could be a useful parameter, since it reflects growth of repair tissue and is also assessed in arthroscopic second-look examinations. We thought that the signal might be a useful visual indicator of maturity of the graft, especially in comparison with the signal of adjacent normal articular cartilage. Effusion is an important clinical factor which could be readily appreciated in an MR scan, while oedema of the underlying bone marrow is a phenomenon which may reflect the process of graft remodelling and attachment to the subchondral bone. It also indicates abnormal bone loading secondary to an immature cartilage cover and thus can be a source of pain and thereby affect function. There was marked improvement in these parameters between three and 12 months; by one year, more than 90% of lesions had scores which would be considered normal or nearly normal indicating graft maturity with the production of normal hyaline articular cartilage. However, the best way to confirm this is to compare these MRI findings with those at second-look surgery and core biopsies of the lesions. Second-look surgery was performed in 26% of the patients allowing us to make a visual assessment of repair of the cartilage, which generally agreed with the MR score at 12 months with moderate linear correlation. It seems that the MRI was less forgiving in assessing the maturation of cartilage, since there were more abnormal scores compared with the visual scores. Surgeon bias may play a role for the more favourable visual scores. Among the biopsied grafts, three hyaline or hyaline-like grafts had abnormal MR scores, while only one fibrocartilage graft had an abnormal score. Although the number of grafts with second-look examination and biopsies are relatively small, the trend suggests that MRI may be as accurate as arthroscopic visual scoring and biopsy in determining graft maturation into hyaline articular cartilage. We acknowledge that image interpretation requires experience. A musculoskeletal radiologist working closely with a surgeon who provides feedback is fundamental to this learning process. MRI is an evolving technology which will improve as new software and techniques become available.

With regard to clinical outcome, none of these MRI parameters, individually or as an overall score, showed any

strong linear correlation with the subjective or objective IKDC scores. The three-month MR scan does not seem to be very useful clinically, since it does not correlate with the clinical score and regardless of the MR score at three months, 88% are still found in IKDC normal or nearly normal knees at one year. The overall MR score at 12 months suggests that 81.6% of lesions have normal or nearly normal cartilage at the site of repair, and this corresponds to the rate of subjective improvement of 81% at one year and 88% objectively normal or nearly normal knees at one year. However, there was no linear correlation between the MRI criteria and the objective knee scores. Of the 13 core biopsies obtained, nine (70%) were hyaline or hyaline-like while two (15%) were mixed fibrohyaline cartilage and two (15%) were definite fibrocartilage. This distribution appears to follow the trend for the clinical results; interestingly, the objective clinical knee scores for all these were normal or nearly normal, including the fibrocartilage grafts. It is known that fibrocartilage is not as durable as normal hyaline cartilage and it would be helpful to see the clinical outcomes on longer term follow-up. Also, it would be interesting to correlate the MRI at 12 months with the clinical outcome at a longer follow-up, and to determine if it would have prognostic value. Lastly, it seems that none of the other morphological findings described on MRI, such as graft hypertrophy, clefts, or fissuring, seems to affect the clinical outcome at one year.

We have only used ACI for the past two years. This study therefore is a short-term follow-up which may help to guide expectations of both the patient and clinician. We recommend 12-month MRI to be a reasonable non-invasive means of assessing maturation of the graft after ACI. Longer term follow-up will ultimately determine its value for prognostication.

One or more of the authors have received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this article.

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