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Longitudinal analysis of $T_{1\rho}$ and T_2 quantitative MRI of knee cartilage laminar organization following microfracture surgery

Alexander A. Theologis^{a,b,c}, William W. Schairer^{a,b}, Julio Carballido-Gamio^b, Sharmila Majumdar^b, Xiaojuan Li^b, and C. Benjamin Ma^{c,*}

^aSchool of Medicine, University of California, San Francisco (UCSF), San Francisco, CA, USA

^bMusculoskeletal Quantitative Imaging Research, Department of Radiology, UCSF, San Francisco, CA, USA

^cDepartment of Orthopaedic Surgery, UCSF, San Francisco, CA, USA

Abstract

Objective—To quantitate longitudinally the radiographic properties of different layers of repaired tissue following microfracture (MFx) surgery using $T_{1\rho}$ and T_2 magnetic resonance imaging (MRI).

Design—10 patients underwent MFx surgery to treat symptomatic focal cartilage defects (FCD). Sagittal three-dimensional (3D) water excitation high-spatial resolution (HR) spoiled gradient recalled (SPGR) for quantitative $T_{1\rho}$ and T_2 mapping were acquired for each patient 3–6 months and 1 year after surgery. Cartilage compartments were segmented on HR-SPGR images, and $T_{1\rho}$ and T_2 maps were registered to the HR-SPGR images. $T_{1\rho}$ and T_2 values for the full thickness of deep and superficial layers of repaired tissue (RT) and normal cartilage (NC) were calculated, and compared within and between respective time points. A p-value <0.05 is considered statistically significant.

Results—The majority of FCD were found in the MFC. The average surface area of the lesions did not differ significantly overtime. At 3–6 months, RT had significantly higher full thickness $T_{1\rho}$ and T_2 values relative to NC. At 1 year, this significant difference was only observed for $T_{1\rho}$ values. At 3–6 months follow-up, the RT's superficial layer had significantly higher $T_{1\rho}$ and T_2 values than the deep layer of the RT and the superficial layer of NC. At 12 months, the superficial layer of the RT had significantly higher $T_{1\rho}$ values than the RT's deep layer and the NC's superficial layer.

Conclusion— $T_{1\rho}$ and T_2 MRI are feasible methods for quantitatively and noninvasively monitoring the maturation of repaired tissue following microfracture surgery over time.

Keywords

Microfracture; $T_{1\rho}$; T_2 ; Quantitative MRI; Focal cartilage defects

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*Corresponding author at: University of California, San Francisco School of Medicine, Department of Orthopaedic Surgery, Mission Bay Ortho Institute, 1500 Owens Street, San Francisco, CA 94158. Tel.: +1 415 353 2808; fax: +1 415 885 9643. maben@orthosurg.ucsf.edu (C.B. Ma).

Conflict of interest statement

None of the authors have financial or any other interests relating to the manuscript.

1. Introduction

Knee injuries are extremely common and are often seen in otherwise healthy, active patients. The traumatic force on the knee often results in focal cartilage defects (FCDs) of the weight-bearing articular surfaces. These focal injuries are accompanied by swelling, pain, and instability of the joint, and can alter the mechanics and loading of the joint, which increases a patient's risk of developing osteoarthritis [1]. There are several surgical procedures for the repair of FCDs, most common of which is the microfracture (MFX) procedure. MFX is performed by inducing multiple subchondral channels into the subchondral bone, which induces bleeding and subsequent clot formation within the FCD. The formed clot houses pluripotent mesenchymal progenitor cells from the intramedullary cavity, which subsequently differentiate and generate a new articular surface [2]. The ideal goal of all cartilage resurfacing procedures, including MFX, is to produce a tissue that provides morphologic and mechanical properties similar to those of native cartilage [3]. However, in clinical practice, a fibrocartilaginous tissue is often produced following MFX, which is prone to degeneration over time and often limits a patient's functional capacity and quality of life [4–7]. Thus, it is critical to have a sensitive, specific, and safe modality that is efficiently capable of evaluating longitudinally the integrity of the fibrocartilage tissue after MFX surgery.

The current gold standard for evaluation of regenerated tissue (RT) following MFX is second-look arthroscopy with or without concomitant cartilage biopsy [8–10]. Second-look arthroscopy has several advantages, as it allows for direct visualization of the repaired tissue's surface and indentation measurements allow for assessment of the RT's mechanical integrity [11]. Arthroscopic biopsies, however, are invasive procedures associated with significant surgical morbidity, making routine use impractical and uncommon. In contrast, magnetic resonance imaging (MRI) is a noninvasive method for visualization and evaluation of articular cartilage in the knee [11–18]. Several studies have used T_2 MRI to characterize the biochemical and morphologic properties of normal cartilage (NC) and RT following cartilage repair procedures because it is sensitive to the concentration, orientation, and integrity of collagen, as well as the water content in articular cartilage [11–22]. A newer sequence that has been shown to complement T_2 MRI in evaluation of articular cartilage's macromolecular properties is $T_{1\rho}$ mapping [19, 23–27]. $T_{1\rho}$ probes the interactions between water molecules and the cartilage extracellular matrix, specifically proteoglycans [22–27]. Thus, an increased $T_{1\rho}$ value in repaired tissue relative to normal cartilage indicates a graft with a relatively underdeveloped extracellular matrix. While quantitative T_2 MRI has been used to analyze the three different physiologic layers of repaired tissue cartilage (tangential, intermediate, and radiate) following MFX surgery [11, 13–18, 28], $T_{1\rho}$ has never been used in this capacity.

Thus, in this nonrandomized prospective cross sectional study we use $T_{1\rho}$ and T_2 MRI to assess longitudinally the radiographic properties of the deep and superficial layers of repaired tissue following microfracture (MFX) surgery. We hypothesize that over time the repaired tissue produced by MFX will have radiographic properties suggestive of an immature extracellular matrix.

2. Method

2.1. Subjects

Patients were included in the study if they had a full thickness osteochondral defect in any compartment of the knee detected on knee arthroscopy. Ten patients (five women, five men; mean age: 37.4 ± 9.9 years; age range 24–54 years) underwent microfracture surgery for treatment of full thickness cartilage defects in the knee. The decision to proceed with

microfracture surgery was made by the surgeon at the time of surgery. Among other factors, this decision was affected by lesion size. All procedures were performed by a single surgeon. All procedures were approved by the Committee on Human Research at our institution and informed consent was obtained from each patient. Patients were excluded from the study if they had a history of osteoarthritis or inflammatory arthritis, previous surgery on the affected knee, and repeated injuries to the knee during the follow-up period. In addition, patients who required surgical intervention for other injuries, including meniscal, collateral ligament, and posterior cruciate ligament tears, were excluded from the study.

MRI scans were obtained at two timepoints: (1) 3–6 months, the time at which patients are transitioned from non-weightbearing to weightbearing status, and (2) 1 year, the time at which patients return to pre-injury level of activity. Data were nonrandomized, gathered prospectively, and analyzed cross-sectionally.

2.2. Magnetic Resonance Imaging

Patients were scanned with a 3 T General Electric MR scanner (General Electric Healthcare, Milwaukee, WI, USA) using an 8-channel quadrature transmit/8-channel phased array receive knee coil (General Electric Healthcare, Milwaukee, WI). Each patient was scanned at 3 to 6 months, and again at 1 year post-operatively to facilitate longitudinal assessment of the repaired tissue. Each patient received a sagittal 3D water excitation high-resolution spoiled gradient-echo (HR-SPGR) sequence, and a 3D quantitative $T_{1\rho}$ and T_2 sequence. Parallel imaging with array spatial sensitivity technique (ASSET) was performed on all sequences with an acceleration factor of 2.

The imaging parameters for SPGR images were: TR/TE=15/6.7 ms, flip angle=12°, field of view (FOV)=14 cm, matrix size=512×512, slice thickness=1 mm, receiver bandwidth (RBW)=31.25 kHz, number of excitations=1. The sagittal 3D $T_{1\rho}$ -weighted images were acquired using spin-lock techniques and 3D SPGR acquisition as previously developed [29]. The duration of the spin-lock pulse was defined as time of spin-lock (TSL), and the strength of the spin-lock pulse was defined as spin-lock frequency (FSL). The number of a pulses after each $T_{1\rho}$ magnetization preparation was defined as views per segment (VPS). There was a relatively long delay (time of recovery, Trec) between each magnetization preparation to allow enough and equal recovery of the magnetization before each $T_{1\rho}$ preparation. The imaging parameters for the $T_{1\rho}$ -weighted images were: TR/TE=9.3/3.7 msec; FOV=14 cm, matrix size=256×192, slice thickness=3 mm, bandwidth (BW)=31.25 kHz, VPS=48, Trec=1.5 s, TSL=0, 10, 40, 80 msec, FSL=500 Hz. Lastly, sagittal 3D quantitative T_2 mapping was acquired by adding a nonselective T_2 preparation imaging sequence [30, 31] to the same SPGR sequence as for $T_{1\rho}$ mapping. Imaging parameters of the T_2 sequence were the same as $T_{1\rho}$ except for: TE=4.1, 14.5, 25, 45.9 ms. All sequences and imaging parameters utilized in this study have been previously validated in phantoms and in vivo [30]. The total scan time was ~20 min for $T_{1\rho}$ and T_2 mapping. $T_{1\rho}$ and T_2 mapping were assessed in all subjects.

2.3. Cartilage processing and $T_{1\rho}$ and T_2 mapping

Following MR image acquisition, images were processed off-line on a Sun Workstation (Sun Microsystems, Mountain View, CA, USA). Regenerated tissue (RT) and the healthy surrounding cartilage (NC) were identified on the HR-SPGR image, as this sequence has the best resolution for anatomic identification. Cartilage identification was assessed independently by an observer and the surgeon who performed the operation, and was confirmed with surgical images and notes. Following the identification of the RT, the respective cartilage compartment and contours around the cartilage regions of interest (ROI)

were made on the HR-SPGR and were segmented semi-automatically using in-house software developed with MATLAB (Mathworks, Natick, MA, USA) (Fig. 1A,B) [32].

After segmentation, a perpendicular line to the articular cartilage surface and subchondral bone surface was generated automatically in the RT and NC. $T_{1\rho}$ and T_2 maps were subsequently reconstructed using a Levenberg–Marquardt monoexponential inhouse-developed fitting algorithm. $T_{1\rho}$ - and T_2 -weighted image intensities obtained for different TSLs and TEs were fitted pixel-by-pixel to the following equations, respectively:

$$S(\text{TSL}) \propto \exp(-\text{TSL}/T_{1\rho})$$

$$S(\text{TE}) \propto \exp(-\text{TE}/T_2)$$

The reconstructed $T_{1\rho}$ and T_2 maps were rigidly registered to the previously acquired high-resolution $T_{1\rho}$ and T_2 -weighted SPGR images using the VTK CISG Registration Toolkit [33]. The first TSL image and first TE image were used to compute the transformation for $T_{1\rho}$ and T_2 maps, respectively. 3D regions of interest for RT and NC were overlaid on the registered $T_{1\rho}$ and T_2 maps (Fig. 1C).

2.4. Determination of laminar $T_{1\rho}$ and T_2 values

The $T_{1\rho}$ and T_2 values for the deep and superficial layers of RT and NC for each region were calculated using an in-house developed laminar analysis program developed with Matlab [34]. Briefly, for each point in the bone–cartilage interface (cAB) of the cartilage segmentations, a vector normal to the cAB and ending at the articular surface was computed. All the normal vectors were then sampled at equally spaced 20 points using bicubic interpolation. The mean $T_{1\rho}$ and T_2 values from point 1–10 and 11–20 were then calculated as $T_{1\rho}$ and T_2 for deep and superficial layers, respectively (Fig. 1D).

2.5. Data analysis

$T_{1\rho}$ and T_2 values of the full thickness of RT were compared to respective full thickness values in NC in the same treatment group within and between time points. Deep and superficial $T_{1\rho}$ and T_2 values of RT were compared to corresponding laminar values in NC in the same treatment group within and between time points. A paired Student's *t*-test was used for statistical analysis. A *p*-value <0.05 was considered statistically significant.

3. Results

3.1. Focal cartilage defect characteristics

The majority of patients undergoing microfracture surgery had focal cartilage defects in the medial femoral condyle (*n*=6/10; Table 1). Two patients were treated for FCD in the trochlea and the other two patients were treated for lateral femoral condyle lesions (Table 1). The average surface area for the lesions at 3–6 months is 2.93 cm [2] (1.02–5.63 cm [2]) and at 12 months is 2.88 cm [2] (1.02–5.28 cm [2]) (Table 1). No statistical difference was found between the surface areas at both timepoints (Table 1).

3.2. Full thickness

No significant differences in the full thickness $T_{1\rho}$ and T_2 values were found between the normal cartilage over time. However, at 3–6 months and 1-year follow-up, the repaired tissue was found to have significantly higher $T_{1\rho}$ values than those of the normal surrounding cartilage (Fig. 2A). The repaired tissue was also found to have higher T_2 values at both timepoints, although the difference was significant only at 3–6 months follow-up (Fig. 2B).

3.3. Laminar analysis

For the normal cartilage, the $T_{1\rho}$ and T_2 values of the superficial layer were significantly higher than the values of the deep layer at each follow-up time point (Fig. 3A, B). Also, the $T_{1\rho}$ and T_2 values of the normal cartilage's deep and superficial layers were not significantly different than respective layers between each time point (Fig. 3A,B). At 3–6 months follow-up, $T_{1\rho}$ values for the deep and superficial layers of the repaired tissue were significantly higher than the values for the respective layers of the normal cartilage (Figs. 3A and 4). Also at 3–6 months follow-up, T_2 values for the deep and superficial layers of the repaired tissue were significantly higher than the values for the respective layers of the normal cartilage (Fig. 3B). At 1-year follow-up, while the $T_{1\rho}$ values of the repaired tissue's superficial layer were significantly greater than the $T_{1\rho}$ values of the normal cartilage's superficial layer (Fig. 3A), there was no difference in the T_2 values of the repaired tissue's superficial layer and those of the normal cartilage's superficial layer (Fig. 3B). The deep layers of the repaired tissue and normal cartilage had similar $T_{1\rho}$ and T_2 values at 1-year follow-up (Fig. 3A,B). While there were no significant differences between T_2 values for the deep and superficial layers of repaired tissue over time (Fig. 3B), the $T_{1\rho}$ values for the deep layers of the repaired tissue at 1 year were significantly lower than the $T_{1\rho}$ values for the deep layers of the repaired tissue at 3-months (Fig. 3A).

On an individual basis, nine out of the 10 patients were found to have a 12.4% decrease in their repaired tissues deep layer's $T_{1\rho}$ signal over time, and seven out of the 10 patients had a 13.0% decrease in their repaired tissues superficial layer's $T_{1\rho}$ signal over time (data not shown). In regard to T_2 values, eight out of the 10 patients had a 15.3% decrease in their repaired tissues deep layer's T_2 signal over time, and seven out of the 10 patients had a 22.9% decrease in their repaired tissues superficial layer's $T_{1\rho}$ signal over time (data not shown).

4. Discussion

The ideal cartilage resurfacing procedure would produce a repair tissue that over time develops an extracellular matrix with a similar proteoglycan and collagen shape, concentration, and zonal organization to that of normal hyaline cartilage. Microfracture (MFx) surgery is one of many arthroscopic cartilage resurfacing procedures used to treat focal cartilage defects (FCD) of the knee, and it commonly produces a fibrocartilaginous repair tissue (RT). As fibrocartilage lacks the structural properties of hyaline cartilage, including resistance to compressive and shear strains, MFx RT is prone to degeneration over time and regular evaluation of its integrity is paramount. The current “gold standard” for evaluation of RT following MFx is second-look arthroscopy with concomitant cartilage biopsy [8–10]. Because this approach is invasive and associated with significant surgical morbidity, noninvasive quantitative MRI is a popular modality that is commonly used to and capable of evaluating RT after MFx. The majority of work in this arena has focused on T_2 mapping to characterize the biochemical and morphologic properties of RT [11–22]. More recently, our group showed that $T_{1\rho}$ is an accurate and reproducible method for monitoring regeneration of RT following MFx [28]. To our knowledge, no study has evaluated the radiographic properties of different zones of RT following MFx using $T_{1\rho}$. Thus, we have addressed this question in this nonrandomized, prospective, cross sectional study.

Normal cartilage in this study served as an internal control, as the RT of each patient was compared to their own NC. It is important to note that normal articular hyaline cartilage contains three different zones, radial (deepest), transitional (middle), and radiate (superficial), which are defined by the orientation of the collagen fiber matrix. Due to this zonal variation, normal articular hyaline cartilage has a consistent, reproducible increase in quantitative $T_{1\rho}$ and T_2 values from the deepest to most superficial layers. Consistent with

this observation, we found that our patients' regions of normal cartilage all had significantly higher $T_{1\rho}$ and T_2 values in the superficial layer compared to the deep layer at both follow-up time points.

Consistent with the notion that surgically produced RT in the early stage has an immature and disorganized arrangement of collagen fibrils and proteoglycans, we found that at 3–6 months after MFX surgery, the average $T_{1\rho}$ and T_2 values of the full thickness RT were significantly higher than normal cartilage. Our laminar analysis of the RT at this early follow-up time point suggests that the immaturity of the extracellular matrix observed in the full thickness graft is due to immaturity of both the deep and superficial layers, as both the deep and superficial layers of the RT were found to have significantly higher $T_{1\rho}$ and T_2 values compared to the deep and superficial layers of the normal cartilage, respectively. Over time, however, the graft's radiographic characteristics significantly change.

We observed that $T_{1\rho}$ values in the deep layers of RT decrease significantly from the 3–6 month to the 12-month time point. The $T_{1\rho}$ values of the RT's superficial layers at 3–6 months remained elevated and were not different than the $T_{1\rho}$ values of the RT's superficial layer at 12 months. As a result, at the 12-month follow-up visit the superficial layer of the RT had significantly higher $T_{1\rho}$ values relative to the deep layer of the RT and to the superficial layer of NC. One may attribute this increase in $T_{1\rho}$ signal to an increase in water content, however, the T_2 values of the RT in the superficial layer are not significantly elevated at 12 months, which suggests that the superficial layer of RT continues to be immature with respect to *proteoglycan* content. The deep layers significantly matured over time and were similar to the NC's deep layers with respect to $T_{1\rho}$ values. The underdevelopment of the superficial layer at 1 year likely accounts for the significantly higher full thickness $T_{1\rho}$ value of the RT compared to NC at 12 months that we observed. This is in contrast to our previous study, in which we found that there was no statistical difference between the $T_{1\rho}$ values for full thickness of the RT and NC at 12 months follow-up. This may be due to the fact that in our previous study there was a significant number of patients that were lost to follow-up between the early and late follow-up timepoints and that there were patients evaluated at the one year follow-up that were not evaluated at the 3–6 month follow-up [28].

With regard to the RT's T_2 characteristics over time, we found that there was no statistical difference between the full thickness T_2 values of the RT and those of NC. This change in T_2 values of the RT to presumed “normalcy” was likely due to a maturation of both the deep and superficial layers with respect to *collagen* content and orientation, as we found that there were no significant differences between the T_2 values of the deep and superficial layers of RT and their respective layers in NC. While the RT likely matured with respect to collagen content, it appears that the collagen organization and zonal variation was not restored, as there was no statistical difference between the T_2 values of the deep and superficial layers of the RT at 12 months. This is consistent with the fact that MFX surgery produces a fibrocartilaginous tissue that lacks distinct collagen layering [4–7]. This lack of zonal variation was also observed by White et al. who found, at 12 months after MFX surgery, a strong correlation between organized T_2 values and normal polarized light microscopy (PLM) findings and between disorganized T_2 values and abnormal PLM findings [15]. They also found a perfect correlation between organized T_2 values and histologic findings of hyaline cartilage and between disorganized T_2 values and histologic findings of fibrous reparative tissue [15]. This fibrocartilaginous tissue is likely to degenerate over time, as Welsch et al. found that the RT at a mean follow up of 28.6 months after MFX surgery had significantly lower full thickness T_2 values compared to NC [14]. Additionally, they found that T_2 values of RT decreased with longer follow-up periods,

which they attributed to a decrease in the repaired tissue's water content and an increase in fibrous tissue [14].

Although many of the results described herein are promising, a number of limitations to this study exist. One limitation is that the deep and superficial cartilage layers analyzed do not correlate with the three physiologic layers of cartilage: tangential, intermediate, and radiate. Although the two layers were used instead of three layers because of limited resolution, it is possible that the deep and superficial layers analyzed herein also have limited resolution. Additional limitations of this study include the small number of patients evaluated, the relatively short length of follow-up, and the fact that no clinical outcome data, arthroscopic evaluations, or histologic samples were correlated. Given the small number of patients evaluated, it is difficult to accurately conclude whether the results obtained herein actually represent differences between the two layers of cartilage evaluated or if the differences are due to chance or selection bias. Additionally, 1 year after MFX injury is a relatively short length of time, and it is possible that the aforementioned $T_{1\rho}$ signal changes may improve or significantly change over time as the repair tissue matures or degenerates. In a review article by Trattnig et al., 1-year follow-up was stated to be an appropriately *early* stage to assess cartilage maturation [35]. Lastly, a possibly significant limitation is partial volume effects. We attempted to minimize this possible confounder by instituting maximum thresholds for $T_{1\rho}$ and T_2 values (150 ms and 100 ms, respectively), and thus, we believe that partial volume effects do not significantly influence our results. However, to further minimize this effect, an increase of in-plane resolution should be the goal. Ultimately, the results of this study should invite further clinical outcome studies with longer follow-up time points, with larger cohorts of patients, and with correlations between $T_{1\rho}$ and T_2 values, clinical outcome scoring systems, and arthroscopic cartilage measurements.

In conclusion, we have demonstrated that $T_{1\rho}$ and T_2 quantitative MRI are feasible methods for quantitatively and noninvasively monitoring the maturation of repaired tissue following microfracture surgery over time.

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Fig. 1.

Sequential steps in cartilage post-processing of patients with focal cartilage defects (FCD) treated with microfracture surgery. (A) For each patient, the cartilage in the knee compartment containing a FCD was segmented on a high-spatial resolution spoiled gradient (HR-SPGR) image. (B) Each cartilage contour on the HR-SPGR images was subsequently divided into two regions of interest: regenerated tissue (RT) and healthy surrounding cartilage (NC). (C) The 3D regions of interest for RT and NC were then overlaid on reconstructed $T_{1\rho}$ and T_2 maps that had been rigidly registered to the previously acquired HR-SPGR images. (D) Using an in-house developed laminar analysis program, the RT and NC regions were divided into a deep and superficial layer (black line) and $T_{1\rho}$ and T_2 values for each layer of each region were collected.

Fig. 2. Longitudinal full thickness $T_{1\rho}$ (A) and T_2 values (B) for focal cartilage defects in patients treated with microfracture (MFx) surgery. (A,B) At 3–6 months after MFx surgery the repaired tissue (RT) had significantly higher $T_{1\rho}$ and T_2 values than NC. (A) At 12 months post-op, $T_{1\rho}$ values of the RT continue to be statistically higher than those of the NC. (B) Conversely, T_2 values of the RT are not statistically different from the T_2 values of the NC at 12 months post-op. Asterisks denote significance at a p-value < 0.05.

Fig. 3.

Longitudinal $T_{1\rho}$ and T_2 laminar analysis values for focal cartilage defects treated with microfracture (MFX) surgery. (A, B) The $T_{1\rho}$ and T_2 values of the superficial layer of normal cartilage (NC) are statistically greater than the deep layer throughout the 12-month follow-up period. (A, B) At 3–6 months follow-up, the repair tissue's (RT) superficial layer has significantly higher $T_{1\rho}$ and T_2 values than the deep layer of the RT and the superficial layer of NC. (A) At 12 months, the superficial layer of the RT has significantly higher $T_{1\rho}$ values than the RT's deep layer and the NC's superficial layer. (B) In contrast, the T_2 values of the superficial layer at 12 months post-op are not significantly different from the values of the deep layer of the RT and the superficial layer of NC. Asterisks denote significance at a p-value < 0.05.

Fig. 4. Representative $T_{1\rho}$ color map of a knee 3–6 months after microfracture surgery for the treatment of a focal cartilage defect. The repaired tissue is seen in the medial femoral condyle as an area with increased signal intensity. The insert (lower left corner) illustrates the boundaries of the repaired tissue (RT; red lines) as well as the separation between deep and superficial layers (black line). It should be noted that the deep and superficial layers of the RT have higher $T_{1\rho}$ signal than the respective layers in the normal cartilage (NC) and that the superficial layer of the RT has higher signal intensity than the RT's deep layer.

Table 1

Location and surface area of focal cartilage defects in patients treated with microfracture surgery.

Patient	Compartment	Surface area (cm ²)	
		3–6 months	12 months
1	MFC	2.36	2.82
2	TRO	2.95	1.87
3	LFC	2.71	2.92
4	MFC	5.63	5.28
5	MFC	3.33	3.55
6	MFC	3.23	2.73
7	MFC	1.52	1.80
8	MFC	4.51	3.08
9	LFC	1.02	1.02
10	TRO	2.03	3.68
Average		2.93	2.88
p-value		0.85	

MFC: medial femoral condyle; LFC: lateral femoral condyle; MT: medial tibia; LT: lateral tibia; TRO: trochlea. Statistical significance set at a p-value <0.05.