MAGNETIC RESONANCE IMAGING FOR TRAUMATIC KNEE INJURY

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MAGNETIC RESONANCE IMAGING FOR TRAUMATIC KNEE INJURY

Magnetische resonantie beeldvorming bij traumatisch knieletsel

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Voor mijn ouders
Voor oma

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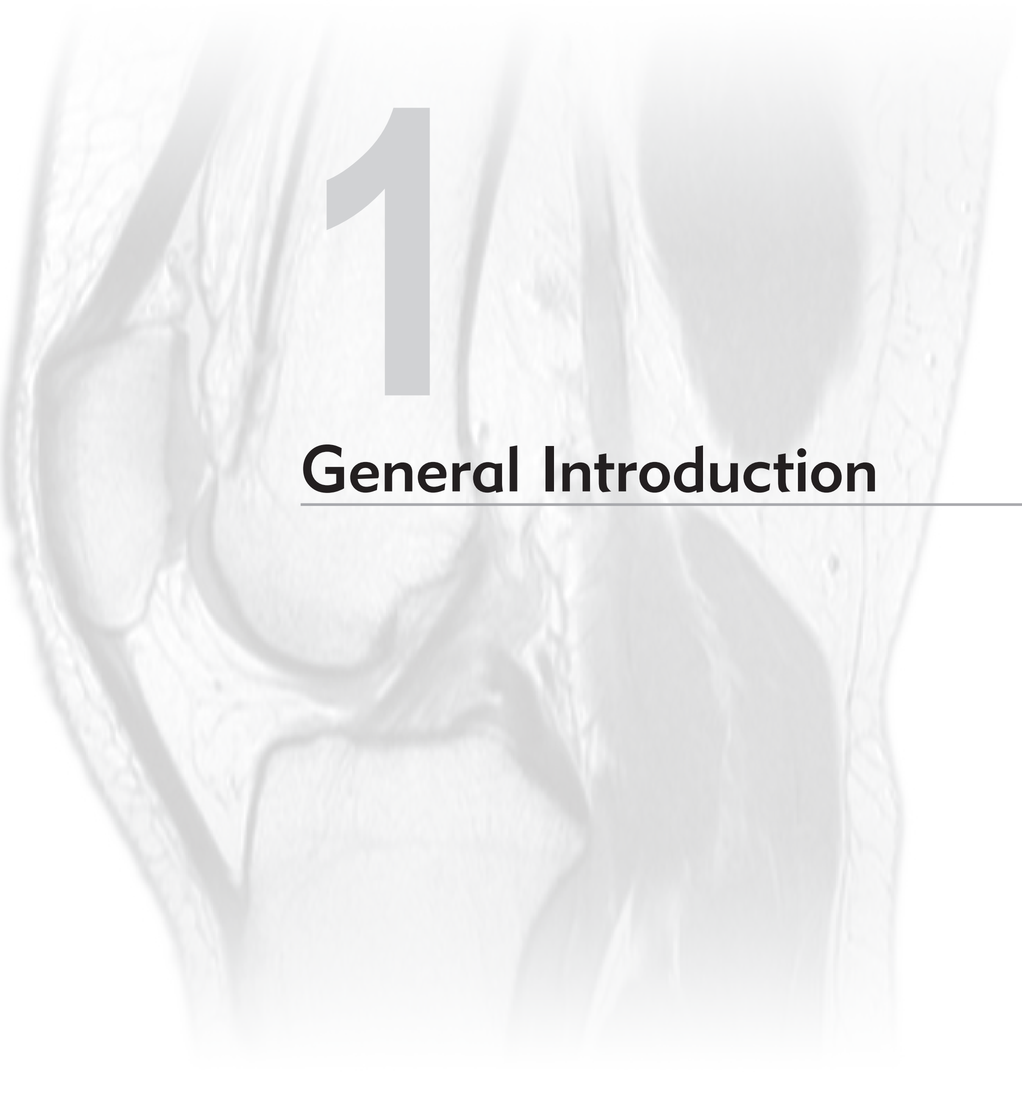

1

General Introduction

Traumatic knee lesions are frequently encountered both in general practice and in the hospital setting. These injuries are often caused by sports and other physical activities and may lead to severe pain and disability (1,2).

The initial evaluation of a patient who sustained a knee trauma is usually aimed at ruling out a fracture. To this end, several clinical decision aids have been developed, of which the so-called Ottawa knee rule is the most widely accepted and commonly used example (3,4). This prediction rule involves taking the clinical history and performing a brief physical examination to determine the likelihood of a fracture and the need for a knee radiograph. Physical examination in the acute stage is, however, often limited by joint swelling, pain, and guarding (5,6). Moreover, only bony abnormalities can be visualized on knee radiography, although many other non-osseous traumatic abnormalities may be present, such as lesions of the ligaments, menisci, tendons, and cartilage.

To evaluate these structures non-invasively and accurately, magnetic resonance imaging (MRI) has been established as the best available imaging technique. Since the introduction of MRI for clinical purposes in the mid-1980s, the technique has improved substantially and is still evolving, especially with the introduction of dedicated knee coils and optimization of pulse sequences. Nowadays, MRI is commonly used for the evaluation of the knee joint and has largely replaced invasive diagnostic arthroscopy for this purpose (7-10). Nevertheless, MRI is rarely performed in the initial evaluation after trauma, but usually at a later stage in case of persisting symptoms. This is largely due to the high costs, limited availability, and long duration of an MRI examination.

Considering the capabilities of MRI and the limitations of thorough physical examination in the acute stage after trauma, one may wonder whether MRI could play a role in the initial evaluation after trauma. One might even hypothesize that despite the costs of MRI, it could be cost-saving from a societal perspective: detailed information in an early stage may result in a more timely diagnosis and treatment in patients who would otherwise have been followed up. Conversely, it may identify patients who do not need specific treatment, and can be discharged from follow-up. In a patient population that consists largely of young and physically active persons, this may lead to shorter absence from work, reduced loss of productivity and hence to lower costs to society.

AIMS AND OUTLINE OF THIS THESIS

The purpose of this thesis was to study various aspects of MRI for traumatic knee injury, starting with a review of MRI for traumatic knee injury and a systematic review on its diagnostic performance. Second, we aimed at assessing the costs and effectiveness of applying a brief MRI examination in the initial evaluation after knee trauma. Finally, our purpose was to evaluate the natural course of meniscal lesions and the development of degenerative knee abnormalities on follow-up MRI.

Review studies on MRI for traumatic knee injury

In chapter 2 we discuss the indications for knee MRI in the setting of trauma, the most commonly used MRI techniques, and we review and illustrate the MRI appearance of the most frequently encountered knee abnormalities.

We performed a systematic review and meta-analysis on the diagnostic performance of MRI of the menisci and cruciate ligaments, described in chapter 3. In this study, we also analyzed whether diagnostic performance differs across lesions and how the diagnostic accuracy is influenced by study design characteristics and magnetic field strength of the MRI scanner.

Randomized controlled trial in the hospital emergency department

We conducted a prospective randomized controlled trial (RCT) to investigate the application of MRI in the initial evaluation after knee trauma, focusing on its value in therapeutic decision-making, its effectiveness, and costs. Patient visiting the emergency department of our hospital because of acute knee trauma were randomized between the current diagnostic work-up (radiography) and a strategy in which radiography was followed by a short MRI examination.

In chapter 4 we study whether such a short MRI examination can aid in the prediction if specific treatment is required after acute knee trauma or if patients can be discharged without the need for further follow-up.

In our RCT, we also collected data on costs and quality of life, and we analyzed the costs and effectiveness for each diagnostic strategy from a societal perspective (11,12). The results of this study, in which patients with acute wrist and ankle trauma were also included, are presented in chapter 5.

In chapter 6 the cost analysis is specifically focused on knee trauma, including an additional modeled diagnostic strategy consisting of selective use of MRI only if radiography showed no fracture.

Using the data of the RCT, we performed a value of information analysis to study the requirements and targets of future outcomes research into the use of MRI for acute knee trauma in the emergency department setting, described in chapter 7.

MRI follow-up study in general practice

As mentioned earlier, traumatic knee abnormalities are also frequent in primary care, with a reported incidence of 5.3 per 1000 patients in Dutch general practice (13). Furthermore, in the Netherlands most patients with knee trauma are managed by the general practitioner (14). As part of a large observational cohort study into knee complaints in general practice (15), we performed an MRI follow-up study in a subgroup of 134 adult patients who visited the general practitioner because of knee trauma. These patients underwent initial MRI between 3 to 6 weeks after trauma, as well as a follow-up MRI after one year.

We evaluated the natural course of meniscal lesions (chapter 8) and the development or progression of knee osteoarthritis (chapter 9) during the one year follow-up. In these studies, we also assessed predictive factors for meniscal status change and for development or worsening of osteoarthritic change after one year.

In chapter 10 the main findings in this thesis are summarized and discussed.

REFERENCES

1. Kujala UM, Taimela S, Antti-Poika I, Orava S, Tuominen R, Myllynen P. Acute injuries in soccer, ice hockey, volleyball, basketball, judo, and karate: analysis of national registry data. BMJ 1995; 311:1465-1468.
2. Yawn BP, Amadio P, Harmsen WS, Hill J, Ilstrup D, Gabriel S. Isolated acute knee injuries in the general population. J Trauma 2000; 48:716-723.
3. Stiell IG, Greenberg GH, Wells GA, et al. Derivation of a decision rule for the use of radiography in acute knee injuries. Ann Emerg Med 1995; 26:405-413.
4. Bachmann LM, Haberzeth S, Steurer J, ter Riet G. The accuracy of the Ottawa knee rule to rule out knee fractures: a systematic review. Ann Intern Med 2004; 140:121-124.
5. Hardaker WT, Jr., Garrett WE, Jr., Bassett FH, 3rd. Evaluation of acute traumatic hemarthrosis of the knee joint. South Med J 1990; 83:640-644.
6. Mitsou A, Vallianatos P. Clinical diagnosis of ruptures of the anterior cruciate ligament: a comparison between the Lachman test and the anterior drawer sign. Injury 1988; 19:427-428.
7. Elvenes J, Jerome CP, Reikeras O, Johansen O. Magnetic resonance imaging as a screening procedure to avoid arthroscopy for meniscal tears. Arch Orthop Trauma Surg 2000; 120:14-16.

8. Weinstabl R, Muellner T, Vecsei V, Kainberger F, Kramer M. Economic considerations for the diagnosis and therapy of meniscal lesions: can magnetic resonance imaging help reduce the expense? World J Surg 1997; 21:363-368.
9. Vincken PW, ter Braak BP, van Erkel AR, et al. Effectiveness of MR imaging in selection of patients for arthroscopy of the knee. Radiology 2002; 223:739-746.
10. Carrino JA, Schweitzer ME. Imaging of sports-related knee injuries. Radiol Clin North Am 2002; 40:181-202.
11. Oostenbrink JB, Koopmanschap MA, Rutten FFH. Handleiding voor kostenonderzoek, methoden en richtlijnprijzen voor economische evaluaties in de gezondheidszorg. Amstelveen: College voor zorgverzekeringen, 2000.
12. Hunink MGM, Glasziou PP. Decision making in health and medicine - integrating evidence and values. Cambrige: Cambridge University Press, 2001.
13. Van der Linden MW, Westert GP, de Bakker DH, et al. Tweede nationale studie naar ziekten en verrichtingen in de huisartspraktijk: klachten en aandoeningen in de bevolking en in de huisartspraktijk. Utrecht, Bilthoven: NIVEL, Rijksinstituut voor volksgezondheid en milieu., 2004.
14. Cardol M, van Dijk L, de Jong JD, et al. Tweede Nationale Studie naar ziekten en verrichtingen in de huisartspraktijk. Huisartsenzorg: wat doet de poortwachter ? Utrecht, Bilthoven: NIVEL/RIVM, 2004.
15. Heintjes EM, Berger MY, Koes BW, Bierma-Zeinstra SM. Knee disorders in primary care: design and patient selection of the HONEUR knee cohort. BMC Musculoskelet Disord 2005; 6:45.

2

MRI for Traumatic Knee Injury: A Review

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ABSTRACT

Magnetic resonance imaging (MRI) is a well-established technique for detecting internal derangements of the knee joint with high diagnostic accuracy. It is an effective tool to select patients for targeted therapeutic arthroscopy. In this article, indications for knee MRI and most commonly used MRI techniques are outlined, followed by an overview of the most frequently encountered traumatic knee derangements in daily practice and their appearance and grading system on MRI. Lesions discussed include fractures, osteochondral lesions, bone bruise, cruciate and collateral ligament lesions, and meniscal tears. Finally, common pitfalls and recent developments in knee MRI are addressed.

Magnetic resonance imaging (MRI) is a well-accepted imaging modality in the diagnostic workup of patients with knee complaints and has largely replaced diagnostic arthroscopy for this purpose (1-4). Whereas conventional radiographs may only reveal large osseous lesions, MRI is capable of depicting soft-tissue abnormalities, such as meniscal lesions, cruciate ligament and collateral ligament lesions, tendinous lesions, and loose bodies, which may lead to targeted therapeutic arthroscopy. In addition, subtle osseous abnormalities such as radiographically occult fractures, bone marrow edema, and osteochondral lesions can be diagnosed with MRI. Previous studies have demonstrated a high diagnostic accuracy of knee MRI as compared to arthroscopy, in particular with regard to meniscal tears and cruciate ligament ruptures (5-7). This article starts with a brief discussion on the indications for knee MRI in the setting of trauma. The most commonly used MRI examination techniques are outlined next, followed by an overview of the most frequently encountered traumatic knee abnormalities in daily practice and their MRI characteristics. Finally, several common pitfalls and recent advances in knee MRI are discussed.

INDICATIONS FOR KNEE MRI

Many studies have reported on the indications for MRI of the knee joint in various clinical settings. In the context of trauma, MRI is generally considered a valuable diagnostic tool when there is a history of acute knee trauma (8), posttraumatic limited or painful range of motion, or mechanical knee symptoms, such as catching, locking, snapping, or crepitus (9). Previous studies have evaluated the value of MRI in the acute stage after trauma, and found that MRI has limited cost effectiveness in this setting (10,11). MRI is therefore usually performed at a later stage if symptoms persist. Although the diagnostic performance of knee MRI is high, close correlation with the clinical history and findings on clinical examination is essential to avoid misinterpretation (12).

MRI EXAMINATION TECHNIQUE

MRI Equipment

Apart from the traditional closed whole-body MRI units, several other magnet designs exist, some of which have been designed specifically for extremity imaging (ie, dedicated extremity closed and open systems) (13). The effect of magnetic field strength, which usually varies between 0.2 and 1.5 Tesla, has been demonstrated to be of no significant influence on diagnostic performance of meniscal and cruciate ligament tears (5); however, a high field strength system is considered necessary for high-resolution imaging of the articular cartilage. A dedicated extremity or knee coil should be used to maximize the signal-to-noise ratio.

Patient Positioning

The patient is usually imaged in the supine position with the knee nearly or fully extended and slightly rotated externally to align

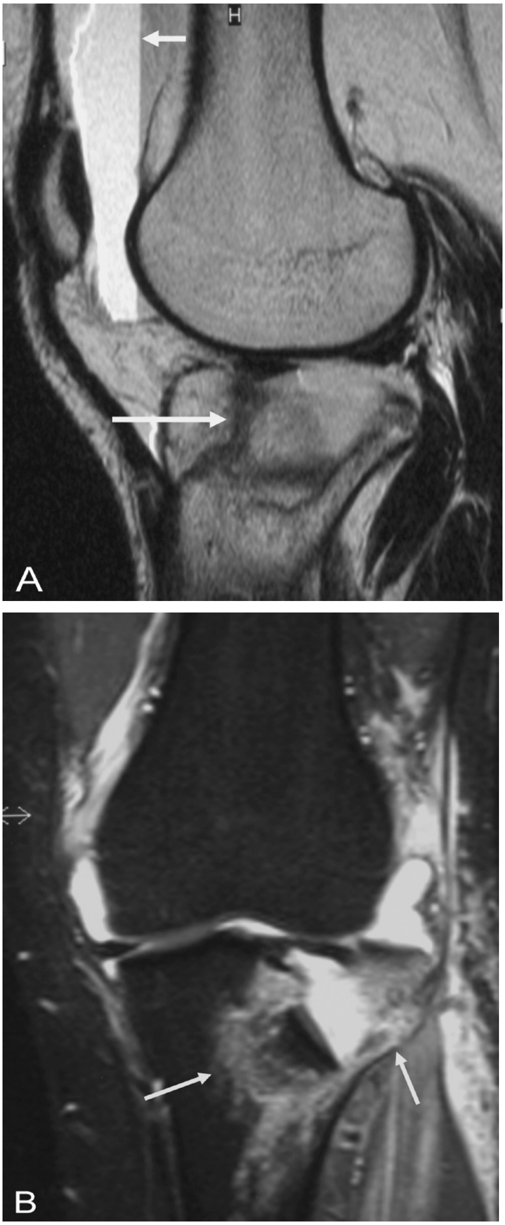


Figure 1. Fracture. (A) Sagittal T2-weighted turbo spin-echo image. Intra-articular fracture of the tibial plateau (long arrow) with an associated lipohemarthrosis in the suprapatellar recess (short arrow). (B) Coronal short tau inversion recovery image shows extensive bone marrow edema surrounding the fracture (arrows).

the anterior cruciate ligament parallel to the sagittal plane for better visualization.

Pulse Sequences

A wide variety of MRI pulse sequences can be performed to produce diagnostic quality images. These include spin-echo, fast (turbo) spin-echo, and gradient-echo sequences, which all have been proven suitable for knee imaging. T1 or proton density-weighted sequences are most suitable for visualizing the ligamentous anatomy. T2 or short tau inversion recovery (STIR) sequences with fat saturation are essential to demonstrate bone marrow edema. Typically, a routine scanning protocol would consist of a combination of one or more of these sequence types performed in the axial, sagittal, and coronal planes using thin sections (maximum 3 mm with an interslice gap of 0.5 to 1 mm). A field-of-view of 12 to 16 cm depending on

Figure 2. Avulsion fracture. Coronal proton density-weighted turbo spin echo image shows an avulsion fracture of the fibular head at the insertion of the conjoint tendon of the fiular collateral ligament and biceps femoris tendon (arrow).

patient size is commonly used with a high-resolution matrix of at least 140 steps in the phase-encoding direction and 256 steps in the frequency-encoding direction. Although many institutions use standardized protocols for routine scanning, individual tailoring is necessary to yield optimal diagnostic performance for specific clinical queries. For example, a thin section axial sequence should be included in the protocol if damage to the patellofemoral joint is suspected and a coronal T2-weighted sequence is necessary to demonstrate collateral ligament lesions.

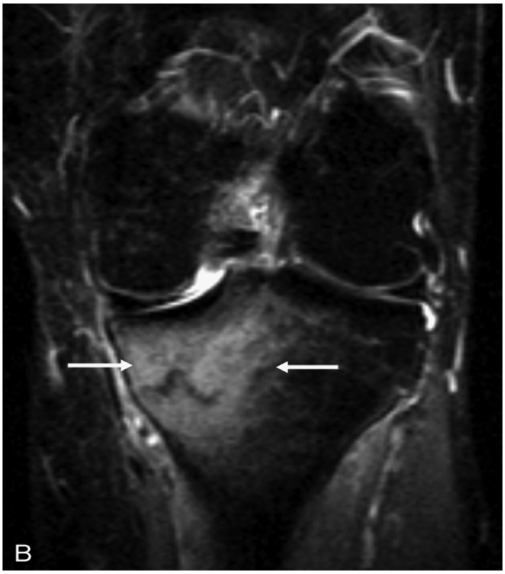


Figure 3. Stress fracture. (A) Coronal proton density-weighted turbo spin echo image. Running athlete with recurrent pain on the medial side of the knee. A stress fracture is demonstrated in the medial tibial metaphysis (arrow), which was not visible on plain radiography. (B) Coronal short tau inversion recovery image. There is extensive bone marrow edema surrounding the stress fracture (arrows).

OSSEOUS AND CHONDRAL LESIONS

Fractures and Dislocations

Occasionally, fractures may be invisible on conventional radiographs. If a fracture is strongly suspected, tomographic techniques such as computed tomography (CT) and MRI

Figure 4. Bone marrow edema. Coronal short tau inversion recovery image shows bone marrow edema in the medial femoral condyle (long arrow) in a patient who sustained a direct hit to the medial side of the knee. In addition, soft-tissue edema is seen superficial to the iliotibial tract (short arrow), indicating a grade 1 lesion or sprain.

may be indicated to reveal a radiographically occult fracture. Fracture lines appear as dark signal intensity lines on all pulse sequences, and are usually surrounded by areas of bone bruise visible on fat-saturated images (Fig. 1). In case of an intra-articular fracture, fatty bone marrow will leak into the joint space, resulting in a lipohemarthrosis, which is usually visible in the suprapatellar recess (Fig. 1A). MRI may also be used to demonstrate avulsion fractures, which can be hard to diagnose on plain radiography if there is no displacement (14) (Fig. 2). Stress fractures may also be difficult to diagnose on plain radiographs, but are well visualized on MRI (Fig. 3). In the setting of a radiographically demonstrated fracture, CT with multiplanar and three-dimensional (3D) reconstructions is often performed to demonstrate the exact course of the fracture lines to guide treatment planning. MRI is, obviously, more suitable for evaluating associated soft-tissue lesions (15,16). Likewise, MRI may be helpful in assessing the full extent of ligamentous disruptions that are invariably present after knee dislocation, as well as demonstrate additional osseous, vascular, or nervous injuries (17).

Patellar dislocations are commonly associated with rupture of the medial patellar retinaculum and this may be well visualized on axial MRI sequences (18).

Figure 5. Kissing contusion. Sagittal T1-weighted 3D fast field echo with spectral presaturation inversion recovery (SPIR) image. Patient with complete ACL rupture following skiing injury. Bone marrow edema is seen in the lateral femoral condyle (long arrow) and the posterolateral aspect of the tibial plateau (short arrow), a so-called kissing contusion, which typically occurs due to the trauma mechanism of a total ACL rupture.

Figure 6. Osteochondritis dissecans. Sagittal T2-weighted turbo spin echo image shows a large defect of the articular surface of the medial femoral condyle (long arrow). Since there is complete detachment of an osteochondral fragment (dislocated to the intercondylar notch, not shown), this lesion was classified as grade 4 osteochondritis dissecans. In addition, a Baker's cyst is present (short arrow), which is most often associated with internal derangements of the knee joint or degenerative osteoarthritis.

Bone Marrow Edema/Bone Bruise

Bone marrow edema is most easily identified on T2 or STIR sequences with fat suppression on which it appears as an area of high signal intensity (Fig. 4). Bone bruise can occur as an isolated finding usually after a direct hit. More often, though, it is associated with other abnormalities such as ligamentous lesions, and frequently a typical pattern of bone bruise according to type of injury is seen (19). For example, during the mechanism of complete anterior cruciate ligament (ACL) rupture, a transient subluxation combined with impaction between the lateral femoral condyle and the posterolateral aspect of the tibial plateau typically occurs, resulting in a characteristic pattern of bone marrow edema in these locations, which is sometimes referred to as a "kissing contusion" (Fig. 5).

Articular Cartilage Lesions

Damage to the articular cartilage may be caused by acute trauma, but more commonly is the result of chronic repetitive trauma or degenerative change. It may be difficult to distinguish between an acute and chronic chondral lesion, but analyzing the pattern of concurrent lesions such as ligament tears and bone bruise may help in the diagnosis. Osteochondritis dissecans is a local defect of the articular surface most commonly seen in adolescents and young adults. It is usually caused by repetitive trauma and MRI findings range from subchondral edematous changes to complete separation of an osteochondral fragment from the surrounding subchondral bone. Several grading systems

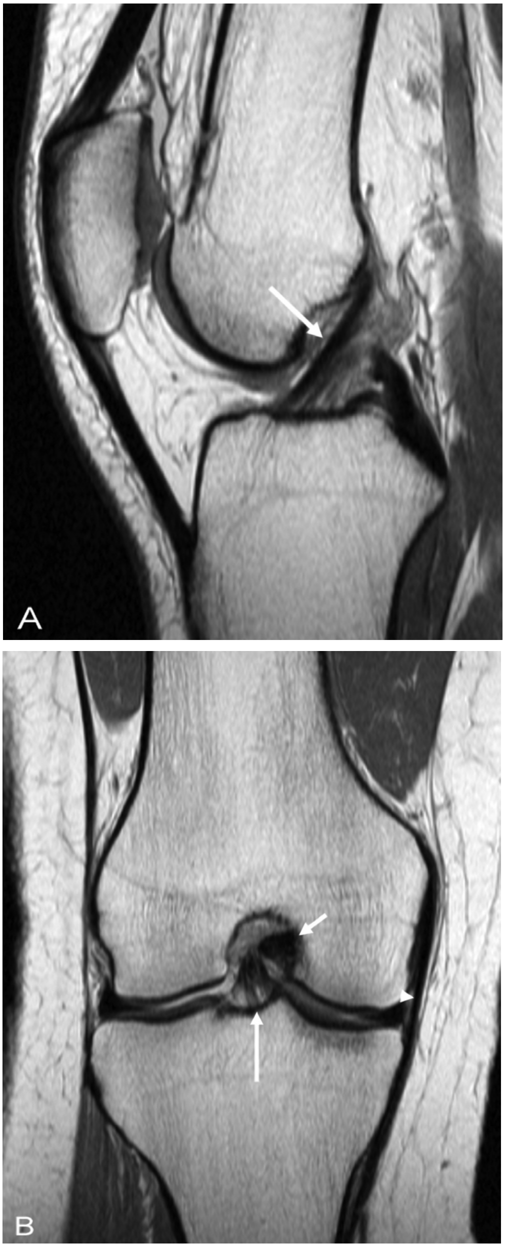


Figure 7. Normal ACL. (A) Sagittal proton density-weighted turbo spin echo image demonstrates the normal ACL as a straight low signal intensity band running from the medial aspect of the lateral femoral condyle to the tibial plateau (arrow). (B) On the coronal proton density-weighted image the insertion site of the ACL on the tibial plateau is well visualized (long arrow). In addition, the attachment of the PCL on the lateral aspect of the medial femoral condyle (short arrow) and a normal MCL (arrowhead) are seen.

exist, which all refer to the integrity of the articular surface and demarcation and stability of the osteochondral fragment (20) (Fig. 6). Chondromalacia is usually diagnosed in the setting of degenerative change and is therefore not discussed here.

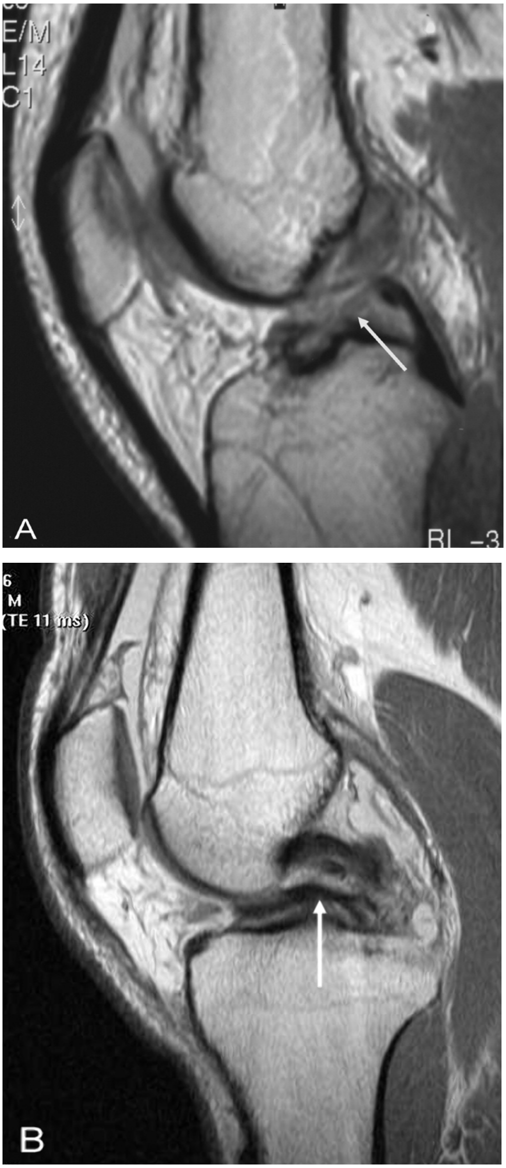


Figure 8. Complete ACL rupture. Sagittal proton density-weighted turbo spin echo images. (A) Nonvisualization of continuous ACL fibers with amorphous high signal intensity material in this area (arrow), consistent with complete ACL rupture. (B) Complete disruption of the ACL fibers with the completely torn ACL lying on the tibial plateau (arrow), resembling the "double PCL sign" that can be seen with bucket handle meniscal tears.

LIGAMENTOUS INJURY

Cruciate Ligament Tears

Anterior Cruciate Ligament (ACL)

The ACL is an intracapsular extrasynovial structure composed of two separate bundles of fibers and is usually evaluated on T2-weighted or proton density-weighted images, where it appears as a straight low-signal intensity band running from the medial aspect of the lateral femoral condyle to the tibial plateau adjacent to the anterior tibial spine. The ACL is usually well evaluated in the sagittal plane, but images in the axial

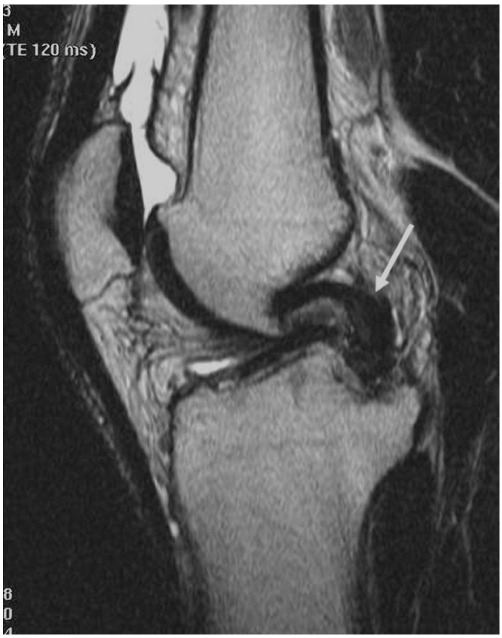


Figure 9. Buckled PCL sign. Sagittal T2-weighted turbo spin echo image. Abnormal alignment of the femur and tibia due to complete ACL rupture, resulting in a buckled appearance of the PCL, the so-called buckled PCL sign (arrow).

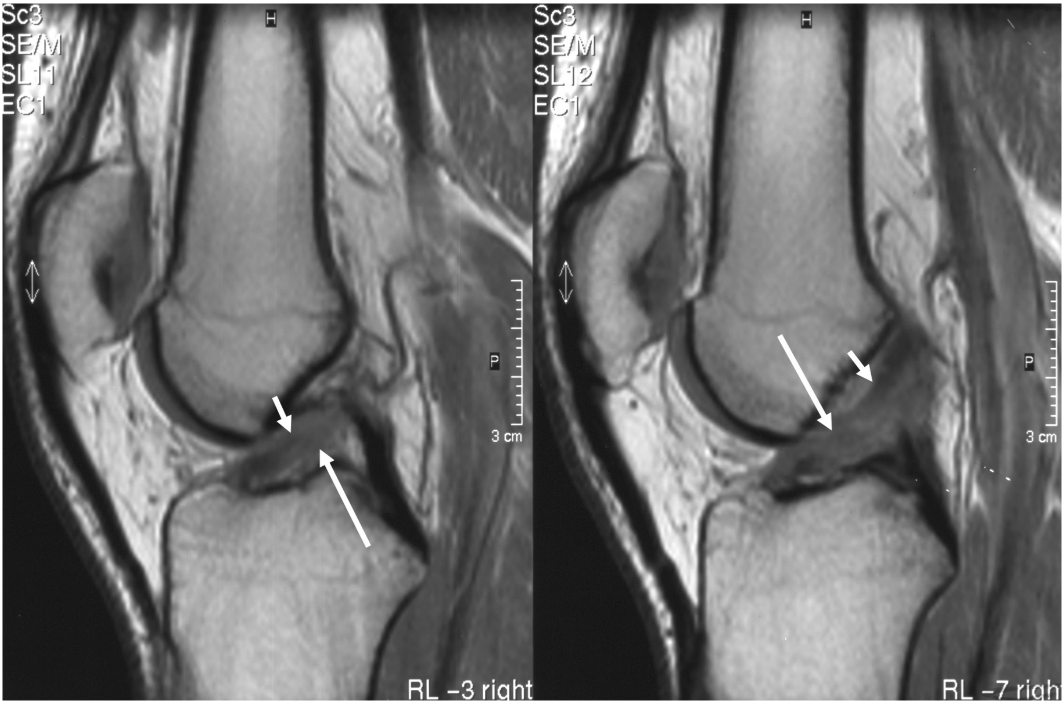


Figure 10. Partial ACL rupture. Two consecutive sagittal proton density-weighted turbo spin echo images. Focal areas of high signal intensity are seen in the course of the ACL, with partial discontinuity of the ACL fibers (long arrows). A couple of intact fibers are also noted (short arrows). Since the knee was stable on physical examination, this lesion was interpreted as a partial or subtotal ACL rupture.

and coronal plane can be helpful in assessing the femoral and tibial attachments (Fig. 7).

Primary signs of a total ACL rupture are a complete disruption of the ACL fibers, abnormal signal intensity within the ligament and in the surrounding region, abnormal slope of the ACL, and nonvisualization of ACL fibers both in the sagittal and coronal planes (Fig. 8). Hemorrhage and edema may appear as an amorphous mass producing mass effect. Many indirect signs of ACL rupture have been described, such as the "anterior drawer sign," "buckled PCL sign," and the aforementioned "kissing contusion" (21-24). The anterior drawer sign refers to an abnormally anterior position of the tibial plateau relative to the femoral condyle in the extended knee, which is normally prevented by an intact ACL. Related to this is a buckled appearance of the PCL on sagittal images (the buckled PCL sign), which is caused by the abnormal alignment of femur and tibia (Fig. 9). The presence of one or more of these indirect signs increases the likelihood of, but does not rule out, an ACL rupture. Usually, however, the diagnosis of complete ACL rupture can be made using primary signs alone. In partial ACL ruptures, focal areas of high signal may be seen within the ACL, with largely intact fibers and a

Figure 11. Normal PCL. The normal PCL is visualized as a dark band running from the lateral aspect of the medial femoral condyle to the posterior tibial plateau (long arrow) on this sagittal proton density-weighted turbo spin echo image. Also note the presence of a meniscofemoral ligament of Humphrey (short arrow), which may mimic a loose body.

clinically stable knee (Fig. 10). Partial ACL ruptures are difficult to diagnose and differentiate from complete tears and clinical correlation is essential (25).

Posterior Cruciate Ligament (PCL)

The normal PCL is visualized as a dark structure running from the lateral aspect of the medial femoral condyle to attach on the posterior tibial plateau (Figs. 7B and 11).

Since it is composed of one bundle of fibers, it appears more uniformly hypointense than the ACL. The same primary signs of ACL rupture can be applied to the PCL (Fig. 12). Isolated PCL lesions are rare and PCL ruptures most commonly occur due to a direct blow on the anterior tibia with a flexed knee in the setting of a “dashboard injury" (26).

Collateral Ligament Tears

Medial Collateral Ligament (MCL)

The MCL can be divided into two layers: the superficial fibers and the deep fibers that are attached to the joint capsule and the medial meniscus. The two layers are separated by a potential space, the tibial collateral bursa, which can be filled with fluid in the setting of a MCL lesion. The MCL is best visualized on coronal images where it appears as a dark band extending from the medial femoral condyle to insert on the medial aspect of the tibia approximately 4-5 cm below the joint line (Fig. 7B). Lesions of the MCL are graded as follows: Grade 1 (sprain) lesions are defined as high signal intensity superficial to the MCL representing edema, with intact MCL fibers (Fig. 13A). In grade 2 (partial tear) lesions, fluid signal extends partially through the MCL, although some fibers remain intact (Fig. 13B). In grade 3 lesions, complete discontinuity of the MCL fibers is seen along with surrounding edema, consistent with a complete rupture (Fig. 13C). MCL injuries are usually caused by valgus stress, and are often associated with other knee derangements.

The combination of an ACL tear, MCL tear, and medial meniscal tear occurs with valgus stress to the knee while the foot is fixed on the ground, and is also known as the “unhappy triad” or O’Donoghue’s triad (27).

Figure 12. PCL ruptures. Sagittal proton density-weighted turbo spin echo images. (A) Thickened PCL with focal areas of high signal intensity and partial discontinuity of the PCL fibers (arrow), consistent with a partial PCL rupture. (B) Complete non-visualization of the PCL fibers with high signal intensity in this area (arrow), indicating a PCL rupture. (C) Complete disruption of all PCL fibers indicative of a complete midsubstance tear of the PCL (arrow).

Lateral Collateral Ligament (LCL)

The LCL complex consists of several individual components. The fibular collateral ligament (or the lateral collateral ligament proper) extends from the lateral femoral condyle and merges with the biceps femoris tendon to form the conjoint tendon, which inserts on the fibular head. The iliotibial tract is a continuation of the tensor fascia lata and inserts at Gerdy's tubercle on the anterolateral aspect of the tibia (Fig. 4). Like the MCL, the LCL is best visualized on coronal images. Lateral collateral ligament injuries are usually classified similarly as medial collateral ligament lesions, using the 3-point grading system as outlined above. Lesions of the LCL are most often caused by varus stress and therefore may be associated with impression fractures of the medial tibial plateau. In addition, LCL ruptures are frequently seen together with other injuries of the posterolateral corner (28) (Fig. 14).

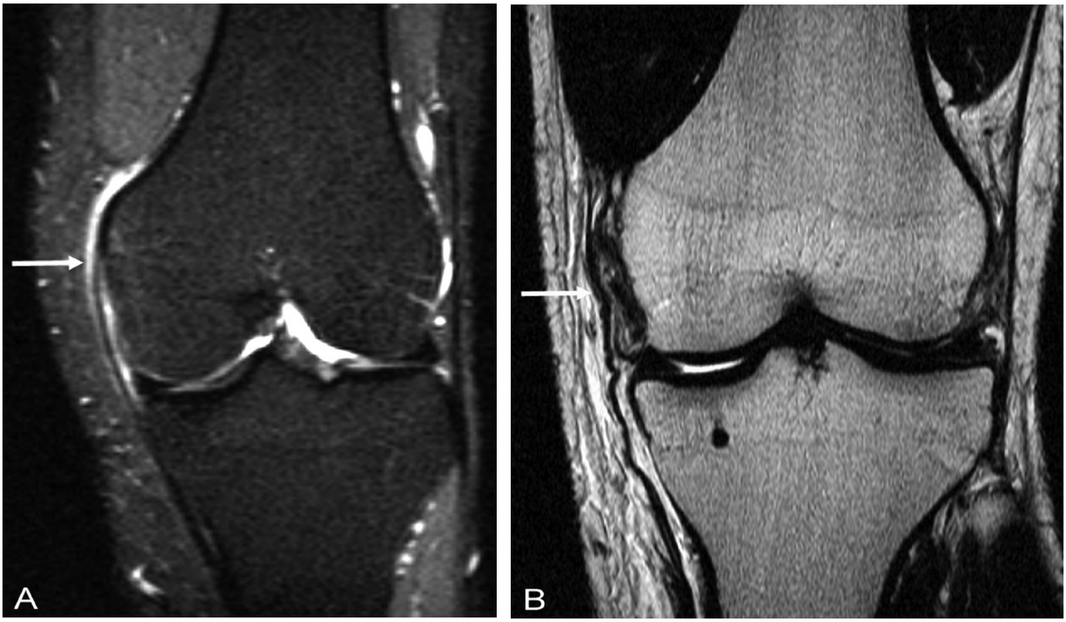


Figure 13. MCL lesions. (A) Coronal turbo inversion recovery magnitude image demonstrates edema surrounding intact MCL fibers (arrow), consistent with a grade 1 lesion. (B) Coronal T2-weighted turbo spin echo image shows a partial disruption of the MCL fibers with surrounding edema and a wavy appearance of the remaining fibers (arrow), indicating a grade 2 (partial) rupture. (C) A complete (grade 3) rupture of the MCL is visualized on this coronal short tau inversion recovery image. Complete discontinuity of the MCL fibers is seen with extensive soft-tissue edema in this region (arrow).

Figure 14. Complete LCL rupture. Coronal T2-weighted turbo spin echo image. There is complete discontinuity of the LCL and biceps femoris tendon (arrow), indicating a total rupture. Extensive soft-tissue edema is seen in this region. In addition, the patient had severe injury to the posterolateral corner, including rupture of the posterior joint capsule, as well as a total ACL rupture and partial PCL rupture.

MENISCAL PATHOLOGY

The menisci serve an important role in knee function, stability and load transmission, and are composed of fibrocartilage fibers. These are oriented mostly in a circumferential manner in the peripheral one third of the meniscus and both transverse and circumferential in the central two thirds of the meniscus. Because of this difference, the periphery of the meniscus is biomechanically more important than the inner part, and consequently a torn meniscus can still facilitate load transmission as long as the periphery remains intact. The periphery of the meniscus is vascularized and appears as the "red zone" on arthroscopy. Therefore, a tear that is confined to the periphery has greater healing potential than a tear that also involves the avascular central portion, also known as the "white zone" arthroscopically. Depending on the section, the normal MRI appearance of the meniscus on sagittal sections is either that of a single bow-tie shaped structure in the periphery or two triangles with facing apices representing the anterior and posterior horns more centrally (Fig. 15). The anterior and posterior horns of the lateral meniscus are approximately equal in size, whereas the posterior horn of the medial meniscus is nearly twice as large as the anterior horn (29). The normal meniscus demonstrates low signal intensity on all pulse sequences, and should be evaluated on both sagittal and coronal images.

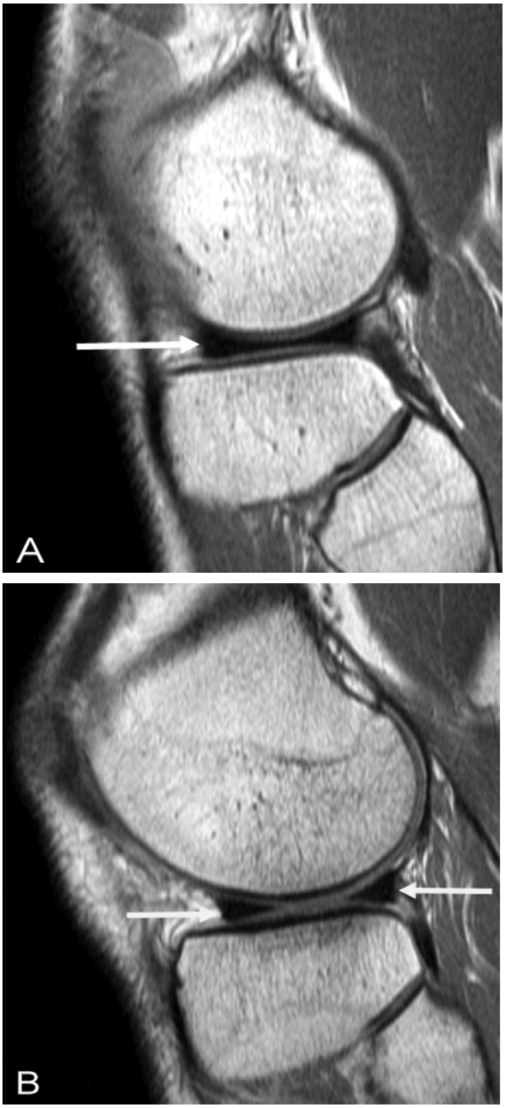


Figure 15. Normal lateral meniscus. Sagittal proton density-weighted turbo spin echo images. (A) In the peripheral part, the normal meniscus demonstrates a single bow-tie-shaped configuration (arrow). (B) More centrally, the normal meniscus is visualized as two triangles with facing apices representing the anterior and posterior horns (arrows).

Meniscal Tears

Two criteria for diagnosing a meniscal tear are commonly used: (1) an intrasubstance area of intermediate or high signal intensity that unequivocally extends to the articular surface, and (2) abnormal meniscal morphology (30,31). Intrasubstance signal is graded as follows: Grade 1 represents in-

Figure 16. Grading system of meniscal lesions. Sagittal proton density-weighted turbo spin echo images of the medial meniscus. (A) Globular high intermediate signal intensity that does not extend to the articular surface (arrow) representing a grade 1 lesion (degenerative change). (B) Linear high signal that does not extend to the inferior or superior articular surface (arrow), indicating a grade 2 lesion (degenerative change). (C) Linear high signal intensity that intersects the inferior articular surface (arrow) representing a grade 3 lesion (meniscal tear). (D) Complex grade 4 tear extending to both the superior and inferior articular surfaces (arrow).

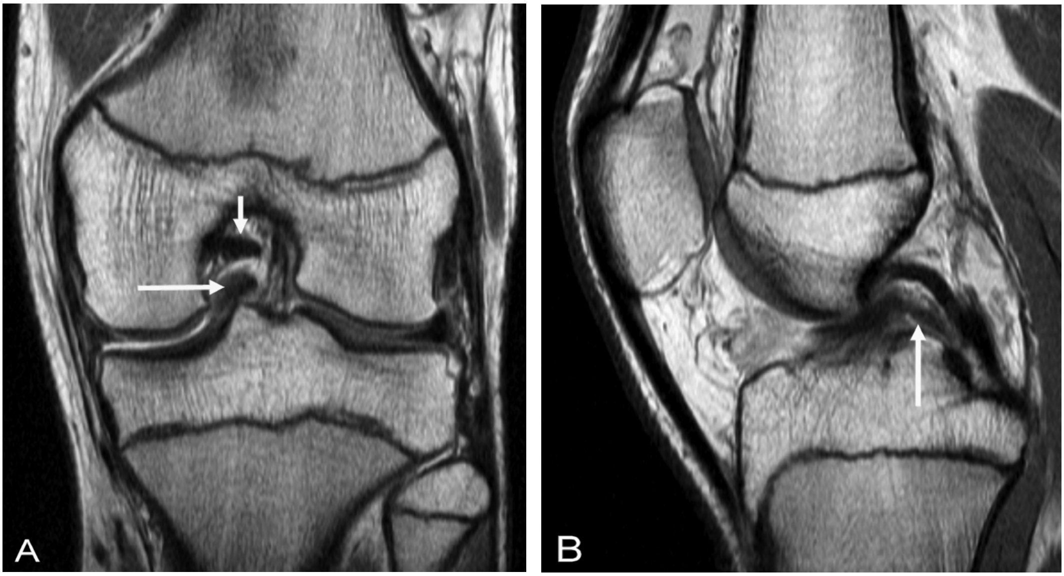


Figure 17. Bucket handle tear of the posterior horn of the medial meniscus. (A) The displaced meniscal fragment (the "handle") is visualized in the intercondylar notch (long arrow) under the PCL (short arrow) on this coronal proton density-weighted turbo spin echo image. (B) Sagittal proton density-weighted image shows the displaced fragment parallel to the PCL (arrow), the so-called double PCL sign.

trameniscal high signal intensity of irregular or globular appearance that is confined within the meniscus and does not extend to the articular surface (Fig. 16A). In grade 2 the signal is linear and does not intersect the inferior or superior articular surface (Fig. 16B). It may, however, contact the capsular margin at the posterior aspect of the meniscus. Both grade 1 and grade 2 lesions do not represent a tear, but indicate mucinous and mucoid intrasubstance degenerative change and are usually encountered after the third or fourth decade (32). In children and adolescents, prominent vasularity may resemble grade 1 or grade 2 lesions. Grade 3 lesions represent meniscal tears and are characterized by linear high or intermediate signal intensity that extends to the superior and/or inferior articular surface (Fig. 16C). Grade 4 is sometimes added to indicate a complex tear with multiple components or fragmentation (Fig. 16D). Several types of tears with different etiology, prognosis, and treatment should be distinguished. Horizontal tears, also called degenerative tears, are considered the result of severe meniscal degeneration and most commonly affect the posterior horn of the medial meniscus. These tears are usually asymptomatic and therefore often left untreated. Radially or longitudinally oriented tears and complex tears are most often the result of trauma and usually symptomatic (33). They have the tendency to progress in size or complexity, and fragmentation may occur, which can cause severe symptoms such as locking or snapping. Treatment, which nowadays typically consists of arthroscopic partial meniscectomy, is usually indicated in these cases.

Figure 18. Flipped meniscus sign. Sagittal proton density-weighted turbo spin echo images of the lateral meniscus shows a bucket handle tear of the posterior horn. A meniscal fragment has been displaced anteriorly (arrow), resulting in the appearance of an abnormally large anterior horn, the so-called flipped meniscus sign.

Several secondary signs of a meniscal tear have been reported, most of which are related to the presence of a "bucket-handle tear" (34-36). This is a specific type of vertical or oblique tear in the posterior horn that extends longitudinally toward the meniscal body and anterior horn, usually with displacement of the central meniscal portion toward the intercondylar notch (Fig. 17A). The displaced fragment (the "handle") may be seen under the PCL on sagittal images,

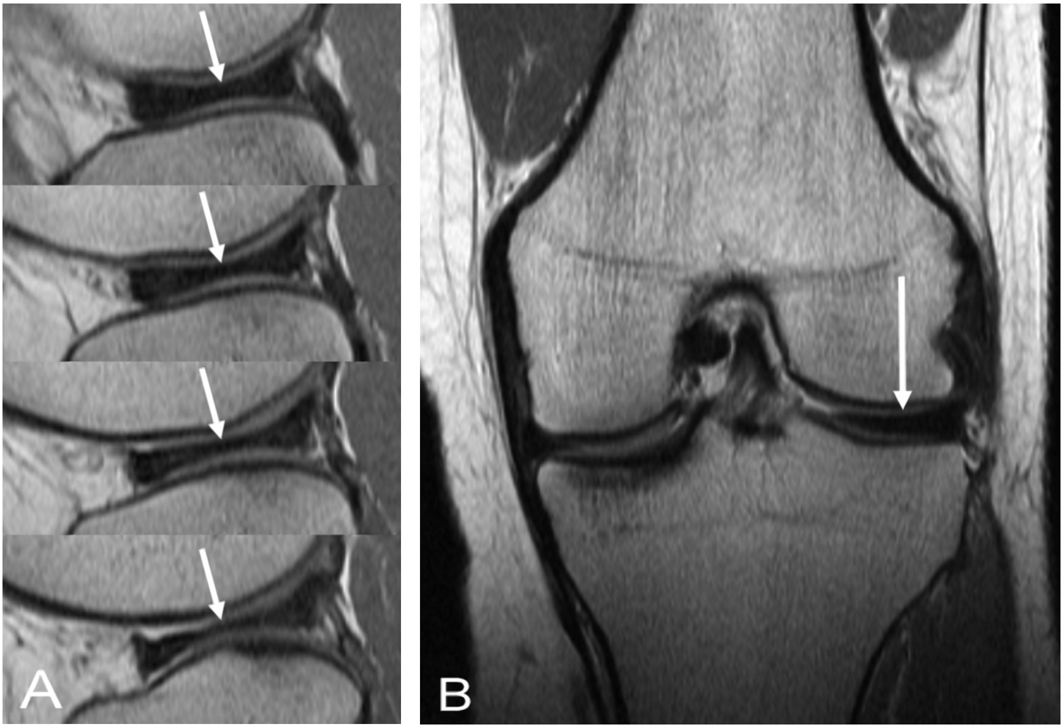


Figure 19. Discoid meniscus. (A) Four consecutive 3-mm sagittal proton density-weighted turbo spin echo images of the central portion of the lateral meniscus show continuity between the anterior and posterior horns (arrows), indicating a discoid meniscus. (B) Coronal proton density-weighted turbo spin echo image through the midportion of the knee demonstrates an abnormally wide lateral meniscal body (arrow), representing a discoid meniscus.

Figure 20. Meniscal cyst. Coronal T2-weighted turbo spin echo image demonstrates a meniscal cyst of the lateral meniscus (long arrow). The cyst is continuous with a horizontal cleavage tear of the lateral meniscus (short arrow).

resulting in the so-called double PCL sign (37,38) (Fig. 17B). The "absent bow-tie sign" refers to the absence of the normal bow-tie-shaped appearance of the meniscal periphery in the sagittal plane, due to the displacement of the central portion in the presence of a bucket-handle tear (39,40). The "flipped meniscus sign" refers to a meniscal fragment originating from the posterior horn or the entire posterior horn that has moved anteriorly to sit directly adjacent to or on the anterior horn of the ipsilateral meniscus, which may give the appearance of an abnormally large anterior horn (41) (Fig. 18).

Discoid Meniscus

A discoid meniscus is considered a developmental abnormality and is characterized by partial or complete covering of the

Figure 21. Transverse meniscal ligament. (A) Sagittal proton density-weighted turbo spin echo image. The transverse meniscal ligament (arrow) may mimic a tear of the anterior horn of the lateral meniscus. (B) On the coronal image, the course of the transverse meniscal ligament is nicely shown (arrow).

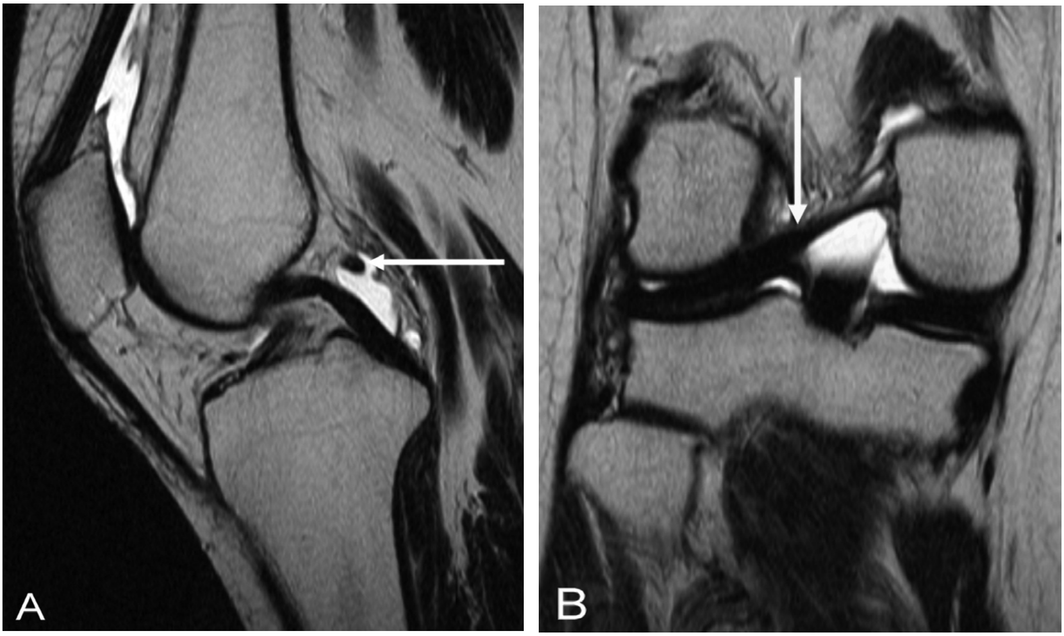


Figure 22. Meniscofemoral ligament of Wrisberg. (A) Sagittal T2-weighted turbo spin echo image. The meniscofemoral ligament of Wrisberg resembles a loose body surrounded by fluid (arrow). (B) The ligament has an unusually thick appearance in this case and is well visualized on the coronal T2-weighted image (arrow).

central portion of the tibial plateau by meniscal tissue. Discoid menisci are far more common on the lateral side and may cause mechanical symptoms when there is extension into the intercondylar notch. They are also associated with an increased risk both of degenerative abnormalities and tears. On MRI, a discoid meniscus can be diagnosed on sagittal images through the midportion of the knee, where a continuity between the anterior and posterior horns is seen instead of the normal bow-tie and triangular appearance (42) (Fig. 19A). On coronal images, the discoid meniscus appears abnormally wide and the diagnosis can be made if it measures more than 15 mm in width (43) (Fig. 19B).

Meniscal Cyst

A meniscal cyst is a fluid-filled structure adjacent to a meniscus, which appears as an intermediate signal intensity mass on T1-weighted images and hyperintense on T2-weighted images, sometimes lobulated or septated. Meniscal cysts are strongly associated with a horizontal cleavage tear of the meniscus and often a connecting neck between the tear and the cyst can be visualized (44,45) (Fig. 20). The cysts may become fairly large, which is thought to be caused by a ball valve mechanism. They can become symptomatic usually on the medial side, since they may impress on the medial collateral ligament.

Meniscal cysts tend to recur following resection or aspiration, especially if the underlying meniscal tear is left untreated.

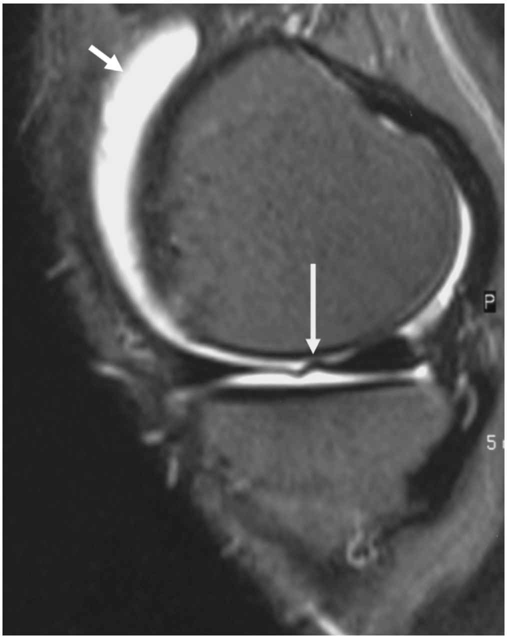


Figure 23. Meniscal flounce. Sagittal T2-weighted turbo spin echo image demonstrates a wrinkled appearance of the central portion of the medial meniscus (arrow), the so-called meniscal flounce. This is a normal variant and should not be misdiagnosed as a tear. In addition, joint effusion is seen in the suprapatellar recess (short arrow).

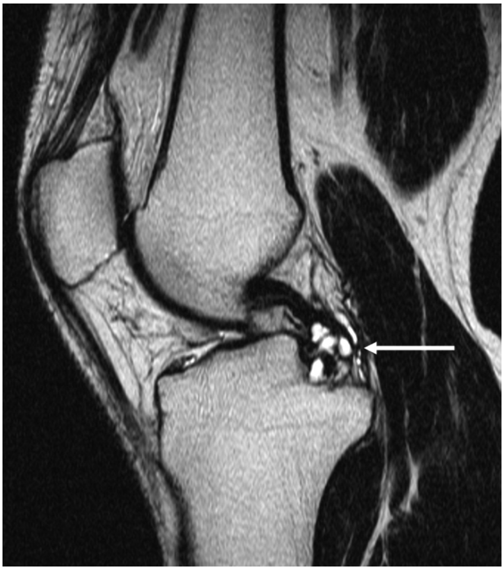


Figure 24. PCL ganglion. Sagittal T2-weighted turbo spin echo image. A well-defined globular lesion with high signal intensity is seen surrounding the distal portion of the PCL (arrow), representing a ganglion of the PCL.

PITFALLS

There are several pitfalls to be aware of when interpreting knee MRI, most of which are related to normal anatomical structures or normal variants that may mimic loose meniscal fragments or tears. For example, the transverse meniscal ligament may be falsely interpreted as a tear of the anterior horn of the lateral meniscus (Fig. 21). Similarly, the meniscofemoral ligaments of Humphrey (Fig. 11) and Wrisberg (Fig. 22) may mimic loose bodies or tears in the posterior horn of the lateral meniscus. The space between the periphery of the posterior horn of the lateral meniscus and popliteus tendon may resemble a rupture of the posterior horn of the lateral meniscus. Misinterpretation can be avoided by tracing the suspicious structure on sequential images. The free edge of the meniscus may occasionally demonstrate a wavy or wrinkled shape (Fig. 23). This so-called meniscal flounce most often involves the medial meniscus and is considered a normal variant or a transient physiologic distortion that may vary according to knee position (46). The presence of a meniscal flounce does not increase the likelihood of a meniscal tear (47,48). A potential pitfall in the interpretation of cruciate ligament tears is the ACL or PCL ganglion, which is shown as a focal globular area of fluid signal within or adjacent to the ligament (Fig. 24). Distortion of the ligament may occur due to mass effect. The presence of a focal well-defined collection and the absence of other signs of traumatic injury are key to the correct diagnosis (49).

RECENT DEVELOPMENTS

Similar to those in other body areas, MRI techniques for knee imaging continue to evolve. The introduction of high-field 3.0-T MRI scanners for clinical practice has created new possibilities to image knee lesions with increased signal-to-noise ratio (SNR). This can be invested in shorter scanning time or increased spatial resolution. Recent studies have reported excellent image quality of 3.0-T knee MRI, but some of the studies also conclude that 3.0-T MRI is more prone to magnetic susceptibility artifacts and chemical shift artifacts than 1.5-T imaging (50-53). Further research is needed to assess the advantages of 3.0-T versus 1.5-T MRI, in particular whether better image quality also improves diagnostic performance and patient management. In recent years, there has been great interest in the imaging of articular cartilage. This is mainly because of the introduction of new therapeutic options for chondral defects, such as autologous chondrocyte transplantation, where detailed preoperative evaluation and posttreatment follow-up are important (54,55). MRI imaging of cartilage has been controversial and the reported diagnostic performance of traditional 2D fast spin echo (FSE) and 3D spoiled gradient echo (SPGR) sequences vary. Better results have been reported with novel cartilage-specific pulse se quences, such as 3D SPGR with spatial pulses (SS-SPGR) (56) and 3D steady-state free precession (SSFP) sequences (57,58). Recent studies have shown promising results with cartilage imaging at 3.0 T (59,60), but more research is required before these techniques can be applied in daily clinical practice.

SUMMARY

This review article illustrates that MRI is an effective and accurate technique in the diagnostic workup of traumatic knee abnormalities, and that it is an appropriate screening tool for therapeutic arthroscopy. The MRI interpretation and classification of the most frequently encountered traumatic knee abnormalities were discussed. One should be aware of several pitfalls in the diagnosis of meniscal tears and cruciate ligament tears. Recent advantages in knee MRI mainly focus on 3.0-T imaging and cartilage imaging, but further research in these areas is warranted.

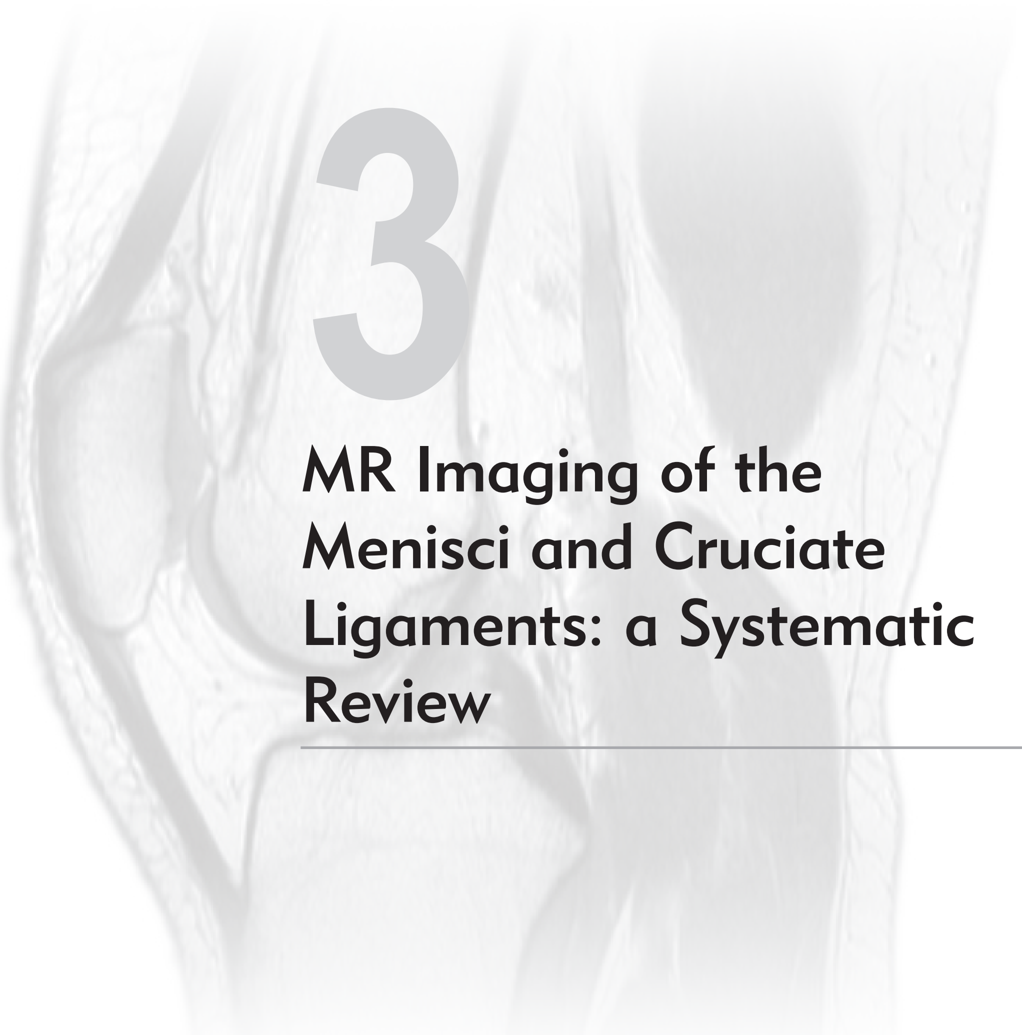
REFERENCES

1 Ruwe PA, Wright J, Randall RL, Lynch JK, Jokl P, McCarthy S. Can MR imaging effectively replace diagnostic arthroscopy? Radiology 183(2): 335-339, 1992.
2 Bui-Mansfield LT, Youngberg RA, Warme W, Pitcher JD, Nguyen PL. Potential cost savings of MR imaging obtained before arthroscopy of the knee: evaluation of 50 consecutive patients. AJR Am J Roentgenol 168(4):913-918, 1997.
3 Vincken PW, Ter Braak BP, Van Erkel AR, et al. Effectiveness of MR imaging in selection of patients for arthroscopy of the knee. Radiology 223(3):739-746, 2002.
4 Vincken PW, Ter Braak AP, Van Erkel AR, et al. MR imaging: effectiveness and costs at triage of patients with nonacute knee symptoms. Radiology 242(1):85-93, 2007.
5 Oei EH, Nikken JJ, Verstijnen AC, Ginai AZ, Hunink MGM. MR imaging of the menisci and cruciate ligaments: a systematic review. Radiology 226(3):837-848, 2003.
6. Fischer SP, Fox JM, Del Pizzo W, Friedman MJ, Snyder SJ, Ferkel RD. Accuracy of diagnoses from magnetic resonance imaging of the knee. A multi-center analysis of one thousand and fourteen patients. J Bone Joint Surg Am 73(1):2-10, 1991.
7. Mackenzie R, Palmer CR, Lomas DJ, Dixon AK. Magnetic resonance imaging of the knee: diagnostic performance studies. Clin Radiol 51(4): 251-257, 1996.
8. Maurer EJ, Kaplan PA, Dussault RG, et al. Acutely injured knee: effect of MR imaging on diagnostic and therapeutic decisions. Radiology 204(3):799-805, 1997.
9. McNally EG, Nasser KN, Dawson S, Goh LA. Role of magnetic resonance imaging in the clinical management of the acutely locked knee. Skeletal Radiol 31(10):570-573, 2002.
10. Nikken JJ, Oei EH, Ginai AZ, et al. Acute peripheral joint injury: cost and effectiveness of low-field-strength MR imaging—results of randomized controlled trial. Radiology 236(3):958-967, 2005.
11. Oei EH, Nikken JJ, Ginai AZ, et al. Acute knee trauma: value of a short dedicated extremity MR imaging examination for prediction of subsequent treatment. Radiology 234(1):125-133, 2005.
12. American College of Radiology (ACR) and the Society of Skeletal Radiology (SSR). Practice Guideline for the Performance and Interpretation of Magnetic Resonance Imaging (MRI) of the Knee, 2005.
13. Cotten A, Delfaut E, Demondion X, et al. MR imaging of the knee at 0.2 and 1.5 T: correlation with surgery. AJR Am J Roentgenol 174(4):1093-1097, 2000.
14. Mellado JM, Ramos A, Salvado E, Camins A, Calmet J, Sauri A. Avulsion fractures and chronic avulsion injuries of the knee: role of MR imaging. Eur Radiol 12(10):2463-2473, 2002.
15. Kode L, Lieberman JM, Motta AO, Wilber JH, Vasen A, Yagan R. Evaluation of tibial plateau fractures: efficacy of MR imaging compared with CT. AJR Am J Roentgenol 163(1):141-147, 1994.

16. Mui LW, Engelsohn E, Umans H. Comparison of CT and MRI in patients with tibial plateau fracture: can CT findings predict ligament tear or meniscal injury? Skeletal Radiol 36(2):145-151, 2007.
17. Yu JS, Goodwin D, Salonen D, et al. Complete dislocation of the knee: spectrum of associated soft-tissue injuries depicted by MR imaging. AJR Am J Roentgenol 164(1):135-139, 1995.
18. Virolainen H, Visuri T, Kuusela T. Acute dislocation of the patella: MR findings. Radiology 189(1):243-246, 1993.
19. Sanders TG, Medynski MA, Feller JF, Lawhorn KW. Bone contusion patterns of the knee at MR imaging: footprint of the mechanism of injury. Radiographics 20:S135-S151, 2000.
20. De Smet AA, Fisher DR, Graf BK, Lange RH. Osteochondritis dissecans of the knee: value of MR imaging in determining lesion stability and the presence of articular cartilage defects. AJR Am J Roentgenol 155(3): 549-553, 1990.
21. Robertson PL, Schweitzer ME, Bartolozzi AR, Ugoni A. Anterior cruciate ligament tears: evaluation of multiple signs with MR imaging. Radiology 193(3):829-834, 1994.
22. Gentili A, Seeger LL, Yao L, Do HM. Anterior cruciate ligament tear: indirect signs at MR imaging. Radiology 193(3):835-840, 1994.
23. Brandser EA, Riley MA, Berbaum KS, el-Khoury GY, Bennett DL. MR imaging of anterior cruciate ligament injury: independent value of primary and secondary signs. AJR Am J Roentgenol 167(1):121-126, 1996.
24. Tung GA, Davis LM, Wiggins ME, Fadale PD. Tears of the anterior cruciate ligament: primary and secondary signs at MR imaging. Radiology 188(3):661-667, 1993.
25. Umans H, Wimpfheimer O, Haramati N, Applbaum YH, Adler M, Bosco J. Diagnosis of partial tears of the anterior cruciate ligament of the knee: value of MR imaging. AJR Am J Roentgenol 165(4):893-897.
26. Kannus P, Bergfeld J, Jarvinen M, et al. Injuries to the posterior cruciate ligament of the knee. Sports Med 12(2):110-131, 1991.
27. Staron RB, Haramati N, Feldman F, et al. O'Donoghue's triad: magnetic resonance imaging evidence. Skeletal Radiol 23(8):633-636, 1994.
28. Miller TT, Gladden P, Staron RB, Henry JH, Feldman F. Posterolateral stabilizers of the knee: anatomy and injuries assessed with MR imaging. AJR Am J Roentgenol 169(6):1641-1647, 1997.
29. Miller TT, Staron RB, Feldman F, Cepel E. Meniscal position on routine MR imaging of the knee. Skeletal Radiol 26(7):424-427, 1997.
30. Crues JV 3rd, Mink J, Levy TL, Lotysch M, Stoller DW. Meniscal tears of the knee: accuracy of MR imaging. Radiology 164(2):445-448, 1987.
31. Reicher MA, Hartzman S, Duckwiler GR, Bassett LW, Anderson LJ, Gold RH. Meniscal injuries: detection using MR imaging. Radiology 159(3):753-757, 1986.

32 Stoller DW, Martin C, Crues JV 3rd, Kaplan L, Mink JH. Meniscal tears: pathologic correlation with MR imaging. Radiology 163(3):731-735, 1987.
33. Boks SS, Vroegindeweij D, Koes BW, Hunink MGM, Bierma-Zeinstra SM. Magnetic resonance imaging abnormalities in symptomatic and contralateral knees: prevalence and associations with traumatic history in general practice. Am J Sports Med 34(12):1984-1991, 2006.
34. Wright DH, De Smet AA, Norris M. Bucket-handle tears of the medial and lateral menisci of the knee: value of MR imaging in detecting displaced fragments. AJR Am J Roentgenol 165(3):621-625, 1995.
35. Dorsay TA, Helms CA. Bucket-handle meniscal tears of the knee: sensitivity and specificity of MRI signs. Skeletal Radiol 32(5):266-272, 2003.
36. Magee TH, Hinson GW. MRI of meniscal bucket-handle tears. Skeletal Radiol 27(9):495-499, 1998.
37. Singson RD, Feldman F, Staron R, Kiernan H. MR imaging of displaced bucket-handle tear of the medial meniscus. AJR Am J Roentgenol 156(1):121-124, 1991.
38. Weiss KL, Morehouse HT, Levy IM. Sagittal MR images of the knee: a low-signal band parallel to the posterior cruciate ligament caused by a displaced bucket-handle tear. AJR Am J Roentgenol 156(1):117-119, 1991.
39. Helms CA, Laorr A, Cannon WD Jr. The absent bow tie sign in bucket-handle tears of the menisci in the knee. AJR Am J Roentgenol 170(1): 57-61, 1998.
40. Watt AJ, Halliday T, Raby N. The value of the absent bow tie sign in MRI of bucket-handle tears. Clin Radiol 55(8):622-626, 2000.
41. Haramati N, Staron RB, Rubin S, Shreck EH, Feldman F, Kiernan H. The flipped meniscus sign. Skeletal Radiol 22(4):273-277, 1993.
42. Silverman JM, Mink JH, Deutsch AL. Discoid menisci of the knee: MR imaging appearance. Radiology 173(2):351-354, 1989.
43. Samoto N, Kozuma M, Tokuhisa T, Kobayashi K. Diagnosis of discoid lateral meniscus of the knee on MR imaging. Magn Reson Imaging 20(1):59-64, 2002.
44. Campbell SE, Sanders TG, Morrison WB. MR imaging of meniscal cysts: incidence, location, and clinical significance. AJR Am J Roentgenol 177(2):409-413, 2001.
45. Tyson LL, Daughters TC Jr, Ryu RK, Crues JV 3rd. MRI appearance of meniscal cysts. Skeletal Radiol 24(6):421-424, 1995.
46. Park JS, Ryu KN, Yoon KH. Meniscal flounce on knee MRI: correlation with meniscal locations after positional changes. AJR Am J Roentgenol 187(2):364-370, 2006.
47. Yu JS, Cosgarea AJ, Kaeding CC, Wilson D. Meniscal flounce MR imaging. Radiology 203(2):513-515, 1997.
48. Kim BH, Seol HY, Jung HS, Cha SH, Park CM, Lim HC. Meniscal flounce on MR: correlation with arthroscopic or surgical findings. Yon-sei Med J 41(4):507-511, 2000.

49. Recht MP, Applegate G, Kaplan P, et al. The MR appearance of cruciate ganglion cysts: a report of 16 cases. Skeletal Radiol 23(8):597-600, 1994.
50. Craig JG, Go L, Blechinger J, et al. Three-tesla imaging of the knee: initial experience. Skeletal Radiol 34(8):453-461, 2005.
51. Magee T, Williams D. 3.0-T MRI of meniscal tears. AJR Am J Roentgenol 187(2):371-375, 2006.
52. Ramnath RR, Magee T, Wasudev N, Murrah R. Accuracy of 3-T MRI using fast spin-echo technique to detect meniscal tears of the knee. AJR Am J Roentgenol 187(1):221-225, 2006.
53. Lutterbey G, Behrends K, Falkenhausen MV, et al. Is the body-coil at 3 Tesla feasible for the MRI evaluation of the painful knee? A comparative study Eur Radiol 17:503-508, 2007.
54. Tins BJ, McCall IW, Takahashi T, et al. Autologous chondrocyte implantation in knee joint: MR imaging and histologic features at 1-year follow-up. Radiology 234(2):501-508, 2005.
55. James SL, Connell DA, Saifuddin A, Skinner JA, Briggs TW. MR imaging of autologous chondrocyte implantation of the knee. Eur Radiol 16(5):1022-1030, 2006.
56. Yoshioka H, Alley M, Steines D, et al. Imaging of the articular cartilage in osteoarthritis of the knee joint: 3D spatial-spectral spoiled gradient-echo vs. fat-suppressed 3D spoiled gradient-echo MR imaging. J Magn Reson Imaging 18(1):66-71, 2003.
57. Reeder SB, Pelc NJ, Alley MT, Gold GE. Rapid MR imaging of articular cartilage with steady-state free precession and multipoint fat-water separation. AJR Am J Roentgenol 180(2):357-362, 2003.
58. Kornaat PR, Reeder SB, Koo S, et al. MR imaging of articular cartilage at 1.5T and 3.0T: comparison of SPGR and SSFP sequences. Osteoarthritis Cartilage 13(4):338-344, 2005.
59. Gold GE, Reeder SB, Yu H, et al. Articular cartilage of the knee: rapid three-dimensional MR imaging at 3.0 T with IDEAL balanced steady-state free precession–initial experience. Radiology 240(2):546-551, 2006.
60. Kornaat PR, Koo S, Andriacchi TP, Bloem JL, Gold GE. Comparison of quantitative cartilage measurements acquired on two 3.0T MRI systems from different manufacturers. J Magn Reson Imaging 23(5):770-773, 2006.



3

MR Imaging of the Menisci and Cruciate Ligaments: a Systematic Review

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Radiology 2003;226(3):837-48

ABSTRACT

PURPOSE: To systematically review and synthesize published data on the diagnostic performance of magnetic resonance (MR) imaging of the menisci and cruciate ligaments and to assess the effect of study design characteristics and magnetic field strength on diagnostic performance.

MATERIALS AND METHODS: Articles published between 1991 and 2000 were included if at least 30 patients were studied, arthroscopy was the reference standard, the magnetic field strength was reported, positivity criteria were defined, and the absolute numbers of true-positive, false-negative, true-negative, and false-positive results were available or derivable. Pooled weighted and summary receiver operating characteristic (ROC) analyses were performed for tears of both menisci and both cruciate ligaments separately and for the four lesions combined, by using random effects models. Differences were assessed according to lesion type.

RESULTS: Twenty-nine of 120 retrieved articles were included. Pooled weighted sensitivity was higher for medial meniscal tears than that for lateral meniscal tears. However, pooled weighted specificity for the medial meniscus was lower than that for the lateral meniscus. In summary ROC analyses performed per lesion, various study design characteristics were found to influence diagnostic performance. Higher magnetic field strength significantly improved discriminatory power only for anterior cruciate ligament tears. When all lesions were combined in one overall summary ROC analysis, magnetic field strength was a significant but modest predictor of diagnostic performance.

CONCLUSION: Diagnostic performance of MR imaging of the knee is different according to lesion type and is influenced by various study design characteristics. Higher magnetic field strength modestly improves diagnostic performance, but a significant effect was demonstrated only for anterior cruciate ligament tears.

INTRODUCTION

Since its introduction for clinical use in the mid-1980s, the role of magnetic resonance (MR) imaging in the diagnosis of knee lesions has been established. MR imaging has proved reliable and safe and offers advantages over diagnostic arthroscopy, which is currently regarded as the reference standard for the diagnosis of internal derangements of the knee. Arthroscopy is an invasive procedure with certain risks and discomfort for the patient and is preferably performed only for treatment purposes, provided that alternative noninvasive diagnostic modalities such as MR imaging are available (1,2).

Results of numerous diagnostic studies have been published in which MR imaging and arthroscopy of the knee were compared, and most have shown good diagnostic performance in detecting lesions of the menisci and cruciate ligaments. As a result, MR imaging has been increasingly used in the diagnostic work-up of knee lesions, but the high costs of purchasing and maintaining a high-field-strength MR imager and the often limited availability of such a unit has restricted its widespread use for this purpose. The use of middle- and low-field-strength MR imagers has created the possibility of using MR imaging more routinely in the diagnostic work-up of knee disorders at a lower cost. In addition, low-field-strength dedicated extremity MR imagers have been designed specifically for extremity imaging, and because of their compact size and low field strength, costs can be kept relatively low compared with those of middle- and high-field-strength imagers. The reported diagnostic performance of low-field-strength MR imaging is variable, however, which raises the question of whether low-field-strength MR imaging can reliably replace middle- and high-field-strength MR imaging for evaluation of knee lesions.

With the vast number of articles on MR imaging of knee lesions with a wide range in study design, imaging techniques, and results, it is difficult to get a good idea of the diagnostic performance of MR imaging and the factors that influence its accuracy. We found some limited review articles in which investigators attempted to summarize published results of MR imaging of the knee (2,3). To our knowledge, however, no systematic review with a meta-analysis of the diagnostic performance of MR imaging of the knee has been published to date.

The purpose of this study was to systematically review and synthesize the published data on the diagnostic performance of MR imaging of the knee, focusing on tears of the menisci and cruciate ligaments, and to assess the effect of study design characteristics and magnetic field strength on diagnostic performance. We followed published guidelines for conducting diagnostic meta-analyses (4).

MATERIALS AND METHODS

Selection of Articles

We conducted a MEDLINE search of the English-language literature to identify original articles published between January 1991 and December 2000 on the diagnostic performance of MR imaging of knee lesions. Combinations of the following search terms were used: "magnetic resonance imaging," "knee," "meniscus," "cruciate ligament," and "arthroscopy." All articles that could not be excluded definitively on the basis of the title and abstract were retrieved in full text. We used the criteria for inclusion and exclusion listed in Table 1.

The bibliographies of the original articles were screened to obtain additional references. For the articles that were excluded because absolute numbers or positivity criteria were lacking, we tried to contact the corresponding author to request additional information. Authors were also contacted if there were indications that in more than one article, they reported on overlapping patient populations. If the authors did not respond, we chose the article that provided the most unequivocal and clear data.

Data Extraction

Two authors (E.H.G.O., A.C.M.V.) independently extracted results and characteristics of the study and MR imaging technique for each included article. For this purpose, a standardized data extraction sheet was used. Readers were not blinded to information about the authors, author affiliation, and journal name, since this has been shown to be unnecessary (5). The extracted study characteristics included publication year, country of origin, setting (academic or com-

Table 1. Criteria for inclusion and exclusion of articles

Criteria Type	Criteria
Inclusion	Articles in the English language
	MR imaging used to depict lesions of the medial or lateral meniscus, ACL, or PCL
	At least 30 patients examined
	Findings at arthroscopy used as reference standard
	Magnetic field strength reported
	Positivity criteria for MR imaging defined
	Absolute numbers of true-positive, false-negative, true-negative, and false-positive results available or derivable
Exclusion	Patient population explicitly stated to consist of infants or adolescents
	MR imaging used for postoperative evaluation
	Case-control study
	Results reported for only the medial and lateral meniscus
	Various magnetic field strengths used
	Only the diagnostic value of specific features and indirect signs of knee lesions at MR imaging, such as the empty notch sign, anterior tibial subluxation, or bone bruise, assessed

munity hospital), patient characteristics, and aspects of study design, such as prospective versus retrospective design, inclusion of consecutive patients, and blinding. We also assessed the possibility of verification bias, which arises if patients are selected to undergo the reference test (arthroscopy) on the basis of the outcome of the test being evaluated (MR imaging), giving rise to an overestimation of sensitivity and an underestimation of specificity (6).

Three levels of likelihood were used to classify each study with respect to verification bias. We used "yes" if MR imaging was clearly used as a screening tool for arthroscopy. The category "possible" was assigned if, for unknown or unreported reasons, not all patients underwent both MR imaging and arthroscopy. We assumed that verification bias was absent if both MR imaging and arthroscopy were performed in all consecutive patients that were included in the study. Regarding the characteristics of MR imaging technique, we extracted the magnetic field strength of the MR imager and the number and type of MR imaging sequences.

From the articles in which investigators tabulated the results for different readers, we extracted the data of the first reader, unless the level of experience was explicitly stated to be different among the readers. In the latter case, we extracted the results of the most experienced reader. If results were tabulated for multiple observations per reader, we extracted the data of the first observation. Some articles reported separately the results obtained with multiple MR imagers, which we treated as individual studies if the MR imagers had different magnetic field strengths. If results were reported for multiple MR imaging sequences or techniques with the same MR imager, we extracted the data of the technique that was recommended by the authors.

All discrepancies between our two data extractors were recorded. To determine the level of agreement, κ statistics were calculated for categorical variables, and Spearman correlation coefficients (r values) were calculated for continuous variables. To resolve discrepancies, a third data extractor (J.J.N.) assessed all discrepant items, and the majority opinion was used for analysis.

Data Analysis

Calculation of the natural logarithm of the diagnostic odds ratio.—For every lesion in each study, we calculated the natural logarithm of the diagnostic odds ratio (OR) (D), which represents a summary measure of the diagnostic performance or discriminatory power. This value is the measure of interest in summary receiver operating characteristic (ROC) analyses and is calculated as follows: $D = \ln\{[(TP + 0.5)(TN + 0.5)]/[(FP + 0.5)(FN + 0.5)]\}$, where TP is the true-positive value, TN is the true-negative value, FP is the false-positive value, and FN is the false-negative value. Before calculating D, we first added 0.5 to each value to avoid undefined values of D and its variance resulting from zero values of each (7).

Assessment of publication bias.—We first evaluated the presence of publication bias, which could potentially arise if studies with positive results are more likely to be published than are those with negative results (8). Publication bias can be detected by constructing a funnel plot, in which the number of units measured (the number of knees) is plotted against the measure of interest (in our case, the natural logarithm of the diagnostic OR). In the absence of publication bias, the funnel plot shows a symmetric funnel-shaped distribution, whereas the distribution is asymmetric and skewed if publication bias is involved (9). Symmetry and shape of the funnel plots were judged by means of visual inspection.

Pooled weighted analyses.—To obtain a crude estimate of diagnostic performance of MR imaging in depicting tears of the medial and lateral menisci, anterior crutiate ligaments (ACLs), and posterior cruciate ligaments (PCLs), we performed a pooled weighted analysis per lesion, weighting with the reciprocal of the variance of each study. First, we tested for heterogeneity in effect size among studies, the result of which determines if a fixed or random effects model should be used (10,11). Pooled weighted sensitivity, specificity, and natural logarithm of the diagnostic OR (and 95% CIs) were then calculated by using a random effects model. We regarded two estimates as significantly different if their 95% CIs did not overlap.

Next, pooled weighted analyses for the different lesions were performed for various categories of magnetic field strength separately to obtain an idea of the influence of magnetic field strength on diagnostic performance. The range of field strengths was divided into either three categories (higher than 1.0 T, 0.5–1.0 T, or lower than 0.5 T) or two categories (1.0 T and higher vs lower than 1.0 T).

Summary ROC Analysis per Lesion Type

We subsequently performed summary ROC analysis for each of the lesions separately, which has advantages over pooled weighted analysis. First, the true- and false-positive rates for the different diagnostic studies can be summarized and synthesized, with adjustment for different positivity criteria among studies (12–14). Different positivity criteria exist among studies when institutions use different thresholds for labeling a test result as positive. For example, in one study, an area of high signal intensity in the course of the cruciate ligament may be considered indicative of a rupture, whereas in another study, investigators may require the absence of intact cruciate ligament margins as an additional finding before labeling the test result positive. Second, by using summary ROC analysis, one can identify and adjust for variables that have an influence on diagnostic performance. We applied a random effects model, which accounted for the residual interstudy heterogeneity, which may be present even after adjustment for characteristics such as population size, patient age and sex, positivity criteria, type of MR imager, or verification bias. A random effects regression model was developed in which the natural logarithm of the diagnostic OR of each study was the dependent variable. As the independent variable, a measure of the positivity criteria (S) of the study was calculated as follows: $S = \ln\{[(TP + 0.5)(FP + 0.5)]/[(TN + 0.5)(FN + 0.5)]\}$, where TP is the true-positive value, FP is the false-positive value, TN is the true-negative value, and FN is the false-negative value. We added 0.5 to each value as before to prevent undefined values of the positivity criteria. By using this method, one adjusts for the variations in positivity criteria that are used implicitly or explicitly in different studies and that are assumed to influence diagnostic performance.

Other variables that influence diagnostic performance were identified by adding them to the regression model and by assessing their regression coefficient and influence on the model. The variable, depending on the type, can be included either directly as a continuous variable or as a dummy variable. In this bivariate summary ROC analysis, we considered variables as explanatory if they were statistically significant in the regression model ($P < .05$) or if the regression coefficient was at least 1.0 for dummy variables or 1.0 over the range of the variable values. Variables with a P value between .05 and .10 were retained in the model if their inclusion decreased the method-of-moments τ^2 estimate by at least 10% compared with that in the univariate model. The method-of-moments τ^2 calculation provides a measure of between-study variance and is higher if there is more heterogeneity among studies and zero if studies are homogeneous.

We assessed as potential predictors of diagnostic performance the effect of publication year (continuous variable), country of origin (in North America vs other), type of hospital (academic, community, or not reported), mean age (continuous variable, 35 years or older vs younger than 35 years), inclusion of consecutive patients (yes, no, or not reported), prospective versus retrospective study design, verification bias (yes, no, or possible), blinding of the arthroscopist to the MR imaging result (yes, no, or not reported), magnetic field strength of the MR imager (continuous variable, 1.5 T vs lower than 1.5 T), and number of MR sequences used (continuous variable). In five articles, mean age was not reported, and in the analyses in which mean age was examined, regression analysis was performed for the subset of studies with age available. In all studies, the radiologist was blinded to the arthroscopic findings because MR imaging was always performed prior to arthroscopy. Therefore, only the effect of blinding of the arthroscopist was assessed in this study.

Subsequently, we performed multivariate summary ROC analysis, in which the explanatory variables previously identified in the bivariate analysis were included one by one in a stepwise forward-selection regression model. We started with the variable that decreased the method-of-moments τ^2 estimate the most and kept it in the model on the basis of the same criteria as those used in the bivariate summary ROC analysis. We always retained the measure of positivity criteria (S) in the model, since a difference in positivity criteria among studies is a key concept of summary ROC analysis. Even though the positivity criteria as defined in the articles seemed largely the same, interpretation of MR images of the knee may vary in subtle ways in different hospitals and among different radiologists.

This yielded the final model for each lesion from which multivariate summary ROC curves were plotted, adjusted for significant covariables that were set to the mean values or values indicating the ideal study design, as appropriate.

Overall Summary ROC Analysis of All Lesions

For the purpose of increasing statistical power and precision and comparing the results with those of the separate analyses per lesion, we also analyzed all four lesions in a single model. To compare diagnostic performance among lesion types, we created dummy variables to code if the lesion of interest was a meniscal versus cruciate ligament tear.

The effect of each significant predictor in the final models is reflected by its regression coefficient. A positive regression coefficient indicates better discriminatory power of MR imaging in studies with that predictor, compared with that in studies without the corresponding characteristic. A negative regression coefficient indicates reduced diagnostic performance in studies with that characteristic. Finally, we calculated relative diagnostic ORs of all predictors in the multivariate models by taking the antilogarithm of the regression coefficient. A relative diagnostic OR can be interpreted as the diagnostic performance of a test in studies with a certain characteristic, relative to its performance in studies without that corresponding feature. Thus, a relative diagnostic OR greater than 1.0 indicates that studies with that characteristic yield better diagnostic performance of MR imaging than that in studies without the corresponding feature, whereas a relative diagnostic OR less than 1.0 indicates reduced discriminatory power in studies with that characteristic. All analyses were performed by using STATA (versions 6.0 and 7.0; Stata, College Station, Tex) and SPSS for Windows (version 9.0.0; SPSS, Chicago, Ill) software.

Sensitivity Analyses

To assess the dependence of the five final multivariate models on the results of individual studies, we performed the jackknife type of sensitivity analyses for each model. By using this method, one can determine the contribution of the individual studies to the overall results by performing multiple summary ROC analyses with each article excluded in turn (the jackknife method).

RESULTS

Literature Search and Data Extraction

Our MEDLINE search resulted in 804 articles, of which 120 were retrieved after we evaluated the titles and abstracts. Eighty-nine articles were excluded because (a) the article was a review or descriptive article without original data on diagnostic perfor-

Table 2. Characteristics of included studies

Study	Publication year	Country of origin	Hospital type	Study type	Blinding	Verification bias	Consecutive patients	Mean age (y)
Boeree et al (25)	1991	UK	Community	Retrospective	NR	Yes	NR	34
Fischer et al (26)	1991	USA	NR	NR	NR	Yes	NR	37
Kelly et al (27)	1991	USA	Community	Retrospective	NR	Possible	NR	37
Niitsu et al (28)	1991	Japan	Academic	NR	NR	No	NR	25
Araki et al (29)	1992	Japan	NR	NR	NR	Yes	Yes	31
Gluckert et al (30)	1992	Germany	Academic	Prospective	NR	No	NR	33
Grevitt et al (31)	1992	UK	Community	Prospective	Yes	No	Yes	36
Gross et al (32)	1992	USA	Academic	Retrospective	NR	Yes	Yes	NR
Heron and Calvert (33)	1992	UK	Community	Prospective	No *	Yes	No	38
Barnett (34)	1993	USA	Community	Retrospective	NR	Yes	Yes	NR
De Smet et al (35)	1993	USA	Academic	Retrospective	NR	Yes	Yes	29
Chan et al (36)	1994	USA	Academic	Retrospective	NR	Possible	Yes	37
Gentili et al (37)	1994	USA	NR	Retrospective	NR	Possible	Yes	31
Kinnunen et al (38)	1994	Finland	Academic	Prospective	Yes	No	Yes	36
LaPrade et al (39)	1994	USA	Academic	Prospective	NR	No	NR	34
Chen et al (40)	1995	Taiwan	Academic	Retrospective	NR	Possible	NR	NR
Justice and Quinn (41)	1995	USA	NR	Prospective	No	Possible	Yes	NR
Lerman et al (42)	1995	USA	NR	Retrospective	NR	Yes	NR	37
Barry et al (43)	1996	USA	Academic	Retrospective	NR	Possible	NR	29.7
Lundberg et al (44)	1996	Sweden	Academic	Prospective	No	No	Yes	26
Riel et al (45)	1996	Germany	Academic	Prospective	NR	No	NR	36
Bui-Mansfield et al (46)	1997	USA	Community	Prospective	No	No	Yes	31
Cheung et al (47)	1997	USA	Academic	Retrospective	NR	Possible	No	38
Franklin et al (48)	1997	USA	NR	Prospective	Yes	No	Yes	40
Rappeport et al (49)	1997	Denmark	Academic	Prospective	Yes	No	NR	NR
Weinstabl et al (50)	1997	Austria	Academic	Prospective	NR	Yes	Yes	34.9
Ha et al (51)	1998	USA	Academic	Retrospective	NR	Possible	NR	40
Cotten et al (52)	2000	France	Community	Prospective	NR	Possible	NR	34
Elvenes et al (53)	2000	Norway	Academic	NR	NR	Possible	NR	32

Note: NR = not reported.
Number in parentheses is the reference number.
* No in 85 patients, yes in 15 patients.

mance (n = 20), (b) fewer than 30 patients were studied (n = 9), (c) magnetic field strength was not reported or was variable (n = 13), (d) absolute numbers were not available and could not be derived (n = 19), (e) no positivity criteria at MR imaging were reported (n = 3), (f) results were reported for the medial and lateral meniscus combined (n = 6), (g) only the value of specific indirect signs or features of knee lesions at MR imag-

Table 3. MR imaging technique and characteristics of included studies: medial meniscal tears

Study	Publication year	Magnetic field strength (T)	No. of sequences	No. of patients	TP	FP	TN	FN
Medial meniscal tear								
Boeree et al (25)	1991	0.5	2	129	58	6	63	2
Fischer et al (26)	1991	1.5	3	483	270	33	170	10
Fischer et al (26)	1991	0.35	3	177	70	11	83	13
Fischer et al (26)	1991	1.5	3	86	37	2	45	2
Fischer et al (26)	1991	0.6	3	373	32	9	27	5
Fischer et al (26)	1991	0.35	3	36	8	11	15	2
Kelly et al (27)	1991	0.5	3	60	33	6	20	1
Araki et al (29)	1992	1.5	1	40	19	2	18	1
Gluckert et al (30)	1992	1.5	1	80	34	3	42	1
Grevitt et al (31)	1992	0.2	2	55	23	3	27	2
Heron and Calvert (33)	1992	1.5	3	100	44	3	52	1
Barnett (34)	1993	0.5	6	118	71	4	38	5
De Smet et al (35)	1993	1.5	2	200	100	13	79	8
Kinnunen et al (38)	1994	0.1	3	33	7	5	20	1
LaPrade et al (39)	1994	1.0	5	72	34	1	37	0
Chen et al (40)	1995	1.5	6	50	13	5	30	2
Justice and Quinn (41)	1995	1.5	4	561	360	16	170	15
Lundberg et al (44)	1996	1.5	3	69	14	17	33	5
Riel et al (45)	1996	0.2	6	244	106	3	127	8
Bui-Mansfield et al (46)	1997	1.5	4	50	18	1	29	2
Cheung et al (47)	1997	1.5	5	289	127	23	123	16
Franklin et al (48)	1997	0.2	6	35	19	0	13	3
Rappeport et al (49)	1997	0.1	3	47	12	9	24	2
Weinstabl et al (50)	1997	1.5	2	75	48	4	22	1
Cotten et al (52)	2000	0.2	4	90	50	0	33	7
Cotten et al (52)	2000	1.5	4	90	51	0	33	6
Elvenes et al (53)	2000	0.5	2	41	15	6	20	0

Note: Data are number of patients, unless otherwise indicated. TP = true-positive value, FP = false-positive value, TN = true-negative value, FN = false-negative value.

ing was assessed (n = 15), or (h) the patient population was suspected to overlap with that of another study (n = 4). Furthermore, we excluded one article in which patients and random control subjects were retrospectively selected on the basis of the presence or absence of a definite complete ACL tear (case-control design) without accounting for all patients in the study period (15). Another article was excluded in which the whole knee was used as the unit of analysis (16). All excluded articles, together with the

Table 4. MR imaging technique and characteristics of included studies: lateral meniscal tears

Study	Publication year	Magnetic field strength (T)	No. of sequences	No. of patients	TP	FP	TN	FN
Lateral meniscal tear								
Boeree et al (25)	1991	0.5	2	127	25	2	99	1
Fischer et al (26)	1991	1.5	3	513	81	20	378	34
Fischer et al (26)	1991	0.35	3	192	20	5	148	19
Fischer et al (26)	1991	1.5	3	89	18	3	66	2
Fischer et al (26)	1991	0.6	3	77	9	8	55	5
Fischer et al (26)	1991	0.35	3	36	6	2	27	1
Kelly et al (27)	1991	0.5	3	60	19	5	34	2
Araki et al (29)	1992	1.5	1	40	13	0	27	0
Gluckert et al (30)	1992	1.5	1	80	12	0	68	0
Grevitt et al (31)	1992	0.2	2	55	8	1	45	1
Heron and Calvert (33)	1992	1.5	3	100	17	5	77	1
Barnett (34)	1993	0.5	6	118	21	3	89	5
De Smet et al (35)	1993	1.5	2	200	48	12	130	10
Kinnunen et al (38)	1994	0.1	3	33	1	1	28	3
LaPrade et al (39)	1994	1.0	5	72	14	1	51	6
Chen et al (40)	1995	1.5	6	50	17	3	27	3
Justice and Quinn (41)	1995	1.5	4	561	134	8	390	29
Lundberg et al (44)	1996	1.5	3	69	13	7	36	13
Riel et al (45)	1996	0.2	6	244	38	7	191	8
Bui-Mansfield et al (46)	1997	1.5	4	50	9	0	35	6
Cheung et al (47)	1997	1.5	5	289	69	13	180	27
Franklin et al (48)	1997	0.2	6	35	8	0	26	1
Rappeport et al (49)	1997	0.1	3	47	2	1	41	3
Weinstabl et al (50)	1997	1.5	2	75	17	1	56	1
Cotten et al (52)	2000	0.2	4	90	24	6	55	5
Cotten et al (52)	2000	1.5	4	90	25	3	58	4
Elvenes et al (53)	2000	0.5	2	41	2	4	32	3

Note: Data are number of patients, unless otherwise indicated. TP = true-positive value, FP = false-positive value, TN = true-negative value, FN = false-negative value.

reasons for exclusion, are listed in the table that is available as supplemental material on the Radiology website (Table E1, radiology.rsnajnls.org/cgi/content/full/2263011892/DC1). In this table, each article is classified according to the reason why the article was excluded from our analysis, although multiple reasons may be applicable to one article. We attempted to contact 16 authors for more information, but this did not result in additional articles for inclusion. Thus, 29 articles were included in this meta-analysis,

Table 5. MR imaging technique and characteristics of included studies: cruciate ligament tears

Type of tear	Publication year	Magnetic field strength (T)	No. of sequences	No. of patients	TP	FP	TN	FN
ACL complete tear								
Boeree et al (25)	1991	0.5	2	133	32	11	89	1
Fischer et al (26)	1991	1.5	3	530	100	30	396	4
Fischer et al (26)	1991	0.35	3	193	28	8	157	0
Fischer et al (26)	1991	1.5	3	90	17	3	70	0
Fischer et al (26)	1991	0.6	3	79	13	5	56	5
Fischer et al (26)	1991	0.35	3	41	5	7	27	2
Kelly et al (27)	1991	0.5	3	60	7	3	49	1
Niitsu et al (28)	1991	1.5	1	52	20	3	21	8
Gluckert et al (30)	1992	1.5	1	80	18	1	60	1
Grevitt et al (31)	1992	0.2	2	55	8	4	43	0
Heron and Calvert (33)	1992	1.5	3	99	20	4	73	2
Barnett (34)	1993	0.5	6	118	26	3	89	0
Chan et al (36)	1994	1.5	4	120	19	6	93	2
Gentili et al (37)	1994	1.5	4	89	48	1	39	1
Kinnunen et al (38)	1994	0.1	3	33	5	4	23	1
Chen et al (40)	1995	1.5	6	50	22	3	24	1
Lerman et al (42)	1995	1.5	1	47	23	0	22	2
Barry et al (43)	1996	0.3	4	63	25	4	31	3
Bui-Mansfield et al (46)	1997	1.5	4	50	20	3	27	0
Rappeport et al (49)	1997	0.1	3	47	6	3	37	1
Ha et al (51)	1998	1.5	5	217	54	4	157	2
Cotten et al (52)	2000	0.2	4	90	14	2	73	1
Cotten et al (52)	2000	1.5	4	90	14	0	75	1
PCL complete tear								
Fischer et al (26)	1991	1.5	3	537	2	3	530	2
Fischer et al (26)	1991	0.35	3	198	3	0	195	0
Fischer et al (26)	1991	1.5	3	93	2	1	90	0
Fischer et al (26)	1991	0.6	3	80	1	0	79	0
Fischer et al (26)	1991	0.35	3	41	0	1	40	0
Niitsu et al (28)	1991	1.5	1	52	4	1	47	0
Gluckert et al (30)	1992	1.5	1	80	0	0	80	0
Gross et al (32)	1992	0.3	1	203	13	0	190	0
Heron and Calvert (33)	1992	1.5	3	99	1	0	98	0
Kinnunen et al (38)	1994	0.1	3	33	0	1	32	0
Chen et al (40)	1995	1.5	6	50	4	0	46	0
Bui-Mansfield et al (46)	1997	1.5	4	50	1	8	41	0

Note: Data are number of patients, unless otherwise indicated. TP = true-positive value, FP = false-positive value, TN = true-negative value, FN = false-negative value.

which comprised 27 studies on both menisci, 23 studies on ACL tears, and 12 studies on PCL tears. The articles, together with the corresponding study characteristics, are listed in Table 2. Results for the menisci and cruciate ligaments per study, as well as features of the MR imaging technique, are listed in Tables 3–5. We extracted 379 items from the articles; 46 discrepancies occurred between our two data extractors (Table 6), which were resolved by the third extractor. Depending on the variable, agreement between the two data extractors ranged from moderate to almost perfect (r value range, 0.80–1.00; κ value range, 0.54–1.00).

Table 6. Analyzed variables and measures of agreement between two data extractors for 379 items in 29 articles

Variable	No. of discrepancies *	Spearman r value	κ value
Publication year	0 (0)	1.00	NA
Country of origin	0 (0)	NA	1.00
Academic or community hospital	5 (17)	NA	0.70
Mean age	0 (0)	1.00	NA
Consecutive patients	8 (28)	NA	0.54
Prospective or retrospective study design	6 (21)	NA	0.67
Verification bias	8 (28)	NA	0.59
Blinding of arthroscopist to MR imaging findings	4 (14)	NA	0.71
Magnetic field strength	0 (0)	1.00	NA
Number of pulse sequences	8 (28)	0.80	NA
Natural logarithm of diagnostic OR	7 (8)	0.96	NA
Overall	46 (12)	NA	NA

Note: The Spearman r value was calculated for continuous variables; the κ value for categoric variables. NA = not applicable.
* Numbers in parentheses are percentages.

Publication Bias

At visual inspection, the funnel plots for the menisci showed an almost perfectly funnel-shaped distribution (Fig 1), suggesting that

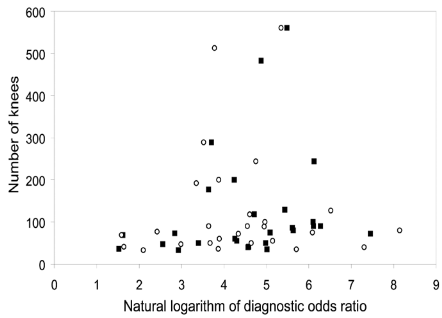


Figure 1. Funnel plot for the menisci in which the number of knees is plotted against the discriminatory power of MR imaging (natural logarithm of the diagnostic OR). For both medial and lateral menisci, the distribution of data points appears to be fairly funnel shaped and symmetric, indicating that publication bias is unlikely. ■ = results for medial meniscus from individual studies, ◯ = results for lateral meniscus from individual studies.

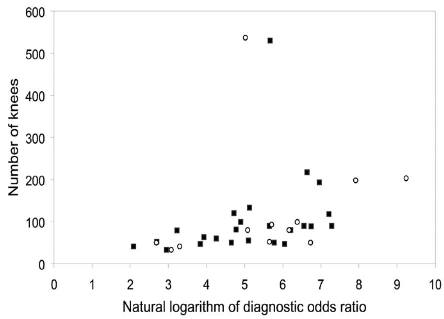


Figure 2. Funnel plot for the cruciate ligaments in which the number of knees is plotted against the discriminatory power of MR imaging (natural logarithm of the diagnostic OR). For both ACL and PCL lesions, the data points show a slightly skewed distribution. There is a considerable number of small studies with low diagnostic performance, however, suggesting the absence of substantial publication bias. ■ = ACL results from individual studies, ◯ = PCL results from individual studies.

publication bias is unlikely. For both cruciate ligaments, the funnel plots were almost funnel shaped, although not perfectly so (Fig 2), but there were sufficient small studies with a low diagnostic performance to suggest the absence of substantial publication bias.

Pooled Weighted Analysis

The test for heterogeneity showed significant results for all lesions, with the exception of PCL tears. We therefore used a random effects model, which can accommodate both heterogeneous and homogeneous effect sizes among studies (10,11). For the diagnosis of meniscal tears (Table 7), pooled weighted sensitivity was higher for the medial meniscus (93.3% [95% CI: 91.7, 95.0]) than that for the lateral meniscus (79.3% [95% CI: 74.3, 84.2]), whereas pooled weighted specificity for medial meniscal tears (88.4% [95% CI: 85.4, 91.4]) was lower than that for lateral meniscal tears (95.7% [95% CI: 94.6, 96.8]). There was no statistically significant difference in sensitivity for complete ACL tears versus PCL tears (Table 7) (94.4% [95% CI: 92.3, 96.6] and 91.0% [95% CI: 83.2, 98.7], respectively), but the specificity for ACL tears was lower than that for PCL tears (94.3% [95% CI: 92.7, 95.9] and 99.4% [95% CI: 98.9, 99.9], respectively).

No significant difference was demonstrated in the pooled natural logarithms of the diagnostic ORs for the different lesions.

The results of the separate pooled weighted analyses for various categories of magnetic field strengths (not tabulated) suggested a modest trend toward better diagnostic performance for higher-field-strength categories. None of the differences were found to approach statistical significance, however, and the CIs were all extremely wide because of a limited number of studies per category of magnetic field strength.

Summary ROC Analysis per Type of Lesion

In the multivariate summary ROC analysis for the medial meniscus, blinding of the arthroscopist was the only predictor of diagnostic performance. For the lateral meniscus, mean age was the only significant variable in the final model (Table 8). Publication year, mean age, and magnetic field strength were predictors in the multivariate model for ACL tears. The final model for PCL tears consisted of publication year, academic hospital setting, verification bias, and number of MR sequences.

Table 7. Pooled weighted results per type of lesion (random effects model)

Lesion	Pooled weighted sensitivity (%)	Pooled weighted specificity (%)	Pooled weighted D* value
Medial meniscal tear	93.3 (91.7, 95.0)	88.4 (85.4, 91.4)	4.38 (3.86, 4.89)
Lateral meniscal tear	79.3 (74.3, 84.2)	95.7 (94.6, 96.8)	4.07 (3.60, 4.54)
ACL complete tear	94.4 (92.3, 96.6)	94.3 (92.7, 95.9)	4.90 (4.28, 5.53)
PCL complete tear	91.0 (83.2, 98.7)	99.4 (98.9, 99.9)	5.42 (4.40, 6.45)

Note: Numbers in parentheses are 95% CIs.
* D = natural logarithm of the diagnostic OR.

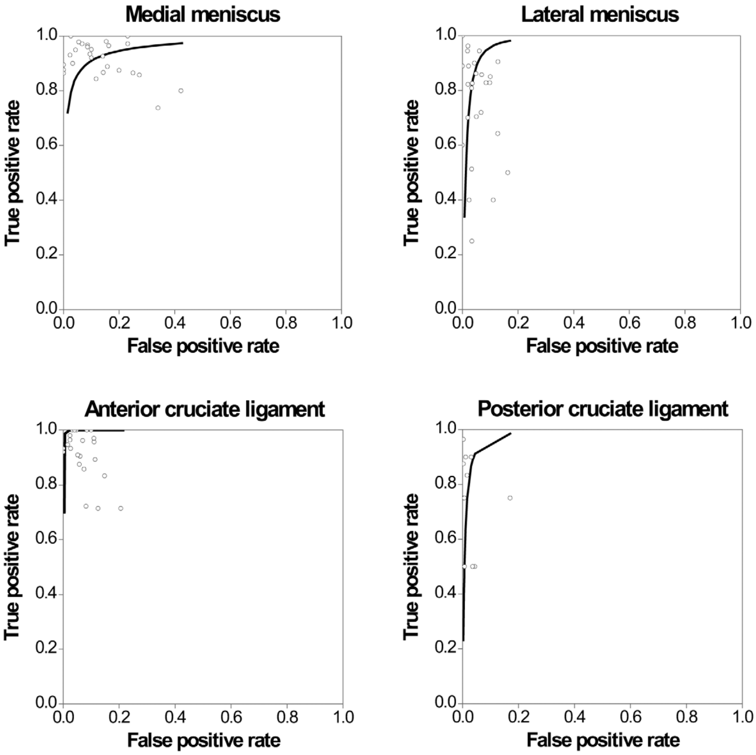


Figure 3. Summary ROC curves for the four types of lesions separately and the results of the individual studies (O) on the basis of the final models per lesion. Upper left: Summary ROC curve for medial meniscal tears. The dummy variable for blinding was set to zero, according to clinical practice, in which MR imaging is ideally performed before arthroscopy. Upper right: Summary ROC curve for lateral meniscal tears, adjusted to a patient aged 30 years. Lower left: Summary ROC curve for ACL tears, adjusted to publication in 1995, a patient aged 30 years, and a 1.0-T MR imager. Lower right: Summary ROC curve for PCL tears, adjusted for publication in 1995, academic hospital setting, three MR sequences in the imaging protocol, and absence of verification bias. The adjusted summary ROC curves demonstrate the differences in diagnostic performance among the lesion types. Whereas overall discriminatory power is not much different for the menisci, diagnostic performance is clearly better for the ACL compared with that for the PCL.

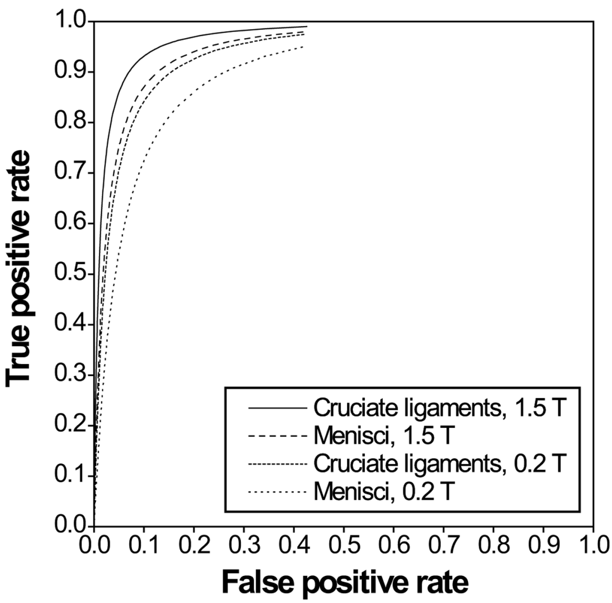


Figure 4. Multivariate summary ROC curves based on the final regression model with all lesions combined. Curves are shown for both menisci and both cruciate ligaments combined. Curves were adjusted to patients aged 30 years and both 0.2- and 1.5-T MR imagers. The curves for cruciate ligaments are further up toward the upper left corner, as are the curves for high-field-strength MR imaging, suggesting better discriminatory power compared with that of the menisci and low-field-strength MR imaging.

Table 8. Multivariable summary ROC models per type of lesion and for all lesions combined (random effects model)

Covariable	Regression coefficient	Relative diagnostic OR	P value	Method-of-Moments τ^2
Medial meniscal tear (27 studies)				
Positivity criteria	-0.32 (-0.87, 0.23)	0.73 (0.42, 1.26)	0.25	1.22
Blinding arthroscopist to MR imaging findings	-1.09 (-2.68, 0.50)	0.34 (0.07, 1.65)	0.18	NA
Lateral meniscal tear (23 studies) *				
Positivity criteria	0.39 (-0.12, 0.90)	1.48 (0.89, 2.46)	0.14	0.69
Mean age	0.11 (-0.04, 0.25)†	1.12 (0.96, 1.28)	0.14	NA
ACL complete tear (20 studies) ‡				
Positivity criteria	0.64 (0.10, 1.18)	1.90 (1.11, 3.25)	0.02	0.18
Publication year	0.25 (0.08, 0.41)†	1.28 (1.08, 1.51)	0.004	NA
Mean age	0.12 (0.00, 0.24)†	1.13 (1.00, 1.27)	0.05	NA
Magnetic field strength	1.21 (0.40, 2.02)§	3.35 (1.49, 7.54)	0.003	NA
PCL complete tear (12 studies)				
Positivity criteria	0.22 (-0.72, 1.16)	1.25 (0.49, 3.19)	0.64	0.00
Publication year	0.21 (-0.92, 1.34)†	1.23 (0.40, 3.82)	0.72	NA
Academic hospital	1.89 (-0.68, 4.46)	6.62 (0.51, 86)	0.15	NA
Verification bias	4.23 (0.28, 8.18)	68.72 (1.32, 3569)	0.04	NA
Number of MR sequences	-0.75 (-2.28, 0.78)‖	0.47 (0.10, 2.18)	0.34	NA
All lesions combined (76 studies) #				
Positivity criteria	0.06 (-0.15, 0.28)	1.06 (0.86, 1.32)	0.56	0.87
Meniscus vs. cruciate ligament	-0.66 (-1.33, 0.01)	0.52 (0.26, 1.01)	0.05	NA
Mean age	0.12 (0.03, 0.21)†	1.13 (1.03, 1.23)	0.009	NA
Magnetic field strength	0.68 (0.12, 1.23)§	1.97 (1.13, 3.42)	0.02	NA

Note:
Numbers in parentheses are 95% CIs.
NA = not applicable.
A positive regression coefficient indicates better discriminatory power of MR imaging in studies with that characteristic compared with that in studies without the corresponding characteristic, and a negative regression coefficient indicates reduced diagnostic performance in studies with that characteristic. A relative diagnostic OR greater than 1.0 indicates better diagnostic performance of MR imaging in studies with that characteristic compared with that in studies without the corresponding feature, and a relative diagnostic OR less than 1.0 indicates decreased diagnostic performance in studies with that characteristic.
* Subset analysis including 23 of 27 studies with age reported.
† Value is the change per year.
‡ Subset analysis including 20 of 23 studies with age reported.
§ Value is the change per unit Tesla.
‖ Value is the change per additional sequence.
\# Subset analysis including 76 of 89 studies with age reported.

The summary ROC curves based on the final regression models, together with the results of the individual studies, are plotted in Figure 3. For the medial meniscus, we set the dummy variable for blinding to zero according to clinical practice, where arthroscopy is ideally performed on the basis of and with knowledge of the MR imaging findings.

The summary ROC curve for lateral meniscal tears was plotted for a patient aged 30 years. For the ACL, the publication year was set to 1995, and the curve was plotted for a patient aged 30 years with use of a 1.0-T MR imager. The curve for PCL lesions was adjusted to publication in 1995, an academic hospital setting, use of three MR sequences, and the absence of verification bias. The adjusted summary ROC curves have different positions in ROC space (Fig 3), indicating that there are differences in diagnostic performance among the types of lesions. Whereas overall discriminatory power is not much different for the menisci, diagnostic performance is clearly better for the ACL compared with that for the PCL, since the curve for the ACL is located more toward the upper left corner.

Overall Summary ROC Analysis of All Lesions

In the multivariate summary ROC analysis with all lesions combined, the meniscal tear versus cruciate ligament dummy variable (relative diagnostic OR, 0.52 [95% CI: 0.26, 1.01]), mean age (relative diagnostic OR, 1.13 [95% CI: 1.03, 1.23]), and magnetic field strength (relative diagnostic OR, 1.97 [95% CI: 1.13, 3.42]) were statistically significant predictors of diagnostic performance (Table 8). Although the dummy variable for meniscal versus cruciate ligament tears was of borderline significance, we kept it in the model because the nature of these lesions is totally different, and furthermore, it allowed comparison of the lesions. In Figure 4, summary ROC curves are shown for menisci and cruciate ligaments separately. The curves were plotted with the mean age covariable set at 30 years for both 0.2- and 1.5-T MR imagers.

Compared with that for the menisci, the curve for cruciate ligaments is further up toward the upper left corner, suggesting better discriminatory power. Similarly, the curves for high-field-strength MR imaging show better diagnostic performance compared with those for low-field-strength MR imaging.

Sensitivity Analyses

The jackknife sensitivity analyses, in which articles were excluded one by one from the final models, did not demonstrate any disproportionate influences of individual studies. In the models for ACL tears and the overall model with all lesions combined, the effect of magnetic field strength remained relatively stable in the sensitivity analysis (relative diagnostic OR ranges, 2.63–4.41 and 1.80–2.16, respectively), and this effect was always statistically significant.

DISCUSSION

In this systematic review and meta-analysis, attention was focused on tears of the menisci and cruciate ligaments, which are primarily caused by traumatic mechanisms. Our results confirm those of previous studies, which show MR imaging to be a highly accurate diagnostic tool for detecting tears of the menisci and cruciate ligaments.

The results show that diagnostic performance is better for cruciate ligament tears than that for meniscal tears. With regard to the menisci, our results demonstrate that the sensitivity and specificity differ significantly for the medial and lateral meniscus.

Whereas MR imaging is more sensitive in the diagnosis of medial meniscal tears, the specificity is higher for lateral meniscal tears. However, the natural logarithm of the diagnostic OR, which is an overall measure of diagnostic performance that incorporates both sensitivity and specificity, is not significantly different for the two lesions, indicating that radiologists probably use different points along the same underlying ROC curve when evaluating the two lesions. The results confirm that findings of the two menisci are preferably considered separately in studies in which the diagnostic performance of MR imaging was assessed to avoid performance underestimation. Thus, our criterion to include only articles in which results for medial and lateral menisci were reported separately seems to be justified. Moreover, in clinical practice, it is usually a lesion of either the medial or lateral meniscus that is suspected, making diagnostic performance statistics for both menisci combined less meaningful.

To increase statistical precision, a pooled weighted analysis with both menisci combined into one model is possible, provided that an appropriate technique (eg, summary ROC analysis) for combining lesions with different points on the same ROC curve is used, which is what we did. We acknowledge, however, that this type of pooled combined analysis may result in data for some patients being included more than once in the same regression model, which induced some dependence among observations.

With regard to the cruciate ligaments, we considered complete tears only, because these injuries are by far more serious than are partial ruptures. Whereas complete ruptures mostly necessitate intensive physical therapy or reconstructive surgery, partial tears usually do not require specific treatment.

Apart from the menisci and cruciate ligaments, there are more derangements involving the knee that might be visualized with MR imaging. Articular cartilage lesions may also have a traumatic origin and cause serious symptoms. Except for full-thickness lesions (Ficat grade IV or V), however, the role of MR imaging in detecting articular cartilage defects has not been well established. Especially for lesions that are limited to half of the cartilage thickness (Ficat grade I–III), the diagnostic accuracy of MR imaging seems poor (17–19). We performed a MEDLINE search of articles on MR imaging of knee cartilage, but among the articles that we found, we considered the patient population, grading system, definition of disease, and regions studied as too heterogeneous to justify a meta-analysis. For example, patient populations varied from patients who experienced trauma to patients with known osteoarthritis. Grading systems had a range of three to six categories, and positivity criteria varied from anything abnormal to full-thickness defects. Finally, in some studies, the knee cartilage was subdivided into regions, such as the lateral and medial femoral condyle or even the different facets of the patella, whereas in other articles, investigators considered the whole knee to be a unit of analysis.

To avoid missing important articles, we applied broad criteria for our MEDLINE search. This resulted in 804 retrieved references, most of which were clearly not suitable for inclusion in our systematic review and were excluded on the basis of either the title or the abstract. As an illustration, a substantial number of articles about other pathologic conditions in the knee or about postoperative MR imaging, cadaveric examinations, case reports, and even the meniscus in the temporomandibular joint were found among these 804 studies. After this initial selection, 120 articles were considered potentially eligible for inclusion, 20 of which were subsequently excluded because they did not present data on diagnostic performance.

We applied criteria for inclusion and exclusion that are commonly used in evidence-based medicine, as well as criteria that were related to the aims of the present study and the methods that we intended to use. Studies with a sample size of fewer than 30 patients were excluded because small samples contribute little to the results of a meta-analysis. In addition, our purpose to assess the effect of magnetic field strength on diagnostic performance required that the magnetic field strength of the MR imager be reported in all included studies. Similarly, a summary ROC analysis is only possible if the absolute numbers of true-positive, false-negative, true-negative, and false-positive results are available or derivable.

Our literature search was limited to articles published between 1991 and 2000. We acknowledge that there have been relevant publications between 1985 and 1990, some of which would have fulfilled the inclusion criteria of this meta-analysis. However, the question arises whether the MR imaging techniques used in the earlier period can be compared with the improved techniques and sequences of more recent years.

Furthermore, we limited our literature search to articles published in the English language. It has been shown that inclusion of only English-language articles does not influence the results of a meta-analysis (20). Moreover, the decision as to which other languages to include will, in our view, always be based on highly arbitrary and geographically dependent criteria, namely, the ability of the data extractors to understand other languages.

We included only studies in which arthroscopy was regarded as the standard of reference. This procedure has always been the reference standard for the diagnosis of internal derangements of the knee, against which alternative diagnostic modalities should be compared. However, the use of arthroscopy alone as the reference standard has been criticized because some parts of the joint cannot be brought into view properly. The posterior horn of the medial meniscus is an especially difficult area to visualize, and the arthroscopic diagnosis of meniscal tears in this region is often assigned on the basis of probing rather than visualizing the meniscus. Quinn and Brown (21) retrospectively analyzed the arthroscopic videotapes of false-positive MR imaging results and found that the suspected area of the meniscus was never visualized in these cases. Therefore, false-negative findings at arthroscopy could potentially account for many false-positive MR imaging results.

Likewise, the PCL is not usually visualized during arthroscopy if the ACL is intact, and in this case, physical examination is often performed with the patient anesthetized to demonstrate a rupture of the PCL. As a result, arthroscopy is ideally performed with knowledge of the findings from the preceding MR examination.

We first summarized and combined the data in a pooled weighted analysis performed separately for each lesion. This type of analysis has certain limitations, since it does not take into account the differences in positivity criteria that were used in the studies. For the lesions that we included in this meta-analysis, however, we found that articles were highly comparable with regard to the definition of disease at MR imaging. In all included articles, the meniscus was evaluated and graded by using the original or slightly modified criteria that were introduced previously by Reicher et al (22) or Crues et al (23). On the basis of these criteria, a meniscal tear is diagnosed if an intrameniscal area of high signal intensity extends to the articular surface, whereas an area of high signal intensity that does not reach the surface is considered degenerative. Since degenerative changes of the menisci are common and usually asymptomatic findings in patients after the 3rd decade (24), our interest was focused on meniscal tears only.

With regard to the status of the cruciate ligaments, a complete tear was usually defined as nonvisualization of the ligament in its expected position or high signal intensity in the course of the ligament in the absence of intact margins. Even though positivity criteria were largely the same among studies, we considered a summary ROC analysis appropriate, since, in our view, there will always be implicit variations in interpretation in different settings and by different radiologists.

The results of our meta-analysis stress the importance of adequate study design when conducting a study on diagnostic performance. Especially, the presence of verification bias was found to dramatically increase the diagnostic performance for PCL tears. Also, blinding the performer of the reference test (arthroscopy) to the findings of the test under evaluation (MR imaging) was predictive in the final model for medial meniscal tears. In every included study, the radiologist who interpreted the MR images was blinded to the arthroscopy result. This reflects clinical practice, in which MR imaging is usually and ideally performed prior to arthroscopy. Therefore, the effect of blinding the MR image interpreter to the result of the reference test was not assessed in this meta-analysis. In addition, mean age of the patient population was a statistically significant predictor for various lesions. This finding implies that the age distribution of the patient population should be described sufficiently in diagnostic performance studies.

The effect of publication year on the diagnostic performance probably reflects the progress in MR imaging technique over the past 15 years with regard to the MR imagers and the sequences used. Whereas in the early years of MR imaging, only spin-echo and gradient-echo sequences were performed, nowadays the choice of sequences that can be incorporated in the imaging protocol has expanded, with various types of fat-suppression techniques and three-dimensional acquisitions that enable reconstructions in every plane. Moreover, the influence of publication year could represent a learning process over the years among interpreters of MR images of the knee.

Higher magnetic field strength of the MR imager improved the diagnostic performance for ACL tears, and a modest effect was demonstrated when all lesions were combined in one model. In the pooled weighted analyses per lesion for different magnetic field strength categories, a trend was observed toward better diagnostic performance for higher magnetic field strengths, but this effect was far from significant, probably because too few studies were available per category of magnetic field strength. We can only speculate whether the effect would have been statistically significant if more existing studies would have fulfilled our inclusion criteria. Except for the ACL, however, no effect was demonstrated in the summary ROC analysis per lesion, which is a more powerful technique for assessing predictors of diagnostic performance. Only for PCL tears was the number of sequences a predictor in the final multivariate model. Unexpectedly, this effect was negative with increasing numbers of sequences. The status of the PCL can usually be assessed well on the basis of a few images in the sagittal plane.

We conclude that MR imaging is highly accurate in the diagnosis of tears of the menisci and cruciate ligaments. MR imaging is an appropriate screening tool for therapeutic arthroscopy, making diagnostic arthroscopy unnecessary in most patients. Diagnostic performance of MR imaging differs significantly for menisci and cruciate ligaments and for the medial and lateral meniscus and is influenced by characteristics of study design, patient age, and magnetic field strength. The effect of magnetic field strength, however, was only statistically significant for ACL tears. The influence of study design characteristics and patient age should be taken into consideration whenever a diagnostic performance study on MR imaging of the knee is designed or reported.

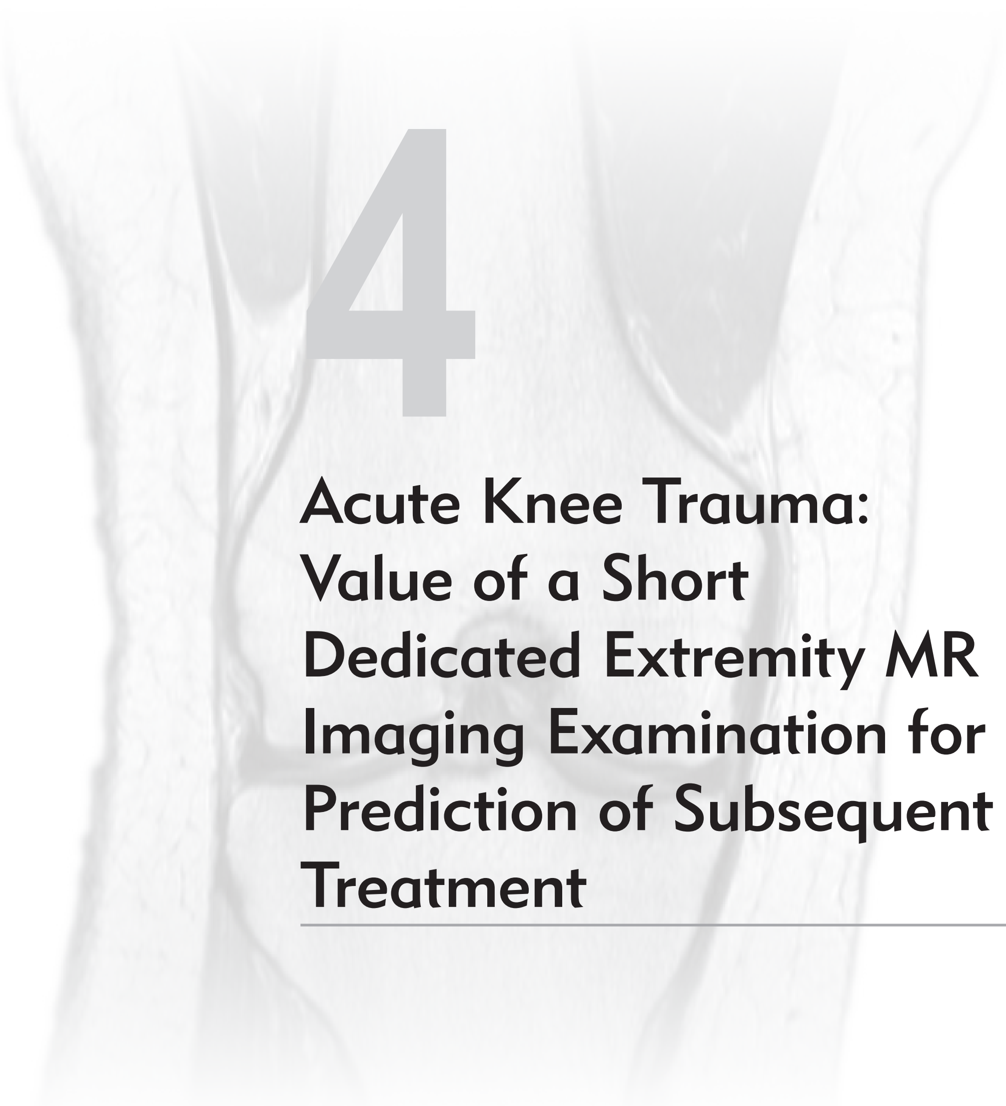
REFERENCES

1. Rangger C, Klestil T, Kathrein A, Inderster A, Hamid L. Influence of magnetic resonance imaging on indications for arthroscopy of the knee. Clin Orthop 1996; 330:133-142.
2. Rappeport ED, Mehta S, Wieslander SB, Lausten GS, Thomsen HS. MR imaging before arthroscopy in knee joint disorders? Acta Radiol 1996; 37:602-609.
3. Mackenzie R, Palmer CR, Lomas DJ, Dixon AK. Magnetic resonance imaging of the knee: diagnostic performance studies. Clin Radiol 1996; 51:251-257.
4. Irwig L, Tosteson AN, Gatsonis C, et al. Guidelines for meta-analyses evaluating diagnostic tests. Ann Intern Med 1994; 120:667-676.
5. Berlin JA. Does blinding of readers affect the results of meta-analyses?University of Pennsylvania Meta-analysis Blinding Study Group. Lancet 1997; 350:185-186.
6. Begg CB, Greenes RA. Assessment of diagnostic tests when disease verification is subject to selection bias. Biometrics 1983; 39:207-215.
7. Littenberg B, Moses LE. Estimating diagnostic accuracy from multiple conflicting reports: a new meta-analytic method. Med Decis Making 1993; 13:313-321.
8. Begg CB, Berlin JA. Publication bias and dissemination of clinical research. J Natl Cancer Inst 1989; 81:107-115.
9. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315:629-634.
10. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7:177-188.
11. Fleiss JL. The statistical basis of meta-analysis. Stat Methods Med Res 1993; 2:121-145.
12. Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. Stat Med 1993; 12:1293-1316.
13. De Vries SO, Hunink MG, Polak JF. Summary receiver operating characteristic curves as a technique for meta-analysis of the diagnostic performance of duplex ultrasonography in peripheral arterial disease. Acad Radiol 1996; 3:361-369.
14. Irwig L, Macaskill P, Glasziou P, Fahey M. Meta-analytic methods for diagnostic test accuracy. J Clin Epidemiol 1995; 48:119-130.
15. Vahey TN, Broome DR, Kayes KJ, Shelbourne KD. Acute and chronic tears of the anterior cruciate ligament: differential features at MR imaging. Radiology 1991; 181:251-253.
16. Warwick DJ, Cavanagh P, Bell M, Marsh CH. Influence of magnetic resonance imaging on a knee arthroscopy waiting list. Injury 1993; 24:380-382.
17. Munk B, Madsen F, Lundorf E, et al. Clinical magnetic resonance imaging and arthroscopic findings in knees: a comparative prospective study of meniscus anterior cruciate ligament and cartilage lesions. Arthroscopy 1998; 14:171-175.

18. Kawahara Y, Uetani M, Nakahara N, et al. Fast spin-echo MR of the articular cartilage in the osteoarthrotic knee: correlation of MR and arthroscopic findings. Acta Radiol 1998; 39:120-125.
19. Mori R, Ochi M, Sakai Y, Adachi N, Uchio Y. Clinical significance of magnetic resonance imaging (MRI) for focal chondral lesions. Magn Reson Imaging 1999; 17:1135-1140.
20. Moher D, Pham B, Klassen TP, et al. What contributions do languages other than English make on the results of meta-analyses? J Clin Epidemiol 2000; 53:964-972.
21. Quinn SF, Brown TF. Meniscal tears diagnosed with MR imaging versus arthroscopy: how reliable a standard is arthroscopy? Radiology 1991; 181:843-847.
22. Reicher MA, Hartzman S, Duckwiler GR, Bassett LW, Anderson LJ, Gold RH. Meniscal injuries: detection using MR imaging. Radiology 1986; 159:753-757.
23. Crues JV, III, Mink J, Levy TL, Lotysch M, Stoller DW. Meniscal tears of the knee: accuracy of MR imaging. Radiology 1987; 164:445-448.
24. Stoller DW, Martin C, Crues JV, III, Kaplan L, Mink JH. Meniscal tears: pathologic correlation with MR imaging. Radiology 1987; 163:731-735.
25. Boeree NR, Watkinson AF, Ackroyd CE, Johnson C. Magnetic resonance imaging of meniscal and cruciate injuries of the knee. J Bone Joint Surg Br 1991; 73:452-457.
26. Fischer SP, Fox JM, Del Pizzo W, Friedman MJ, Snyder SJ, Ferkel RD. Accuracy of diagnoses from magnetic resonance imaging of the knee: a multi-center analysis of one thousand and fourteen patients. J Bone Joint Surg Am 1991; 73:2-10.
27. Kelly MA, Flock TJ, Kimmel JA, et al. MR imaging of the knee: clarification of its role. Arthroscopy 1991; 7:78-85.
28. Niitsu M, Anno I, Fukubayashi T, Shimojo H, Kuno S, Akisada M. Tears of cruciate ligaments and menisci: evaluation with cine MR imaging. Radiology 1991; 178:859-864.
29. Araki Y, Ootani F, Tsukaguchi I, et al. MR diagnosis of meniscal tears of the knee: value of axial three-dimensional Fourier transformation GRASS images. AJR Am J Roentgenol 1992; 158:587-590.
30. Gluckert K, Kladny B, Blank-Schal A, Hofmann G. MRI of the knee joint with a 3-D gradient echo sequence: equivalent to diagnostic arthroscopy? Arch Orthop Trauma Surg 1992; 112:5-14.
31. Grevitt MP, Pool CJ, Bodley RN, Savage PE. Magnetic resonance imaging of the knee: initial experience in a district general hospital. Injury 1992; 23:410-412.
32. Gross ML, Grover JS, Bassett LW, Seeger LL, Finerman GA. Magnetic resonance imaging of the posterior cruciate ligament: clinical use to improve diagnostic accuracy. Am J Sports Med 1992; 20:732-737.
33. Heron CW, Calvert PT. Three-dimensional gradient-echo MR imaging of the knee: comparison with arthroscopy in 100 patients. Radiology 1992; 183:839-844.
34. Barnett MJ. MR diagnosis of internal derangements of the knee: effect of field strength on efficacy. AJR Am J Roentgenol 1993; 161:115-118.

35. De Smet AA, Norris MA, Yandow DR, Quintana FA, Graf BK, Keene JS. MR diagnosis of meniscal tears of the knee: importance of high signal in the meniscus that extends to the surface. AJR Am J Roentgenol 1993; 161:101-107.
36. Chan WP, Peterfy C, Fritz RC, Genant HK. MR diagnosis of complete tears of the anterior cruciate ligament of the knee: importance of anterior subluxation of the tibia. AJR Am J Roentgenol 1994; 162:355-360.
37. Gentili A, Seeger LL, Yao L, Do HM. Anterior cruciate ligament tear: indirect signs at MR imaging. Radiology 1994; 193:835-840.
38. Kinnunen J, Bondestam S, Kivioja A, et al. Diagnostic performance of low field MRI in acute knee injuries. Magn Reson Imaging 1994; 12:1155-1160.
39. LaPrade RF, Burnett QM, Veenstra MA, Hodgman CG. The prevalence of abnormal magnetic resonance imaging findings in asymptomatic knees: with correlation of magnetic resonance imaging to arthroscopic findings in symptomatic knees. Am J Sports Med 1994; 22:739-745.
40. Chen MC, Shih TT, Jiang CC, Su CT, Huang KM. MRI of meniscus and cruciate ligament tears correlated with arthroscopy. J Formos Med Assoc 1995; 94:605-611.
41. Justice WW, Quinn SF. Error patterns in the MR imaging evaluation of menisci of the knee. Radiology 1995; 196:617-621.
42. Lerman JE, Gray DS, Schweitzer ME, Bartolozzi A. MR evaluation of the anterior cruciate ligament: value of axial images. J Comput Assist Tomogr 1995; 19:604-607.
43. Barry KP, Mesgarzadeh M, Triolo J, Moyer R, Tehranzadeh J, Bonakdarpour A. Accuracy of MRI patterns in evaluating anterior cruciate ligament tears. Skeletal Radiol 1996; 25:365-370.
44. Lundberg M, Odensten M, Thuomas KA, Messner K. The diagnostic validity of magnetic resonance imaging in acute knee injuries with hemarthrosis: a single-blinded evaluation in 69 patients using high-field MRI before arthroscopy. Int J Sports Med 1996; 17:218-222.
45. Riel KA, Reinisch M, Kersting-Sommerhoff B, Hof N, Merl T. 0.2-T magnetic resonance imaging of internal lesions of the knee joint: a prospective arthroscopically controlled clinical study. Knee Surg Sports Traumatol Arthrosc 1999; 7:37-41.
46. Bui-Mansfield LT, Youngberg RA, Warme W, Pitcher JD, Nguyen PL. Potential cost savings of MR imaging obtained before arthroscopy of the knee: evaluation of 50 consecutive patients. AJR Am J Roentgenol 1997; 168:913-918.
47. Cheung LP, Li KC, Hollett MD, Bergman AG, Herfkens RJ. Meniscal tears of the knee: accuracy of detection with fast spin-echo MR imaging and arthroscopic correlation in 293 patients. Radiology 1997; 203:508-512.
48. Franklin PD, Lemon RA, Barden HS. Accuracy of imaging the menisci on an in-office, dedicated, magnetic resonance imaging extremity system. Am J Sports Med 1997; 25:382-388.

49. Rappeport ED, Wieslander SB, Stephensen S, Lausten GS, Thomsen HS. MRI preferable to diagnostic arthroscopy in knee joint injuries: a double-blind comparison of 47 patients. Acta Orthop Scand 1997; 68:277-281.
50. Weinstabl R, Muellner T, Vecsei V, Kainberger F, Kramer M. Economic considerations for the diagnosis and therapy of meniscal lesions: can magnetic resonance imaging help reduce the expense? World J Surg 1997; 21:363-368.
51. Ha TP, Li KC, Beaulieu CF, et al. Anterior cruciate ligament injury: fast spin-echo MR imaging with arthroscopic correlation in 217 examinations. AJR Am J Roentgenol 1998; 170:1215-1219.
52. Cotten A, Delfaut E, Demondion X, et al. MR imaging of the knee at 0.2 and 1.5 T: correlation with surgery. AJR Am J Roentgenol 2000; 174:1093-1097.
53. Elvenes J, Jerome CP, Reikeras O, Johansen O. Magnetic resonance imaging as a screening procedure to avoid arthroscopy for meniscal tears. Arch Orthop Trauma Surg 2000; 120:14-16.



4

Acute Knee Trauma: Value of a Short Dedicated Extremity MR Imaging Examination for Prediction of Subsequent Treatment

Oei EHG, Nikken JJ, Ginai AZ, Krestin GP, Verhaar JAN, van Vugt AB, Hunink MGM

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ABSTRACT

PURPOSE: To assess the predictive value of a short magnetic resonance (MR) imaging examination, in addition to or instead of radiography, performed in patients with acute knee trauma to identify those who require additional treatment versus those who do not and can be discharged without further follow-up.

MATERIALS AND METHODS: The randomized controlled trial and use of collected data for prediction modeling were approved by the institutional review board; informed consent was obtained. Patients with recent knee injury were included in the trial if radiography was ordered. They were randomized into a group undergoing only radiography and a group undergoing radiography plus immediate MR imaging. A 0.2-T dedicated extremity MR imager and four short pulse sequences were used. Univariable and multivariable logistic regression analysis was used to evaluate patient characteristics, trauma mechanism, and findings at radiography and MR imaging for their value in prediction of need for subsequent treatment within the 6-month follow-up.

RESULTS: Data in 189 patients (123 male patients, 66 female patients; mean age, 33.4 years), 109 of whom underwent treatment after their initial visit, were analyzed. Age of 30 years or older, indirect trauma mechanism, radiographic results, and MR imaging results were significant predictors of need for treatment in univariable and multivariable analyses ($P < .05$).

In the multivariable analysis, only abnormal MR imaging results were significantly predictive of need for treatment, and only when MR imaging replaced radiography (odds ratio, 2.61; 95% confidence interval: 1.12, 6.06).

CONCLUSION: Implementation of a dedicated extremity MR imaging examination, in addition to or instead of radiography, performed in patients with traumatic knee injury improves prediction of the need for additional treatment but does not significantly aid in identification of patients who can be discharged without further follow-up. Value of a short MR imaging examination in the initial stage after knee trauma is limited.

INTRODUCTION

Traumatic injuries of the knee joint, which are often caused by sports activities, constitute a large proportion of musculoskeletal trauma encountered in the emergency department. The initial evaluation of knee injuries usually consists of taking the clinical history and performing a physical examination, which involves various manipulative tests (1,2). Although physical examination may aid in establishing the diagnosis at a later stage or with the patient anesthetized, its accuracy in the acute stage has been questioned, especially for meniscal tears, and that accuracy is influenced by many factors (3–5). Moreover, it has been well recognized that thorough physical examination of a recently injured knee with acute hemarthrosis often is difficult because of swelling, pain, and guarding (6–8).

If a fracture is suspected, radiography usually is added to the diagnostic work-up, and such an addition often is based on criteria previously published as the Ottawa Knee Rule (9,10). Traumatic abnormalities, other than a fracture, that cannot be visualized by using radiography may be present in the knee joint. Unlike radiography, magnetic resonance (MR) imaging provides information on soft-tissue damage and has been accepted widely for the evaluation of internal knee derangements. A recent systematic review and meta-analysis demonstrated that MR imaging has a very good performance in diagnosis of tears of the menisci and cruciate ligaments (11). Nonetheless, the routine use of MR imaging in the initial work-up of acute knee injuries has been hampered by the high costs, the limited availability, and the long duration of an MR imaging examination. Low-field-strength dedicated extremity MR imagers have been developed to overcome some of these problems. Because of the compact design and low field strength of these types of imagers, the costs can be kept relatively low compared with the costs of high-field-strength whole-body units. Therefore, low-field-strength dedicated extremity MR imaging has created the possibility to apply MR imaging more routinely in the initial evaluation of knee trauma.

Application of MR imaging as an initial examination tool after knee trauma in the emergency department setting can potentially yield benefit to the patient and the health care system. Detailed imaging information in an early stage may result in more timely diagnosis and treatment in patients who would otherwise have been followed up, with delay of definitive therapy. Conversely, patients could possibly be identified who are unlikely to require specific treatment and who will thus not need reassessment or follow-up. In the light of cost minimization and efficiency, this identification would be beneficial, since these patients do not need to return to the outpatient department. The purpose of this study was to assess the predictive value of a short MR imaging examination, in addition to or instead of radiography, performed in patients who present with acute knee trauma to identify those who require additional treatment versus those who do not and can be discharged without further follow-up.

MATERIALS AND METHODS

Study Design and Population

This study was part of a prospective randomized controlled trial aimed at assessment of the value and cost-effectiveness of dedicated extremity MR imaging in the initial evaluation of all patients with acute knee, ankle, or wrist injury. Data about the three joints were analyzed and reported separately, and the patients included in this study were different from those included in the studies about the wrist and the ankle joints. Although it is not necessary to perform a randomized controlled trial to evaluate the predictive value of MR imaging in acute knee trauma, we used the data from such a trial to do so. Where applicable, we followed published guidelines for reporting the results of randomized controlled trials (12), and otherwise, we used those for reporting results of diagnostic studies (13). The randomized controlled trial, as well as the use of the collected data for prediction modeling, was approved by the institutional review board of Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands.

From August 1999 to May 2001, we recruited patients from the emergency department of our university hospital who were referred for radiography by a traumatologist, orthopedic surgeon, or emergency physician because of traumatic knee injury within the preceding 7 days. We excluded patients who had additional injuries of the head, back, thorax, or abdomen; patients with a compound knee fracture; patients requiring urgent treatment (eg, in case of a threat to the circulation of the leg); and patients with preexisting symptoms in the same knee. Patients were included 7 days per week from 8:00 AM to 11:00 PM. All eligible patients were provided with written and oral information about the aim of the study. After informed consent was obtained, patients were randomized to a group who would undergo the current diagnostic work-up (only radiography) and a group who would undergo radiography and a short dedicated extremity MR imaging examination immediately afterward. Randomization was performed by research staff who were not involved in the further treatment of the patient with use of consecutively numbered sealed envelopes containing computer-generated random assignments. We applied block randomization with a block size of 20 patients to achieve equal numbers of patients in both study arms.

Imaging

Radiography was performed in the anteroposterior and lateral views. In a few patients, additional patellar or tunnel views were obtained because a patellar fracture or a loose body was suspected by the examining physician. For the MR imaging examination, we used a low-field-strength dedicated extremity MR imaging system (Artoscan M; Esaote Biomedica, Genoa, Italy) with a 0.2-T permanent magnet and a dual phased-array knee coil. A larger linear knee coil was used in patients with a very large knee. In regard to the imaging protocol, we aimed at providing a quick examination in the emergency setting that would minimize the costs and burden to the patient. With these goals in mind, we adapted several imaging parameters to reduce total examination time. This adaptation resulted in some loss of image quality, but in a pilot study, the imaging protocol as described in Table 1 was found to be of acceptable quality for the detection of most lesions (14). Average total acquisition time was 6 minutes 7 seconds, with a total examination time, including start-up of the MR imaging unit and patient positioning, of shorter than 15 minutes.

According to daily practice in our hospital, the radiographs were initially assessed by the treating physician in the emergency department. On the next day, all radiographs were reassessed by one of two musculoskeletal radiologists (including A.Z.G.) who had at least 4 years of experience in musculoskeletal radiology at a daily meeting with the treating physician. If the reassessment differed from the initial interpretation, the treatment decision was based on the interpretation of the musculoskeletal radiologist, and the patient was called back for treatment if necessary. The MR images were immediately interpreted by an experienced musculoskeletal radiologist (A.Z.G., with 25 years of experience in musculoskeletal radiology) who was unaware of the results of radiography. The findings on MR images were reported to the treating physicians in the emergency department so that they could aid in the decision of whether to treat or follow up the patient. In a minority of patients (eg, during the weekends and in the evenings), the MR images were assessed by one of the radiology residents, who were in their 2nd–5th year of training, and were reassessed by the musculoskeletal radiologist on the next day. The treating physician was notified of any discrepancies in interpretation, and the patient was called back for treatment if indicated. For both radiographs and MR images, the interpretation of the musculoskeletal radiologist was used in the analysis.

For the purpose of our analysis, the results of radiography and MR imaging were interpreted as abnormal or normal on the basis of the presence or absence of recent traumatic ab-

Table 1. Parameters of short MR imaging protocol

Sequence *	Plane of imaging	Repetition time (msec)	Echo time (msec)	Matrix	Section thickness (mm)	Imaging time range (min:sec)
Half Fourier T1-weighted spin echo	Sagittal oblique	490-720	18-24	192 x 216	5.0	0:49 – 1:08
Proton density-weighted, T2-weighted turbo multi echo	Coronal	2150-2640	28-38, 90	192 x 128	5.0	2:23 – 2:41
Gradient echo †	Coronal	500-595	15-16	192 x 128	5.0	0:48 – 0:53
Short inversion time inversion recovery ‡	Sagittal	1060-1290	24-28	192 x 128	6.0, 7.0	1:37 – 1:46

* For all sequences, the field of view was 200x140 mm, with one signal acquired.
† The flip angle was 75°.
‡ Inversion time was 80-85 msec.

normalities that required treatment. Results of radiography were considered abnormal if a fracture, an epiphysiolysis, a dislocation, or an osteochondral lesion was visible. Results of MR imaging were interpreted as abnormal if one or more of the following were present: a fracture, an epiphysiolysis, a dislocation, an osteochondral lesion, a meniscal tear, a total rupture of the anterior cruciate ligament, a total rupture of the posterior cruciate ligament, a total or partial rupture of the medial collateral ligament, or a total or partial rupture of the lateral collateral ligament. Although a partial rupture of the anterior or the posterior cruciate ligament is obviously a traumatic lesion, we considered the MR imaging results as normal, for the purpose of our analysis, if this was the only visible abnormality, since an isolated partial tear of a cruciate ligament does not usually need specific treatment.

A partial rupture of the collateral ligament, however, usually is treated with a knee brace. Similarly, results of radiography and MR imaging were interpreted as normal (ie, not requiring specific treatment) if only joint effusion, hemarthrosis, soft-tissue edema, bone marrow edema, meniscal degeneration, or osteoarthritis was seen or if the findings suggested an old traumatic lesion. Bone marrow edema does not require specific treatment, but it may be suggestive of an intraarticular lesion, and therefore its presence may increase the likelihood of treatment. Therefore, we reanalyzed the data with isolated bone marrow edema interpreted as an MR imaging finding that required treatment.

Follow-up and Outcome

The outcome measure was additional treatment within 6 months after the initial visit to the emergency department. Treatment was defined as any specific additional therapy, which included surgery, physical therapy with supervised and structured rehabilitation exercises, a plaster cast, and taping.

Patients were followed up as long as they had daily complaints of the affected knee, and this follow-up time was as long as a maximum of 6 months after initial presentation. Data were collected by searching the emergency department records, hospital records, outpatient clinic records, and electronic hospital information system. In addition, we sent questionnaires to all patients, and the questionnaires included questions about whether they had undergone treatment at another institution. These questionnaires were mailed at 1, 6, and 12 weeks and at 6 months after the initial visit to the emergency department. If the questionnaires were not returned, we attempted to interview the patients by telephone. Patient records were reviewed, and patients were interviewed by two of the authors (E.H.G.O. and J.J.N.) and research support staff. The final diagnosis was determined by reviewing all information from diagnostic imaging, follow-up, questionnaires, or arthroscopy or surgery reports, if available.

Since one may argue that the indications for physical therapy often are not well defined, we performed a separate analysis in which physical therapy was not considered a specific treatment.

Statistical Analysis

The data were analyzed according to intention to diagnose and treat by using univariable and multivariable logistic regression analysis. We evaluated the following independent variables for their statistical significance in the prediction of whether treatment was required within 6 months after the initial hospital visit: age (both continuous and dichotomous at various threshold levels), sex, side of trauma, trauma mechanism (indirect or direct trauma), and the results of both radiography and MR imaging (abnormality that required treatment vs no abnormality). The absence of MR imaging information, which was the case in half of our patient population because of the randomized study design, was used as the reference category for the MR imaging results in the analysis (normal or abnormal vs no MR imaging information). This allowed us to determine the additional value of the MR imaging results compared with no MR imaging information.

To account for the fact that the findings at radiography and MR imaging were correlated, we created what we called an overall imaging variable, in which the results of both the radiographic and MR imaging examinations were integrated. In this variable, the following five possible combinations of radiographic and MR imaging results were coded by using four dummy variables: (a) normal radiographic results and no MR imaging information (reference category), (b) normal results of both radiography and MR imaging, (c) abnormal results of radiography and no MR imaging information, (d) discrepant results of radiography and MR imaging, and (e) abnormal results of both radiography and MR imaging.

By using the overall imaging variable, one takes into account the diagnostic interaction between radiography and MR imaging results, which may be involved if two imaging modalities are used together to visualize the same lesion. It is, therefore, a more appropriate manner of analyzing the results of radiography and MR imaging combined, rather than using the two variables separately, in the same regression model.

We first assessed each variable separately with univariable logistic regression analysis and calculated the odds ratio and the 95% confidence interval. Subsequently, we performed multivariable logistic regression analyses, which included all variables that had a P value of less than .10 (χ^2 test) in the univariable analysis. Because we wanted to assess the value of the imaging modalities, we created four models that included the following: radiographic results (model 1), MR imaging results (model 2), radiographic and MR imaging results (model 3), and the overall imaging variable described previously (model 4). We used the Hosmer-Lemeshow goodness-of-fit test to evaluate the calibration of the models. A Hosmer-Lemeshow goodness-of-fit test result that was not significant ($P > .05$) indicated that the model fit well with the observed data (15). The area under the receiver operating characteristic curve was calculated to assess the discriminatory power of each model in distinguishing patients who required treatment from those who could be discharged. A larger area under the receiver operating characteristic curve indicated a higher discriminatory power (16).

To compare the area under the receiver operating characteristic curve across the models, we used the method described by Hanley and McNeil (17), which provides adjustment for the fact that the models were correlated since they were derived from the same sample of patients. The likelihood ratio test, which can be used for comparing nested models, was used to assess the value of MR imaging in addition to radiography with a comparison of models 1 and 3. To compare models that are not nested, one needs to calculate the Akaike information criterion (AIC) for each model and assess the difference in AIC between the models. The AIC of a model is calculated by subtracting two times the degrees of freedom from the χ^2 estimate of the model (18). A higher AIC indicates better model performance. We used this technique to assess the value of MR imaging results as a replacement for radiographic results by comparing the AIC of model 1 with that of model 2 and also to assess the value of MR imaging results in addition to radiographic results by comparing the AIC of model 1 with that of model 4. A difference in AIC larger than 2.00 was considered significant. All analyses were performed by using software (SPSS for Windows, release 10.0.0; SPSS, Chicago, Ill).

Sample Size Calculation

The data for this study were obtained from a randomized controlled trial in which the costs and effectiveness of early MR imaging of knee trauma were evaluated. Hence, the number of independent variables that could be analyzed in the multivariable regression analysis was determined by the number of patients included in the randomized controlled trial: 109 included patients received treatment, and 80 patients did not need treatment. Since at least 10 patients with an event and 10 patients without an event are necessary for each independent variable in the multivariable logistic regression analysis (19), a maximum of eight independent variables could be analyzed.

RESULTS

One hundred ninety-six patients were initially included in the study. Although inclusion was intended to be consecutive, only about half of the eligible patients were included.

The main reason that only half were included was that radiology technologists on service who were supposed to identify eligible patients and ask them to participate in the study often forgot to do so. Six patients were incorrectly included, and they did not fulfill the inclusion criteria at reascertainment (ie, the research staff discovered afterward that these patients should not have been included). One patient presented to our hospital more than 7 days after knee injury, three had a history of preexisting complaints of the knee joint, and another two patients had knee pain of nontraumatic origin. These six patients, together with one patient in whom automutilation was strongly suspected, were

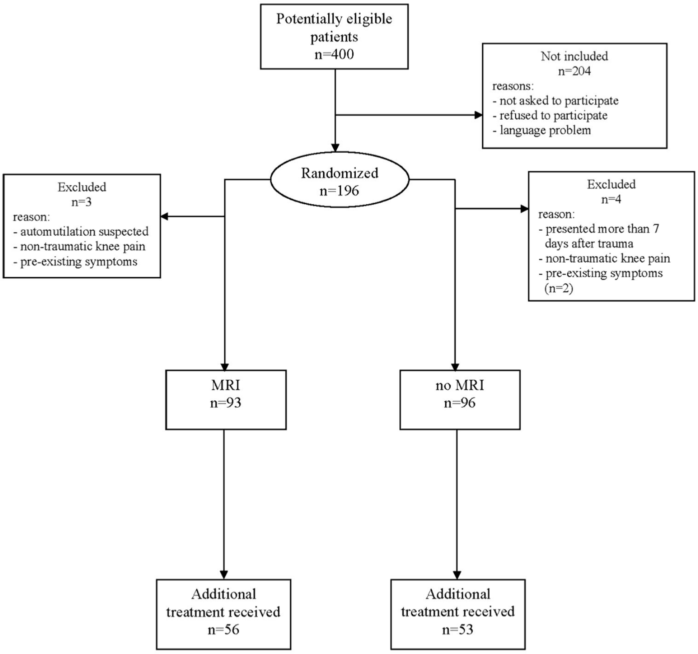

Figure 1. Diagram shows flow of patients passing through the study.

excluded from the analysis. Of the 189 remaining patients (123 male patients, 66 female patients; mean age, 33.4 years), 96 patients were randomized to the group who underwent radiography as the diagnostic strategy and 93 patients were randomized to the group who underwent radiography followed by MR imaging. Female patients (mean age, 36.1 years; range, 16.6–72.9 years) were older than male patients (mean age, 31.9 years; range, 12.6–74.6 years). This difference was of borderline significance ($P = .047$, t test). A diagram that shows the flow of subjects passing through the study is presented in Figure 1.

The lesions that were found at radiography and MR imaging, together with the corresponding frequencies, are listed in Table 2. Figures 2 and 3 present illustrative examples. During the follow-up period, 109 patients underwent treatment, consisting of arthroscopic surgery in 21 patients, which included anterior cruciate ligament reconstruction in one; open surgery in five; drainage in one; and plaster cast immobilization, sometimes supplemented with physical therapy, in 23. Partial meniscectomy was performed in 18 of 21 patients who underwent arthroscopic surgery. Of these 18 patients, 10 had been randomized to the MR imaging diagnostic strategy, and in all these patients the meniscal tear was diagnosed at MR imaging. In the five patients in whom open surgery was performed, the procedure consisted of resection of a fragment of the anterior cruciate ligament combined with reefing of the medial collateral ligament, suturing

Table 2. Frequency of lesions diagnosed with radiography and MR imaging in 180 patients with knee injury

Lesion type	Experimental group (n=93)		Control group (n=96) *
	Radiography	MR imaging	
Fracture	12 (3)	10 (2)	6 (3)
Patella	6 (1)	6 (1)	4 (1)
Femoral condyle			
Medial	0	0	1
Lateral	1	1	0
Tibial plateau	3 (2)	2 (1) †	1 (1)
Intercondylar eminence of tibia	1	0	0 (1)
Fibular head	1	1	0
Anterior cruciate ligament			
Total rupture	0 ‡	17	1 §
Partial rupture	0 ‡	8 (1)	0 ‡
Posterior cruciate ligament			
Total rupture	0 ‡	0	0 ‡
Partial rupture	0 ‡	1	0 ‡
Medial collateral ligament			
Total rupture	1 ‖	2	1 ‖
Partial rupture	0 ‡	8	0 ‡
Lateral collateral ligament			
Total rupture	0 ‡	0 #	0 ‡
Partial rupture	0 ‡	5	0 ‡
Meniscal rupture			
Medial	0 ‡	16 (1)	0 ‡
Lateral	0 ‡	10	0 ‡
Osteochondral lesion	3 (1)	3	2 (2)
Bone marrow edema	0 ‡	22 **	0 ‡

Note: Data are numbers of patients. Data in parentheses are the numbers of additional patients in whom the lesion was suspected but not definitely diagnosed. Some patients had multiple lesions. Since not all patients had a lesion that could be demonstrated at radiography or MR imaging, the number of lesions does not correspond with the number of patients included in each group.

* Patients in the control group underwent only radiography.
† In one patients, a fracture of the tibial plateau demonstrated at radiography was interpreted as bone marrow edema at MR imaging.
‡ This type of lesion cannot be detected with radiography.
§ A total rupture of the anterior cruciate ligament was diagnosed on the basis of findings at radiography because of a characteristic impression fracture of the lateral femoral condyle.
‖ A total rupture of the medial collateral ligament was diagnosed after stress radiography.
\# An old lateral collateral ligament rupture was seen in one patient.
** Bone marrow edema was an isolated finding in four cases. In 18 patients, it was associated with a fracture (four patients), ligamentous lesion (10 patients), or meniscal tear (four patients).

Figure 2a. Sagittal T1-weighted spin-echo MR image (710/24, 192 x 216 matrix, 5-mm section thickness) shows tear (arrow) of anterior cruciate ligament.

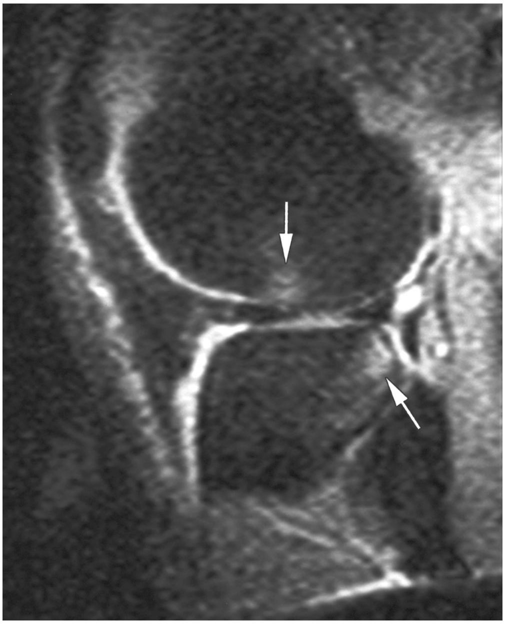

Figure 2b. Short inversion time inversion-recovery MR image (1160/24, 192 x 128, 6-mm section thickness) shows that associated bone marrow edema (arrows) is visible in the lateral femoral condyle and the posterolateral tibial plateau.

of the tendon of the rectus femoris muscle, osteosynthesis of a fracture of the tibial plateau and spongiosaplasty, reinsertion of the medial collateral ligament on the tibia, and fixation of a fragment from osteochondritis dissecans with bone pins. In 59 patients, physical therapy was the only treatment.

The odds ratios and 95% confidence intervals of all demographic, clinical, and imaging variables that were assessed in the univariable logistic regression analysis are presented in Table 3. Age, trauma mechanism, radiographic results, MR imaging results, and the overall imaging variable had a P value of less than .10 (χ^2 test) and were subsequently used in the multivariable analysis. Age of the patient was a significant predictor of treatment as a continuous variable, but the most significant association was found when age was dichotomous, with 30 years as the threshold value (P = .01). Compared with no MR imaging information, abnormal MR imaging results were predictive of the need for treatment, whereas normal MR imaging results were predictive of no treatment required. Similarly, in regard to the overall imaging variable, the category in which radiographic and MR imaging results were both abnormal was significantly predictive of treatment, and the category in which radiographic and MR imaging results were both normal was significantly predictive of no treatment required.

The two intermediate categories had no significant association with treatment. As

Table 3. Results of univariable logistic regression analysis for prediction of need for treatment after acute knee unjury

Predictor	No. of treated patients in group with predictor *	No. of treated patients in reference group *	Univariable OR †	P value ‡
Age §	…	…	1.02 (1.00, 1.04)	.06
Age (≥ 30 y / < 30 y)	64/95 (67)	45/94 (48)	2.25 (1.25, 4.05)	.01
Sex (M / F)	68/123 (55)	41/66 (62)	0.75 (0.41, 1.39)	.36
Side of trauma (L / R)	49/88 (56)	60/101 (59)	0.86 (0.48, 1.53)	.61
Indirect trauma / direct trauma) ‖	76/109 (70)	32/78 (41)	3.31 (1.80, 6.09)	<.001
Radiography (abnormal / normal) #	19/24 (79)	88/161 (55)	3.15 (1.12, 8.85)	.02
MR imaging results **				<.001
Normal	15/42 (36)	53/96 (55)	0.45 (0.21, 0.95)	
Abnormal	41/51 (80)	53/96 (55)	3.33 (1.49, 7.40)	
Overall imaging variable ††				<.001
Normal radiographic and MR imaging results	14/40 (35)	47/85 (55)	0.44 (0.20, 0.95)	
Abnormal radiographic results, no MR imaging information	5/9 (56)	47/85 (55)	1.01 (0.25, 4.03)	
Discrepant radiographic and MR imaging results	28/37 (76)	47/85 (55)	2.52 (1.06, 5.97)	
Abnormal radiographic and MR imaging results	13/14 (93)	47/85 (55)	10.5 (1.32, 84.0)	

* Data in parentheses are percentages.
† Numbers in parentheses represent the 95% confidence interval. A predictor was considered significant if the 95% confidence interval did not include unity.
‡ χ^2 test. Predictors with a P value less than .10 were included in the multivariable analysis.
§ Age was analyzed as a continuous variable, and therefore, no numbers or percentages of treated patients were included.
‖ Analysis was conducted with 187 patients because data in two patients were missing.
Analysis was conducted with 185 patients because data in four patients were missing.
** The reference category was that with no MR imaging information.
†† The reference category was that with negative radiographic results and MR imaging not performed. Analysis was conducted with 185 patients because data in four patients were missing.

expected, sex and side of trauma were not significant in the univariable analysis (P = .36 and .61, respectively).

We created four multivariable models that included the significant variables from the univariable analysis, with different combinations of results of the two imaging modalities (Table 4). All variables were significantly contributive to these models (P < .05 for all, likelikood ratio test).

Model 1 consisted of age, trauma mechanism, and the results of radiography. In model 2, age and trauma mechanism were included, but the results of radiography were replaced with the MR imaging results, and the MR imaging results were significant predictors of the need for treatment only if they were abnormal; however, a normal MR imaging result could not be used to predict that treatment was not required, which was reflected by a 95% confidence interval

Figure 3. Sagittal T1-weighted spin-echo MR image (680/24, 192 x 216 matrix, 5-mm section thickness) shows tear of the posterior horn of the lateral meniscus. A displaced fragment (arrow) is seen posterior to the anterior horn.

of the odds ratio containing unity. Model 3 consisted of age, trauma mechanism, and the results of both radiography and MR imaging using the separate variables for radiographic and MR imaging results (additive combination of models 1 and 2). In this model, the odds ratios of the MR imaging results variable were not significant for both a normal and an abnormal MR imaging result, which suggested that a positive or a negative MR imaging result, versus no MR imaging information available, did not significantly contribute to the prediction of the need for treatment when it was controlled for age, trauma mechanism, and radiographic results. Model 4 consisted of age, trauma mechanism, and the overall imaging variable. Although this variable did significantly contribute to the prediction of treatment (P = .002), only the odds ratio of the category in which both radiographic and MR imaging results were abnormal was significant.

All model performance statistics are tabulated in Table 4. The Hosmer-Lemeshow goodness-of-fit test result was not significant for any of the models, and this finding indicated that all models fit well with the observed data.

The area under the receiver operating characteristic curve, which is a measure of the discriminatory power of the model, was not significantly different when model 1 was compared with model 2, model 1 was compared with model 3, and model 1 was compared with model 4 (P = .53, .91, and .93, respectively). Thus, neither the replacement of radiographic results with MR imaging results (comparison of model 1 and model 2) nor the addition of MR imaging results to radiographic results (comparison of model 1 and model 3 or 4) improved the discriminatory power.

Addition of MR imaging results to model 1 (and thus creation of model 3) significantly improved the model performance (P = .04, likelihood ratio test), indicating that information from MR imaging improved model performance when added to radiographic results. However, as was noted previously, this did not result in a better discrimination between patients who required treatment and patients who could be discharged without follow-up, since both a normal and an abnormal MR imaging result compared with no MR imaging information had a 95% confidence interval that included unity.

Table 4. Multivariable prediction models for prediction of need for treatment after acute knee injury

Predictor and statistic	Model 1	Model 2	Model 3	Model 4
Predictor				
Age ≥ 30 y vs < 30 y	2.88 (1.47, 5.62)	2.38 (1.22, 4.63)	2.62 (1.32, 5.21)	2.52 (1.26, 5.03)
Indirect trauma vs direct trauma	4.89 (2.45, 9.76)	3.40 (1.74, 6.63)	4.17 (2.05, 8.50)	4.15 (2.04, 8.43)
abnormal vs normal radiographic results	5.24 (1.67, 16.4)		3.65 (1.12, 11.9)	
MR imaging results vs no MR imaging information				
Normal		0.53 (0.24, 1.19)	0.58 (0.26, 1.33)	
Abnormal		2.61 (1.12, 6.06)	2.11 (0.89, 5.00)	
Imaging variable *				
Normal radiographic and MR imaging results				0.52 (0.22, 1.21)
Abnormal radiographic results, no MR imaging information				1.90 (0.43, 8.39)
Discrepant radiographic and MR imaging results				1.86 (0.75, 4.65)
Abnormal radiographic and MR imaging results				14.0 (1.62, 121)
Model performance statistics				
Hosmer-Lemeshow goodness-of-fit test†	1.80 (.77)	3.54 (.83)	3.45 (.84)	2.82 (.95)
Area under receiver operating characteristic curve ‡	0.74 (0.67, 0.81)	0.74 (0.67, 0.82)	0.77 (0.70, 0.84)	0.77 (0.70, 0.84)
AIC	28.44	27.71	30.84	30.07

Note: Model 1 contained age, trauma mechanism, and radiographic results; model 2, age, trauma mechanism, and MR imaging results; model 3, age, trauma mechanism, and radiographic and MR imaging results; and model 4, age, trauma mechanism, and overall imaging variable. Except where otherwise indicated, data are odds ratios, and numbers in parentheses represent the 95% confidence interval. All models were fitted for the same 183 patients, with no missing data. A variable was considered significant if the 95% confidence interval did not include unity.

* The reference category was that with normal radiographic results and no MR imaging information.
† Results of this test were not significant for all models, which indicated that the models fit well. Numbers in parentheses are P values.
‡ Numbers of parentheses represent the 95% confidence interval.

The AIC of model 2 was found to be lower than that of model 1, which suggested that MR imaging results as replacements for radiographic results did not improve model performance. Similarly, the performance of model 4 (which included information from MR imaging in the overall imaging variable) was not significantly better than that of model 1. Repeating the analysis with isolated bone marrow edema defined as an

MR imaging finding that required additional treatment did not change the significance of any of the predictors in the univariable and multivariable analyses (data not shown). Similarly, in the separate analysis in which physical therapy was not considered a specific treatment, we found the same significant predictors in the univariable analysis. In the multivariable analysis, age was only a significant predictor in model 1, but the significance of the imaging variables in all models was not affected (data not shown).

Also, all odds ratios of the imaging variables and the model performance statistics were similar.

DISCUSSION

We evaluated the value of MR imaging as a routine screening tool in the initial stage after knee trauma, a setting in which MR imaging has not been widely implemented thus far. The purpose of performing imaging tests in the acute stage is to distinguish patients who require additional treatment from those who do not. This allows patients to be treated appropriately and others to be discharged from follow-up without the need for additional visits or work-up. MR imaging has been advocated as a screening tool prior to therapeutic arthroscopy, since it has proved to be very reliable for noninvasive detection of internal knee derangements (11,20). Application of MR imaging as an initial examination tool in the emergency department setting, however, has been limited because of the associated high costs and other problems, such as burden to the patient, long imaging time, and limited availability of an MR imaging unit.

We used a dedicated extremity MR imaging system, the design of which could overcome most of these problems. Because of the low field strength and the relatively small size of the equipment, such a unit does not require infrastructural changes prior to installation, so that the costs of installation and maintenance of such an MR imaging unit are low compared with those of a high-field-strength whole-body unit. Furthermore, it has been shown that lower magnetic field strength does not substantially reduce the diagnostic performance for most internal knee derangements (11,21–25).

With four multivariable logistic regression models, we assessed the value of a dedicated extremity MR imaging examination, when performed in addition to and instead of radiography, for the prediction of the need for additional treatment in patients with acute knee trauma. Contrary to what we expected, the results of this study suggested that such an MR imaging examination has limited additional value for the prediction of the need for treatment. Although the MR imaging results variable was significant in the prediction of the need for treatment when added to the model with radiographic results, compared with no MR imaging information available, neither abnormal nor normal MR imaging results had significant added predictive value. As an alternative to radiographic results, MR imaging results were only significantly predictive of treatment if they were abnormal, and they did not contribute to the identification of patients who would not require treatment and who could be discharged without follow-up.

Although inclusion was intended to be consecutive, only about half of the eligible patients were randomized. Patients could be included daily from 8:00 AM to 11:00 PM. Many different radiology technologists on service were responsible for asking patients to participate, and they forgot to do so regularly despite multiple efforts by the investigators to improve recruitment. In many instances, patients who were not included could not be traced, so that we could not determine the exact number of missed eligible patients. Since we could not identify a systematic pattern in regard to the characteristics of missed patients, we assume that this suboptimal patient inclusion did not cause substantial selection bias, but it cannot be ruled out.

We used a short MR imaging protocol, which may partly account for the limited additional value of MR imaging that we found in our study. We believe, however, that a more expanded protocol or a protocol that is used in daily practice (routine) for nonemergency patients is not feasible for routine application in the emergency setting because of the excess burden to the patient, with the longer examination time and the higher costs. Furthermore, the aim was to use this protocol as a triage tool to distinguish patients who require treatment from patients who can be discharged without further follow-up. Considering this purpose, we think that a less extensive MR imaging technique than is commonly used for a regular MR imaging examination should suffice.

Our method of interpretation of the MR imaging results also may have influenced the results of this study. We considered an MR imaging study to be abnormal only if one or more lesions that generally require therapy were visible. Visible lesions that are usually not treated, such as a partial rupture of the anterior cruciate ligament, were not counted as abnormal when we used this definition (26,27). Although this is justified in the majority of cases, we recognize that exceptions are possible in specific patient groups, such as professional athletes. Therefore, the results of this study must be judged by taking into consideration the classification method of the MR imaging findings. Although bone marrow edema does not require specific treatment, it can be an indirect manifestation of another lesion; therefore, such a finding may increase the likelihood of treatment. We performed a separate analysis in which isolated bone marrow edema was interpreted as an MR imaging finding that required additional treatment, but results of this analysis did not change the significance of any predictor.

Apart from radiologic techniques, we assessed the predictive value of clinical factors such as age and trauma mechanism. Older age is associated with a higher prevalence of degenerative knee disorders, and this higher prevalence, in turn, is associated with increased likelihood of structural damage after trauma. For example, a meniscal tear occurs more easily in patients who have a meniscus with myxoid degeneration than in those who have an unaffected meniscus. In our analysis, an age of older than 30 years was found to be significantly predictive of treatment required. Older age also is associated with a higher prevalence of preexisting asymptomatic meniscal tears, but symptoms in a patient with such a condition often are not due to that tear itself and will usually resolve within a few months if there are no other abnormalities in the knee joint. Because of the long waiting period for arthroscopy in our institution, it is therefore unlikely that preexisting asymptomatic meniscal tears were unnecessarily treated in our study.

We also recorded whether the mechanism of injury was a direct blow or an indirect trauma, usually due to rotational force or varus or valgus stress, which has been shown to give rise to different patterns of findings at MR imaging (28,29). Whereas a direct hit more often gives rise to a fracture, an indirect trauma more frequently causes meniscal tears, ligament ruptures, and osteochondral lesions and was found to be a significant predictor of the need for treatment in this study.

A potential limitation of this study was that we did not assess the predictive value of findings at physical examination. The accuracy of physical examination of the knee joint, however, has been controversial, especially if performed in the acute stage after injury. It has been widely recognized that extensive joint swelling, pain, or guarding render physical examination without anesthesia inaccurate in the early stage after injury (6–8), which was the period of interest in this study. Moreover, it has been reported that the accuracy of physical examination of the knee is influenced by the experience of the physician (30).

Another limitation of this study was that we defined treatment within the follow-up period as the outcome measure, assuming that this truly reflected the need for treatment in all patients. It is possible, however, that patients were incorrectly discharged from further treatment and follow-up or that patients received unnecessary treatment. We believe that the assumption is justified for patients who were identified as those who did not require therapy. If treatment were incorrectly withheld in the initial stage, these patients would likely have returned and received treatment within the 6 months of follow-up because of persisting symptoms. On the other hand, the appropriateness of a treatment that a patient has already undergone is difficult to assess in retrospect, and we were unable to identify patients who had been treated unnecessarily. Since the treatment of the various lesions was not standardized, the decision to treat and the type of treatment varied across physicians. We would not expect this to influence the results of our study, however, since differences in type of treatment did not affect the outcome measured. Only a difference in the choice of whether or not to treat a patient influenced the outcome, as discussed previously.

Follow-up of patients in this study was limited to a period of 6 months after their initial visit to the emergency department. Although one might argue that we may have incorrectly classified patients in whom treatment was initiated after this 6-month period as having undergone no treatment, we believe that this is rarely the case, since therapy for traumatic lesions of the knee joint is generally initiated soon after the injury, if necessary. Nonetheless, we found that in some cases surgery was performed after the 6-month follow-up period because of the waiting time for arthroscopy. This was the reason why we did not use the need for surgery as an alternative outcome measure in this study. In all of these patients, however, physical therapy had already been initiated within 6 months after first presentation so that these patients were dealt with correctly in our analysis. We acknowledge that the indications for physical therapy are often not well defined, so it can be argued that physical therapy should not count as a specific treatment. Therefore, we repeated the analysis in which physical therapy was not considered a specific treatment, but results of this repeat analysis did not change the conclusions of our study.

With results of this study, one can conclude that a prediction of the need for treatment in patients who present after acute knee trauma can be made on the basis of age, trauma mechanism, and the radiographic results. To apply this prediction rule in clinical practice would require choosing the optimal threshold score, which requires consideration of the likelihood of a treatable lesion and weighing the benefit gained by making a correct prediction against the consequences of making an incorrect prediction, in terms of expected effectiveness and costs. The optimal threshold value of the prediction rule represents the combination of true- and false-positive ratios that yield the greatest expected utility for the patient at acceptable costs to society (16).

We conclude that the value of a dedicated extremity MR imaging examination in the initial stage after knee trauma is limited. A short MR imaging examination, in addition to or instead of radiography, improves the prediction of the need for additional treatment in patients with traumatic knee injury but does not significantly aid in the identification of patients who can be discharged without further follow-up.

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REFERENCES

1. Solomon DH, Simel DL, Bates DW, Katz JN, Schaffer JL. The rational clinical examination: does this patient have a torn meniscus or ligament of the knee? value of the physical examination. JAMA 2001; 286:1610-1620.
2. Smith BW, Green GA. Acute knee injuries. I. History and physical examination. Am Fam Physician 1995; 51:615-621.
3. Scholten RJ, Deville WL, Opstelten W, Bijl D, van der Plas CG, Bouter LM. The accuracy of physical diagnostic tests for assessing meniscal lesions of the knee: a meta-analysis. J Fam Pract 2001; 50:938-944.
4. Kim SJ, Kim HK. Reliability of the anterior drawer test, the pivot shift test, and the Lachman test. Clin Orthop 1995; 317:237-242.
5. Corea JR, Moussa M, al Othman A. McMurray's test tested. Knee Surg Sports Traumatol Arthrosc 1994; 2:70-72.
6. Hardaker WT, Jr, Garrett WE, Jr, Bassett FH, 3rd. Evaluation of acute traumatic hemarthrosis of the knee joint. South Med J 1990; 83:640-644.
7. Mitsou A, Vallianatos P. Clinical diagnosis of ruptures of the anterior cruciate ligament: a comparison between the Lachman test and the anterior drawer sign. Injury 1988; 19:427-428.
8. Simonsen O, Jensen J, Mouritsen P, Lauritzen J. The accuracy of clinical examination of injury of the knee joint. Injury 1984; 16:96-101.
9. Stiell IG, Greenberg GH, Wells GA, et al. Derivation of a decision rule for the use of radiography in acute knee injuries. Ann Emerg Med 1995; 26:405-413.
10. Stiell IG, Wells GA, Hoag RH, et al. Implementation of the Ottawa Knee Rule for the use of radiography in acute knee injuries. JAMA 1997; 278:2075-2079.
11. Oei EH, Nikken JJ, Verstijnen AC, Ginai AZ, Hunink MG. MR imaging of the menisci and cruciate ligaments: a systematic review. Radiology 2003; 226:837-848.
12. Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001; 285:1987-1991.
13. Bossuyt PM, Reitsma JB, Bruns DE, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Radiology 2003; 226:24-28.
14. Nikken JJ. MRI for the initial evaluation of acute wrist, knee, and ankle trauma. Thesis. Rotterdam, the Netherlands: Erasmus MC, 2003.
15. Hosmer DW, Lemeshow S. Assessing the fit of the model In: Applied logistic regression. New York, NY: Wiley, 1989; 135-175.
16. Hunink MG, Glasziou PP, Siegel JE, et al. Decision making in health and medicine: integrating evidence and values Cambridge, England: Cambridge University Press, 2001.
17. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating

characteristic curves derived from the same cases. Radiology 1983; 148:839-843.
18. Akaike H, ed. Information theory as an extension of the maximum likelihood principle Budapest, Hungary: Akademia Kiado, 1973.
19. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996; 49:1373-1379.
20. Vincken PW, ter Braak BP, van Erkel AR, et al. Effectiveness of MR imaging in selection of patients for arthroscopy of the knee. Radiology 2002; 223:739-746.
21. Kersting-Sommerhoff B, Gerhardt P, Golder W, et al. MRT des kniegelenks: erste ergebnisse eines vergleichs von 0,2-T-spezialsystem mit 1,5-T-hochfeldmagnet. [MRI of the knee joint: first results of a comparison of 0.2-T specialized system and 1.5-T high field strength magnet.] Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr 1995; 162:390-395.
22. Vellet AD, Lee DH, Munk PL, et al. Anterior cruciate ligament tear: prospective evaluation of diagnostic accuracy of middle- and high-field-strength MR imaging at 1.5 and 0.5 T. Radiology 1995; 197:826-830.
23. Kladny B, Gluckert K, Swoboda B, Beyer W, Weseloh G. Comparison of low-field (0.2 tesla) and high-field (1.5 tesla) magnetic resonance imaging of the knee joint. Arch Orthop Trauma Surg 1995; 114:281-286.
24. Rutt BK, Lee DH. The impact of field strength on image quality in MRI. J Magn Reson Imaging 1996; 6:57-62.
25. Barnett MJ. MR diagnosis of internal derangements of the knee: effect of field strength on efficacy. AJR Am J Roentgenol 1993; 161:115-118.
26. Sommerlath K, Odensten M, Lysholm J. The late course of acute partial anterior cruciate ligament tears: a nine to 15-year follow-up evaluation. Clin Orthop 1992; 281:152-158.
27. Kannus P, Jarvinen M. Conservatively treated tears of the anterior cruciate ligament: long-term results. J Bone Joint Surg Am 1987; 69:1007-1012.
28. Hayes CW, Brigido MK, Jamadar DA, Propeck T. Mechanism-based pattern approach to classification of complex injuries of the knee depicted at MR imaging. RadioGraphics 2000; 20(special issue):S121-S134.
29.Sanders TG, Medynski MA, Feller JF, Lawhorn KW. Bone contusion patterns of the knee at MR imaging: footprint of the mechanism of injury. RadioGraphics 2000; 20 (special issue):S135-S151.
30. Boeree NR, Ackroyd CE. Assessment of the menisci and cruciate ligaments: an audit of clinical practice. Injury 1991; 22:291-294.

5

Acute Peripheral Joint Injury: Cost and Effectiveness of Low-Field-Strength MR Imaging - Results of Randomized Controlled Trial

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ABSTRACT

PURPOSE: To assess prospectively if a short imaging examination performed with low-field-strength dedicated magnetic resonance (MR) imaging in addition to radiography is effective and cost saving compared with the current diagnostic imaging strategy (radiography alone) in patients with recent acute traumatic injury of the wrist, knee, or ankle.

MATERIALS AND METHODS: Institutional review board approval and informed consent were obtained. Patients with recent trauma of the wrist, knee, or ankle were randomized across two diagnostic strategies: radiography alone (reference group) or radiography followed by a short MR imaging examination (intervention group). Measures of effectiveness included the number of additional diagnostic procedures, time to last diagnostic procedure, and number of days absent from work. Measures of effectiveness were analyzed by using an exact Wilcoxon-Mann-Whitney test. Time to convalescence and quality of life were analyzed by using a t test. Cost analysis was performed from a societal perspective and analyzed by using a t test.

RESULTS: Five hundred patients (207 women, 293 men; mean age, 34.8 years) with acute injury of the wrist, knee, or ankle were randomized. In the intervention group, quality of life for patients with knee injuries was significantly higher during the first 6 weeks, and time to completion of diagnostic work-up was significantly shorter (mean, 3.5 days for intervention group vs 17.3 days for reference group). The number of additional diagnostic procedures was significantly lower in the intervention group versus the reference group (nine vs 35, respectively) for patients with knee injuries. Patients with knee injuries showed the largest difference in costs (intervention group, ¤1820 [$1966]; reference group, ¤2231 [$2409]) owing to a reduction in productivity loss. Costs were higher in patients with wrist injuries and almost equal in patients with ankle injuries. All cost differences, however, were not significant.

CONCLUSION: Compared with radiography, MR imaging in patients with acute wrist or ankle injuries is neither cost saving nor effective in expediting diagnostic work-up or improving quality of life. In patients with knee injuries, a short MR imaging examination shortens the time to completion of diagnostic work-up, reduces the number of additional diagnostic procedures, improves quality of life in the first 6 weeks, and may reduce costs associated with lost productivity.

INTRODUCTION

It is common practice to perform diagnostic imaging for the initial evaluation of acute wrist, knee, or ankle injuries. Most fractures can be detected fairly accurately by using radiography. Radiography, however, provides limited information concerning soft-tissue injury, such as tendon rupture, ligament rupture, or meniscus tears. Moreover, some fractures may be occult to radiography; a well-known example of this is the scaphoid fracture (1–3). Also, osteochondral lesions are sometimes not well visualized at radiography. To demonstrate these lesions, magnetic resonance (MR) imaging would be the most suitable tool. Because MR imaging systems are in heavy demand in various medical disciplines, such systems are often not readily available. Furthermore, the high costs, the relatively long duration of the examination, and the fact that about 5% of patients examined with whole-body MR systems cannot complete the examination because of claustrophobia (4) limit the use of MR imaging for the initial evaluation of acute joint injuries. Many of these constraints, however, may be overcome by the application of relatively inexpensive low-field-strength dedicated extremity MR imaging systems. The purchase and maintenance costs of these systems are considerably lower than those of whole-body systems, and, because only peripheral joints can be imaged, availability is less of a problem. Moreover, claustrophobia is almost ruled out because only the arm or leg of interest is placed within the magnet bore while the patient is lying on a chair next to the MR imager.

Although the addition of an MR imaging examination to the initial diagnostic work-up of patients with recent acute traumatic joint injury will obviously generate extra costs, it is expected that this extra examination may shorten the time to diagnosis. MR imaging at first presentation may also save costs if it obviates further follow-up, additional diagnostic procedures, and temporary treatment measures, such as the use of a plaster cast in cases of a suspected scaphoid fracture. It may also save costs to society if the early diagnosis leads to an earlier treatment and, hence, to an earlier recovery, thereby reducing a loss of productivity. Because the costs of lost productivity can be considerable, reducing the number of days off of work in a minority of patients may justify a short MR imaging examination in all patients. Thus, the purpose of our study was to assess prospectively if a short MR imaging examination performed with low-field-strength dedicated extremity MR imaging in addition to radiography is effective and cost saving compared with the current diagnostic imaging strategy (radiography alone) in patients with recent acute traumatic injury of the wrist, knee, or ankle.

MATERIALS AND METHODS

Study Design

We conducted a prospective, randomized, controlled trial at a university hospital from August 1999 to May 2001. The study was approved by our institutional review board and performed in accordance with the Helsinki Declaration of 1964, amended in

1989. The study was supported in part by an unrestricted grant from Esaote Biomedica, Genoa, Italy. Esaote Biomedica was not involved in any way with the design, data collection, analysis, or reporting of this study. This article reports some of the data and analyses of the study; other data and analyses are reported in different articles (5–7). After receiving written and oral information about the purpose of the study, all participants gave informed consent. We used the Consolidated Standards of Reporting Trials statement to report study results (8).

Three parallel studies were conducted for the wrist, knee, and ankle. Patients were eligible if they had recent injury (within 7 days of trauma) of the wrist, knee, or ankle and if radiography of the affected joint had been requested by specialists or residents in traumatology, orthopedic surgery, or emergency medicine. If more than one joint was affected, inclusion was directed according to the joint that caused the most complaints.

The patients were randomized across two diagnostic strategies: radiography alone (reference group) and radiography followed by a short MR imaging examination (intervention group). Randomization was achieved by drawing from consecutively numbered sealed envelopes containing computer-generated random assignments. Block randomization was applied, and a block size of 20 was used to achieve an equal number of patients in both study groups. Randomization was stratified according to joint, and the envelopes were labeled accordingly.

Patients were excluded if they had substantial injury to the head, back, thorax, or abdomen; if they had a compound fracture; if they were in need of urgent treatment (eg, if they had ankle luxation or an open fracture); if they had preexisting complaints in the same joint; or if they were intoxicated. Patients were enrolled from 8:00 AM to 11:00 PM, 7 days a week, from August 1999 to May 2001. Inclusion was carried out by research staff and by the radiology technologists on service.

Sample Size Calculation

To demonstrate a mean difference in costs of ¤500 ($540), with a standard deviation of the mean difference equal to ¤800 ($864), a sample size of 80 patients (power = .8, α = .05, two-sided test) was required per joint evaluated. Patients were enrolled until at least 80 patients per joint were included.

Radiography and MR Imaging

Radiographs of the wrist were obtained in the lateral and posteroanterior projection and were supplemented with a scaphoid series if a scaphoid fracture was suspected. Radiographs of the knee were obtained in the lateral and anteroposterior projection and were supplemented with patellar or tunnel views if pathologic abnormalities of the patellofemoral joint or intercondylar notch were suspected. Radiographs of the ankle were obtained in the lateral and anteroposterior projection, with 15° endorotation of the foot.

MR imaging was performed with a 0.2-T dedicated extremity MR imaging system (Artoscan M; Esaote Biomedica, Genoa, Italy) immediately after radiography. We used a short MR imaging protocol (Table 1) with one excitation for each sequence by using a rectangular field of view and a limited number of phase-encoding steps. After a software upgrade in February 2000, the T1-weighted spin-echo half-Fourier sequence was replaced with a T1-weighted spin-echo sequence, and, for the turbo multi-echo sequence, the first echo time was shortened from 38 to 28 seconds (on the Artoscan M system, echo time is fixed and cannot be changed by the user). The software upgrade included improved filtering and frequency sampling. The total acquisition time was 5–6 minutes for all joints, with a total examination time (including MR imaging system start-up and patient positioning) of approximately 15 minutes.

Image Interpretation

A radiologist with 25 years experience in musculoskeletal radiology (A.Z.G.) or a radiology resident in the 2nd–5th year of training immediately assessed the MR images and reported findings to the treating physician. If the MR images were assessed by the radiology resident (eg, during weekends or evening hours), the images were reassessed the next day by one of two musculoskeletal radiologists (A.Z.G. or a radiologist with 4 years experience in musculoskeletal radiology). If the interpretation was different, the treating physician was informed.

Radiographs were initially assessed by the treating physician in the emergency department. Radiographs were then reassessed the next day during a reading session with the treating physician by one of the two musculoskeletal radiologists mentioned earlier. If the reassessment differed from the initial assessment for either the MR images or the radiographs, treatment from that moment on was based on the assessment of the musculoskeletal radiologist. No second MR imaging or radiographic examinations were performed between the two readings.

Patient Follow-up

Clinical data were collected from patient hospital records and from the hospital computer system (J.J.N., E.H.G.O). The follow-

Table 1. Parameters of the short MR imaging protocol

Imaging sequence	Repetition time (msec)	Echo time (msec)	Imaging matrix	Section thickness (mm)	Acquisition time (sec)
T1-weighted spin-echo half-Fourier	420-630	18-24	192-256 x 136	3.0-5.0	43-68
Turbo multi-echo (intermediate and T2-weighted)	1980-2480	28-38/90	192-246 x 128	3.0	143-161
Gradient echo *	360-420	15	192 x 152	3.0-5.0	44-53
Short inversion time inversion recovery †	830-1060	24-28	192 x 128	4.0-5.0	97-106

Note: For all sequences, a 200x140-mm, number field of view and one excitation were used.
* Flip angle = 75°.
† Inversion time = 80-85 msec.

up period was for as long as the patient had daily complaints, as recorded on questionnaires, with a maximum follow-up period of 6 months. We expected that this 6-month follow-up period would be long enough to capture all relevant differences in the outcomes between the two strategies. Questionnaires were sent to patients at 1 week, 6 weeks, 3 months, and 6 months after inclusion. These questionnaires included quality-of-life measuring instruments and questions about the number of days absent from work, the number of days to convalescence (ie, the number of days until the patient no longer had daily complaints), medical treatment at other institutions, treatment by a general practitioner, treatment by alternative medicine practitioners, and out-of-pocket expenses. If questionnaires were not returned, we interviewed the patients by telephone (J.J.N., E.H.G.O.) and urged them to return the questionnaire, provided that patients could be reached within two calling attempts. If the patient indicated on the questionnaire that he or she no longer had daily complaints, then follow-up was terminated because no additional effects of the injury were expected.

Measures of Effectiveness

Measures of effectiveness included quality of life, time to completion of the diagnostic work-up, the number of additional diagnostic procedures during follow-up (eg, radiologic imaging, diagnostic arthroscopy, or blood tests), the number of days absent from work, and the number of days to convalescence. We included the number of diagnostic procedures during follow-up to calculate costs and to be sure that the relatively lower quality of the short MR imaging examination did not lead to additional standard MR imaging examinations in the intervention groups. Quality of life was measured with a descriptive instrument (Short Form 36 [SF-36] health survey) (9) and with a valuative instrument (EuroQol), which provided general population values (10,11). The SF-36 health survey consists of 36 questions that are used to assign values to eight health domains (ie, physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health). Role physical and role emotional refer to the degree of interference with work or other daily activities as a result of impaired physical health or emotional problems. The EuroQol uses five questions to obtain a single index value for health status. The time to completion of the diagnostic work-up was defined as the time from initial presentation to the time of last diagnostic imaging or arthroscopic examination. The number of diagnostic procedures was assessed by reviewing the hospital computer system and by asking patients by questionnaire or by telephone inquiry if any diagnostic procedure had been performed at another institution. Likewise, the number of days absent from work and the number of days to convalescence were asked in the questionnaires or, if the questionnaire was not returned, by telephone inquiry.

Analysis of Response

To test for response bias, the baseline characteristics (ie, sex, age, and randomization result [MR imaging vs no MR imaging]) of patients who returned the questionnaires were compared with the baseline characteristics of patients who did not return the questionnaires. Baseline characteristics were compared by using a t test, and a P value of .05 was used as a threshold for statistical significance. To assess if the response rate depended on the severity of disease, we used the variables "treatment" and "number of days absent from work" as proxy measures of the severity of disease and assessed whether the outcome of these variables differed significantly between responders and nonresponders. Although we did not record the ethnicity of the patients, we analyzed if patients with a nonnative name showed a response rate that was different from those with a native name. This analysis allowed us to determine if culturally determined differences in response rate were present.

Statistical Analysis of Effectiveness

The data were analyzed on an intent-to-diagnose and intent-to-treat basis. For both strategies, the number of days to convalescence was compared by using a t test. The number of days to completion of the diagnostic work-up, the number of diagnostic procedures performed during follow-up, the number of days absent from work, and the evaluation of response bias were analyzed by using an exact Wilcoxon-Mann-Whitney test and a χ^2 test. Because of multiple testing, we adjusted the P value significance threshold from .05 to .01.

If a patient indicated on one of the four questionnaires that he or she was free of complaints, we expected no further change in the quality of life for the patient, and the EuroQol and SF-36 health survey data measured at that point in time were extrapolated to the remaining questionnaires. If, at this stage, less than 20 responses were available in either the intervention or reference groups, which were stratified according to joint, then these responses were regarded as too few for meaningful analysis. If the EuroQol and SF-36 health survey data for patients without complaints were not available for extrapolation, then the mean values for the EuroQol and for the eight SF-36 health survey domains were used instead. These mean values were derived from the completed questionnaires in all complaint-free patients. Linear regression analysis was used to determine if these mean values had to be adjusted for age and sex. Imputed values were used in the analysis only if they constituted less than 20% of the data. The preference-based EuroQol score was calculated by using the regression equation, as described by Dolan (12). Differences between the randomized groups for EuroQol and SF-36 health survey domain scores were analyzed by using a t test.

Cost Analysis and Related Statistical Analysis

The cost analysis included measures of all medical and nonmedical costs associated with the initial injury during the 6-month follow-up period that were relevant from a societal perspective. Direct medical costs included the cost of hospital visits, diagnostic and therapeutic procedures, physical therapy inside or outside the hospital, visits to general practitioners, and visits to alternative medical practitioners, as well as the travel costs for each visit. Costs of all diagnostic procedures were calculated by using a bottom-up approach (13) that took into account the initial investment of equipment, additional costs during use, maintenance costs, years of use, discounting and annuitization (14), the number of procedures performed per year, personnel costs, materials used, room rent, housekeeping, administration, and overhead costs. Costs were discounted at a rate of 3% per annum (15). Costs of initial treatment (eg, the costs of a bandage or plaster cast) were calculated likewise. The estimated actual cost of hospital visits and hospital admissions were obtained from the Dutch Council for Care Insurances (13). For costs of surgical procedures, reimbursement tariffs, as established by the Dutch Central Organ for Tariffs in Healthcare, were used. Indirect medical costs (ie, medical costs in life-years gained) were not considered because we did not expect a difference in life-years.

For measurement of direct nonmedical costs, we took into account out-of-pocket expenses and patient time costs. Information on out-of-pocket expenses was derived from the questionnaires or from telephone inquiry. Patient time costs were determined by multiplying the time spent on medical procedures (eg, hospital admissions, outpatient hospital visits, visits to the general practitioner, travel time, and waiting time) by the average net income of patients (both working and not working) who were comparable in age for the year 2000 (Dutch Central Bureau for Statistics, www.cbs.nl) (15).

For indirect nonmedical costs, we assessed costs associated with production losses. Production losses were estimated by using the friction cost method described by Koopmanschap et al (16) and recommended in guidelines for cost-effectiveness analysis (15). This method assumes that production losses are generated only during the time it takes to replace a sick employee–that is, during the friction period. Short-term absence from work may cause limited loss of production because work may be postponed and performed on return, or work may be performed by colleagues. Long-term absence from work generates costs owing to actual production losses, extra costs to maintain production, and the costs of filling a vacancy and, if a permanent replacement is needed, of training a new worker. These costs are called friction costs and are influenced by the unemployment rate and the extent of mobility in the labor market. Friction costs were calculated by using the friction cost data estimated for workers in the Netherlands in 1998, which are based on age and sex and are described by Oostenbrink et al (13). These data were adjusted for a general increase in income in 2000 compared with 1998. The friction period for the year 1998 was estimated at 4 months (13), but because of increased shortage in the labor market, we estimated the friction period to be 6 months for the year 2000 (M. A. Koopmanschap, oral communication, 2002).

Costs were analyzed on an intent-to-diagnose and intent-to-treat basis and were compared by using a t test, with a P value of .05 as the threshold for statistical significance. We performed cost analysis for the three joints separately. Costs are expressed in both euros and in U.S. dollars and were calculated by using the mean exchange rate during the inclusion period (¤1.08 = $1.00).

Sensitivity analysis was used to determine the robustness and generalizability of the study results. One-way sensitivity analysis was conducted by exploring 50%–200% of the baseline value for each single cost and by analyzing the time assigned to each medical procedure, as well as the travel time, friction costs, and friction period. Three-way sensitivity analysis was conducted on the parameters that were most sensitive in the one-way analysis.

All analyses were performed by using statistical software packages (Excel 97 SR-2, Microsoft, Redmond, Wash; SPSS, version 10.0.0, SPSS, Chicago, Ill; and StatXact-4, Cytel Software, Cambridge, Mass).

RESULTS

From August 1999 to May 2001, 500 patients (207 women, 293 men; mean age, 34.8 years; age range, 12.0–85.0 years; standard deviation, 15.1) were included for study. A flow chart of the study design is presented in Figure 1. Although inclusion was intended to be consecutive, only about half of all eligible patients were randomized. This could be attributed not only to patients

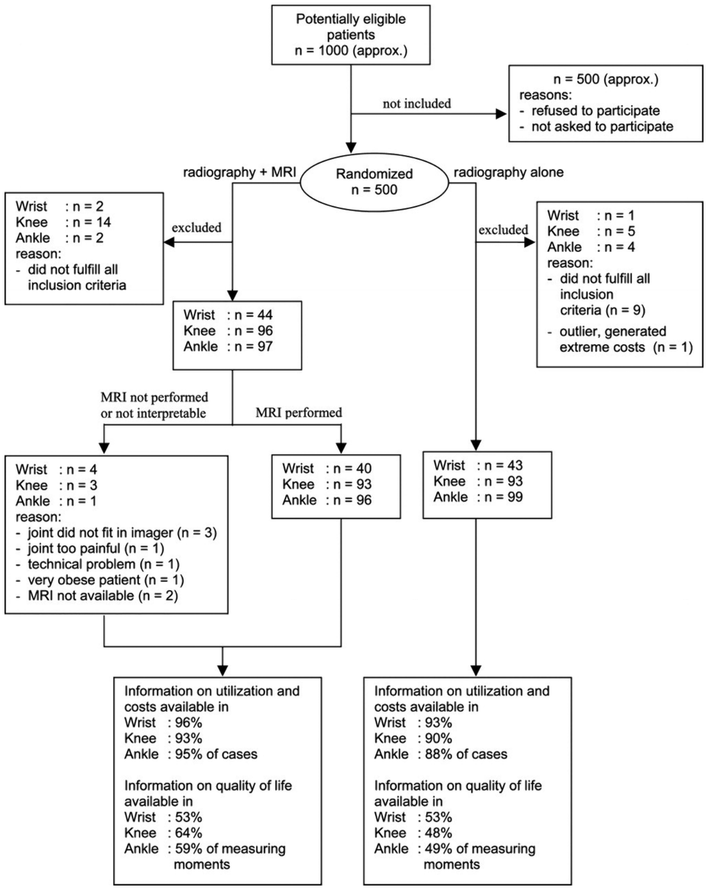

Figure 1. Flow chart demonstrates study design for 500 patients (207 women, 293 men; mean age, 34.8 years) with acute injury of the wrist, knee, or ankle who were randomized across two diagnostic strategies: radiography alone (reference group) or radiography followed by a short MR imaging examination (intervention group). For information on quality of life assessment, measuring moments were defined as responses obtained 1 week, 6 weeks, 3 months, and 6 months after inclusion.

who refused to participate in the study but also to eligible patients who were not asked to participate. This was caused by the fact that patients were enrolled 7 days a week, from 8:00 AM to 11:00 PM, and thus many different on service radiology technologists were supposed to ask patients to participate. Asking patients to participate in the study was forgotten regularly. Because it was often impossible to retrace if these missed patients would have been eligible, the exact numbers of eligible patients who were missed could not be obtained.

Twenty-eight randomized patients were excluded at various points in time after inclusion. On review, 27 patients did not fulfill the inclusion criteria, and one patient was an outlier in several respects. This outlier patient was a 79-year-old woman with a severe luxation fracture of the ankle who came to the hospital only 6 days after the injury. For logistic reasons, she was transported to another hospital where she underwent surgery and was hospitalized for more than 6 months because of many complications. Her medical costs were almost twice the total medical costs of all other patients with ankle injury together, and her time costs were almost three times the total time costs for all patients with ankle injury together.

Of the remaining 472 patients, 237 were allocated to the MR imaging strategy (MR imaging plus radiography) and 235 were allocated to the reference strategy (radiography alone). In eight patients who were allocated to the MR imaging strategy, either MR imaging was not performed or the results were not interpretable. In one patient, a technical failure occurred, and in another patient, the examination was interrupted because of pain. In one obese patient, the image quality was too poor for interpretation, and in two patients, the MR imaging system was not available. In three patients, the joint of interest could not be positioned in the center of the magnet bore: One patient was not able to extend the elbow, one patient had a locked knee, and one patient's knee was too big to fit into the magnet. For analysis, these eight patients remained in the strategy they were originally assigned to.

Response Characteristics

We found no significant difference in sex, age, or the number of days absent from work between patients who had returned questionnaires and patients who had not returned questionnaires. Among patients with ankle injuries, however, the number of patients who returned one or more questionnaires was slightly higher for those who underwent MR imaging than for those who did not (84% vs 72%, respectively; $P = .05$). Furthermore, in patients with knee or ankle injuries, the response rate differed significantly between patients who had undergone additional treatment and those who had not undergone additional treatment (93% vs 61% for patients with knee injury [$P < .01$] and 85% vs 68% for patients with ankle injury [$P = .01$]). An estimated 20% of our patients were nonnatives who had a varying ability to speak the national language. Patients with a nonnative name showed a response rate that was significantly lower than that of patients with a native name (P =

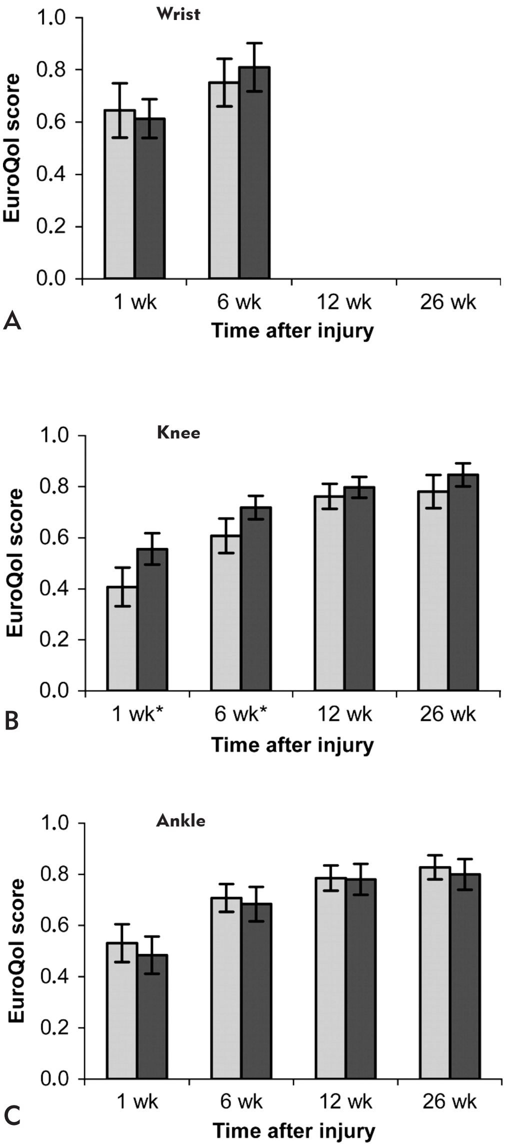

Figure 2. Bar graphs demonstrate mean EuroQol values for radiography alone (light gray bars) and radiography plus MR imaging (dark gray bars) in patients with (a) wrist, (b) knee, and (c) ankle injuries. Error bars indicate 95% confidence intervals. For patients with wrist injuries, 3-month and 6-month scores were omitted because paucity of data precluded meaningful analysis. Quality of life after injury improved over time for all patient groups. The difference between patients who underwent a short MR imaging examination and those who did not was statistically significant (*) only for patients with knee injuries at 1 and 6 weeks. In all joints, differences at long-term follow-up did not differ between randomized groups.

.001, χ^2 test). The patients with nonnative names were evenly distributed between the two randomized groups (P = .23, χ^2 test).

Effectiveness

After extrapolation of EuroQol and SF-36 health survey data in censored patients (ie, those in whom follow-up was ceased because they no longer had complaints), data were used for analysis only if the number of completed questionnaires exceeded 20 in both the intervention and reference groups for each of the joints. More than 20 questionnaires were returned in all groups except for the third and fourth questionnaire in patients with wrist injuries. Linear regression analysis showed that mean EuroQol and SF-36 health survey domain scores of patients without complaints were not significantly influenced by age or sex, and, therefore, the total mean values of EuroQol and SF-36 health survey domain scores were used for imputation. In all four questionnaires, which were stratified according to joint and randomization result, less than 20% of the questionnaires were imputed.

In patients with wrist or ankle injuries, no significant difference was found between the intervention and reference group for EuroQol scores measured at 1 week, 6 weeks, 3 months, and 6 months after injury (Fig 2). In patients with knee injuries, the EuroQol score at 1 week and at 6 weeks was significantly higher in the intervention group (P = .003 and P = .01, respectively; t test). Three months after injury, this difference was no longer significant.

All the SF-36 health survey domains (except general health) demonstrated improvement in quality of life over time (Fig 3). There were, however, a few significant differences between the intervention group and the reference group. For patients with wrist injuries, the vitality and role emotional domains were scored higher in the intervention group at 6 weeks. For patients with knee injuries, the physical functioning score was higher in the intervention group at 1 week. For patients with ankle injuries, the mental health score was lower in the intervention group at 6 weeks and at 6 months.

Only in the intervention group of patients with knee injuries was the number of diagnostic procedures performed during follow-up and the time to completion of the diagnostic work-up significantly lower than that of the reference group (P < .001 and P = .003, respectively) (Table 2). The duration of absence from work did not differ significantly between any of the intervention or reference groups. Although time to convalescence was lower in the intervention group for all joints, this difference was not statistically significant compared with that of the reference group.

Costs

The mean total medical and nonmedical costs associated with joint injury are listed in

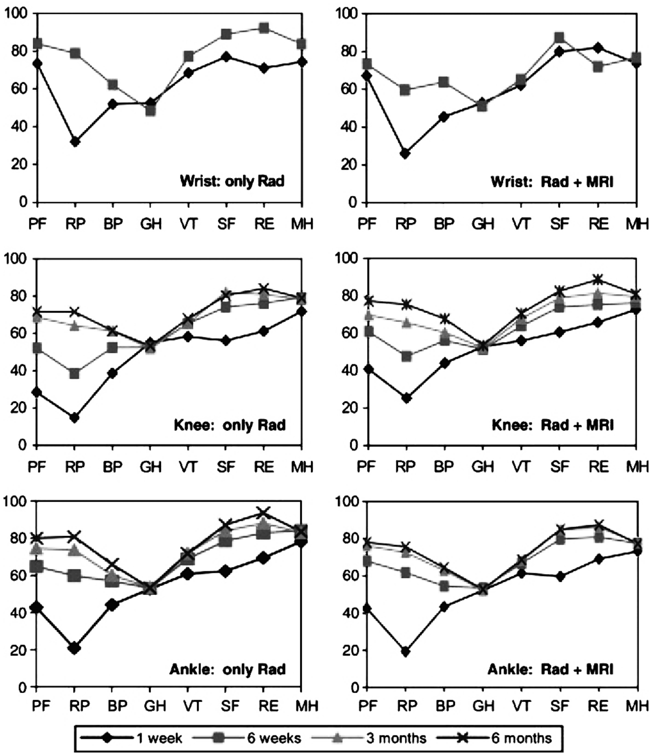

Figure 3. Line graphs demonstrate mean SF-36 health survey domain scores for radiography alone (only Rad) and radiography plus MR imaging (Rad + MRI) in patients with wrist (top), knee (middle), and ankle (bottom) injuries at 1 week, 6 weeks, 3 months, and 6 months. For patients with wrist injuries, 3-month and 6-month scores were omitted because paucity of data precluded meaningful analysis. All SF-36 health survey domain scores improved over time except for those of general health. For patients with wrist injuries, vitality and role emotional domain scores were significantly higher for the intervention group at 6 weeks. For patients with knee injuries, physical functioning score was higher for the intervention group at 1 week. For patients with ankle injuries, mental health score was lower for the intervention group at 6 weeks and at 6 months. BP = bodily pain, GH = general health, MH = mental health, PF = physical functioning, RE = role emotional, RP = role physical, SF = social functioning, VT = vitality. (Note that lines between points are only to improve visual comparability and do not have intrinsic meaning.)

Table 2. Comparison of measures of effectiveness across strategies

Parameter	Wrist			Knee			Ankle		
	Reference group (n=43)	Intervention group (n=44)	P value	Reference group (n=93)	Intervention group (n=96)	P value	Reference group (n=99)	Intervention group (n=97)	P value
No. of additional diagnostic procedures*	6 (2)	3 (0)	.41	35 (28)	9 (3†)	<.001	10 (1)	1 (0)	.04
Mean time to last diagnostic procedure (d)	1.0	4.3	.43	17.3	3.5	.003	3.4	0.1	.10
Mean duration of absence from work (d)	5.0	8.6	.31	12.4	9.6	.36	12.6	11.2	.70
Mean time to convalescence (d)‡	54.3	49.6	.71	76.6	66.2	.45	55.9	54.0	.84

Note: Unless otherwise noted, all differences were tested with the exact Wilcoxon-Mann-Whitney test.
* Numbers in parentheses indicate the number of MR imaging examinations.
† These three patients were among the eight patients in whom the initial short MR imaging examination was not performed or the results were not interpretable.
‡ Difference was tested with t test.

Table 3. Mean costs associated with the initial injury from the societal perspective (in euros)

Costs	Wrist				Knee				Ankle			
	Reference group	Intervention group	Difference	P value	Reference group	Intervention group	Difference	P value	Reference group	Intervention group	Difference	P value
Medical	344	306	-38	.59	606	691	85	.51	328	368	40	.48
Travel	12	10	-2	.32	16	17	1	.52	12	11	-1	.29
Friction	519	766	247	.42	1510	993	-517	.18	1285	1265	-20	.96
Time	31	24	-7	.53	99	118	19	.70	35	30	-5	.73
Total	905	1106	201	.53	2231	1820	-411	.35	1660	1675	15	.98

Note: For the difference in costs between the intervention and the reference groups, a negative sign indicates a reduction of costs with use of MR imaging.
All P values were calculated by using a *t* test.

Table 4. One-way sensitivity analysis of the mean total cost difference between intervention strategy and reference strategy

	Wrist				Knee				Ankle			
Parameter	**50%**	**100%**	**200%**	**Range**	**50%**	**100%**	**200%**	**Range**	**50%**	**100%**	**200%**	**Range**
Friction costs	77	201	448	371	-153	-411	-929	776	24	15	-5	29
Friction period	165	201	201	36	-264	-411	-412	148	133	15	14	119
Short MR imaging examination	172	201	257	85	-440	-411	-355	85	-14	15	71	85
Outpatient visit	222	201	159	63	-425	-411	-385	40	21	15	2	19
Time costs	204	201	194	10	-421	-411	-392	29	17	15	10	7
Hospital day	208	201	185	23	-418	-411	-398	20	14	15	15	1
Physiotherapy	200	201	201	1	-416	-411	-402	14	22	15	-1	23
Standard MR imaging examination	201	201	201	0	-408	-411	-418	10	16	15	14	2
Radiography	214	201	173	41	-413	-411	-408	5	11	15	22	11
Surgical therapy	208	201	185	23	-410	-411	-415	5	9	15	25	16
General practitioner visit	195	201	211	16	-411	-411	-412	1	12	15	19	7

Note: The costs difference between the two strategies was recalculated for each single variable at 50% and 200% to assess the influence of variation of that value on the total cost difference. A negative cost difference indicates a reduction in costs with use of MR imaging. The range is a measure of the sensitivity of the cost difference of that variable. Only the 11 most sensitive variables are presented. Costs are in euros.

Table 3. The largest difference in total costs was found in patients with knee trauma. This difference was attributable to a reduction in the friction costs with use of MR imaging. In patients with wrist injuries, the friction costs increased slightly with the use of MR imaging. In patients with ankle injuries, costs were similar in both the intervention and reference group. For all three joints, the differences in costs were not significant.

Sensitivity Analysis

One-way sensitivity analysis in patients with wrist or knee injuries showed that friction costs were the most sensitive single variable of total cost difference between the intervention group and reference group (Table 4). In patients with ankle injuries, friction costs were similar in both groups, and, therefore, variation did not influence the difference between these groups as much as in the other two joints. In patients with knee or ankle injuries, the duration of the friction period was also influential. The cost of the short MR imaging examination was the third most sensitive variable in all groups. Three-way sensitivity analysis of friction costs, friction period, and short MR imaging examination costs demonstrated that, within a plausible range of values for the analyzed variables, conclusions for the wrist and the knee did not change. For patients with ankle injuries, the results were sensitive for the friction period.

DISCUSSION

Only a few cost analysis studies have been published on the application of MR imaging in joint trauma. Most of these studies were performed in the United Kingdom and consider the National Health Service perspective (17–19). To our knowledge, no studies have been performed that assess the cost-effectiveness of MR imaging in acute joint trauma from a societal perspective.

We expected that the main benefit of early diagnosis of acute trauma in the wrist, knee, or ankle by using a dedicated extremity MR imaging system would be twofold—that is, a decrease in the need for follow-up and a reduction in the time to convalescence. A decreased need for follow-up could lead to potential cost savings by reducing follow-up visits, additional imaging examinations, diagnostic arthroscopy, and temporary treatment measures. This, in turn, would also reduce patient time, travel, and friction costs. A reduction in the time to convalescence would result from a reduction in the time to diagnosis, which is associated with earlier treatment. This could lead to cost savings for society owing to an earlier resumption of work (ie, a reduction in friction costs). The aforementioned effects could lead to a total cost reduction provided that the cost savings outweigh the additional costs of performing a short dedicated extremity MR imaging examination in every patient.

In our patient population, we could not demonstrate that a short MR imaging examination in addition to radiography provided cost savings from a societal perspective. In patients with knee injuries, however, the mean total costs were substantially lower in the intervention group because of the reduced costs of lost productivity, but this difference was not statistically significant. The influence of a short MR imaging examination on other outcomes was demonstrated only in patients with knee injuries; quality of life was improved in the first 6 weeks, the number of examinations during follow-up was lower in the intervention group, and the time to diagnosis was reduced by 12 days. Both the duration of absence from work and the time to convalescence did not differ significantly between the intervention group and the reference group for all three joints.

The addition of MR imaging to the initial diagnostic evaluation had no influence on the quality of life 3–6 months after injury, as measured with the EuroQol and SF-36 instruments. The short-term (1–6 weeks) EuroQol outcome in patients with knee injuries was, however, significantly higher in the intervention group compared with the reference group. This may reflect a more adequate initial treatment in the intervention group. Another possible explanation would be that, despite randomization, the intervention group had less severe injuries than the reference group. There were, however, no indications of a difference in the severity of injury between the two groups; there was no significant difference in number of patients receiving treatment, the number of hospital admissions, or the length of hospital stay between the two groups.

In the SF-36 health survey, the valuation of general health was strikingly similar in all groups and did not change over time, whereas all other domains improved over time. A traumatic injury of the wrist, knee, or ankle apparently does not affect a patient's appreciation of his or her general health. This might be caused by the fact that, for most injuries, total recovery is expected, and, therefore, the patient does not consider the injured joint as a sign of impaired general health.

A limitation of this study is the setting in which it was performed. The Dutch health care system is faced with the problem of long and variable waiting lists. The variation in waiting lists for outpatient visits and surgical procedures may have influenced the time to convalescence as an outcome measure. At our hospital, the waiting list for arthroscopy at the time of the trial was 5 months. We therefore used the time to the last diagnostic procedure as a more representative measure. Likewise, it is plausible that the friction costs were also influenced by the waiting lists. Although the extra friction costs caused by waiting lists were incurred in both the intervention group and the reference group, the increase of these costs in both groups could have masked a difference between the groups. Furthermore, friction costs were the most sensitive single variable influencing the cost difference between the randomized groups. Because these costs are influenced by income and by the state of the labor market, the results of the study are probably applicable only to societies comparable to the Dutch society.

We recognize that early detection and surgical treatment of a condition is not always necessary for recovery. Some meniscal tears, triangular fibrocartilage complex lesions, or ligament injuries may heal without specific treatment (20). In this perspective, the presence of waiting lists not only is unfavorable for the patient but also may allow time for the natural recovery of a condition.

The fact that not all eligible patients were asked to participate may have introduced a selection bias if either more or fewer patients with obvious injuries were preferentially not asked to participate. In the more seriously injured patients, MR imaging is likely to have had more additional diagnostic value than in patients with minor injury; therefore, this bias would cause the effects and potential cost reduction of a short MR imaging examination to be underestimated.

The response rate on the questionnaires was low for all groups. At the moment of enrollment, the importance of completing the questionnaires was stressed, and patients were urged to return the questionnaires. If the questionnaires were not returned in time, the patients were called by phone. Despite our efforts, the response rate was less than optimal. Typical response rates for postal questionnaires are about 60%–65% (21–30). A reason for the lower response rate in our study may be that patients are less willing to take the effort to respond if the disease does not have a major effect on their health and if the disease is not likely to last long.

Another factor influencing the response rate is the fact that nonnative participants may have had difficulty understanding the national language. The lower response rate for patients with a nonnative name may be attributable to their limited knowledge of the language or possibly to cultural differences. Patients with nonnative names were evenly distributed between the two randomized groups, so their relatively large contribution to the high nonresponse rate is not likely to have caused response bias. For the analysis of costs, we were much less dependent on the low response rate because we could retrieve most data from the hospital computer system and patient records, which were complemented by telephone inquiry.

In this pragmatic randomized controlled trial, no blinding was used. Patients knew whether an MR imaging examination was performed or not. This influenced the response rate of patients with ankle injury in that patients who had undergone MR imaging were more likely to return their questionnaires. It also potentially influenced the time to convalescence because patients may have been reassured by a negative MR imaging result. Reassurance is, however, part of performing MR imaging and should not be regarded as a bias in this context. Blinding could have been achieved by performing a placebo MR imaging examination or by not providing the information obtained at MR imaging (31). Because of the expected confusion and opposition of patients with an acute joint injury to such a study design, as well as ethical considerations of not providing information, we chose a nonblinded pragmatic study design.

Part of the pragmatic design of the study was the MR imaging system software upgrade that occurred during the study, which may have improved image quality in the latter part of the study. Because MR imaging software upgrades can be expected in daily practice, we considered the upgrade acceptable in this pragmatic study. The extent of acceptance of the short MR imaging examination by clinicians may also have introduced a bias. We noticed that clinicians were sometimes hesitant to use the results of the short MR imaging examination in their decisions. This acceptance curve of the new technology may have biased the outcome of the study in favor of the reference strategy. Nevertheless, we did find that if a short MR imaging examination had been performed in the acute setting, patients were less likely to undergo further examinations during follow-up.

In this study, a short MR imaging protocol was used to make the examination time acceptable for routine use in the emergency department, as well as to reduce costs. A shortening of the duration of the MR imaging examination comes at the cost of some loss in image quality, but in a pilot study (32), we found that the image quality was acceptable to demonstrate most clinically important lesions. It is likely that, by using this short MR imaging protocol, some injuries will be missed that would have been detected if a standard protocol had been used. It is therefore important to realize that the goal of the short MR imaging examination was not to replace standard MR imaging but to diminish diagnostic uncertainty at the initial evaluation of the patient, thereby resulting in a decrease in total costs and in a potential gain in effectiveness. If the lower quality of the short protocol MR images results in a wrong diagnosis, this would likely lead to an increase in costs and a decrease in effects, including a decrease in quality of life. If the overall effect of an initial diagnostic strategy, including routine short MR imaging examination, results in an overall decrease in costs without loss of effectiveness, or even an increase in effectiveness, the new strategy is worth considering.

Although we could not demonstrate with statistical significance that the application of a short MR imaging examination in all patients with knee injuries is cost saving from a societal perspective, our results suggest that this might well be the case because the overall costs were considerably higher in patients with knee injuries if MR imaging was not performed. For patients with wrist injuries, the strategy, including the short MR imaging examination, increased the total costs without a change in effectiveness. For patients with ankle injuries, the application of MR imaging did not change the total costs and had little influence on the effects.

In conclusion, compared with radiography alone, MR imaging in patients with acute wrist or ankle injury is neither cost saving nor more effective in expediting the work-up or improving quality of life, but, in patients with acute knee injury, MR imaging shortens the diagnostic work-up, reduces the number of diagnostic procedures during follow-up, improves quality of life in the first 6 weeks, and, although not statistically significant, may reduce costs associated with lost productivity.

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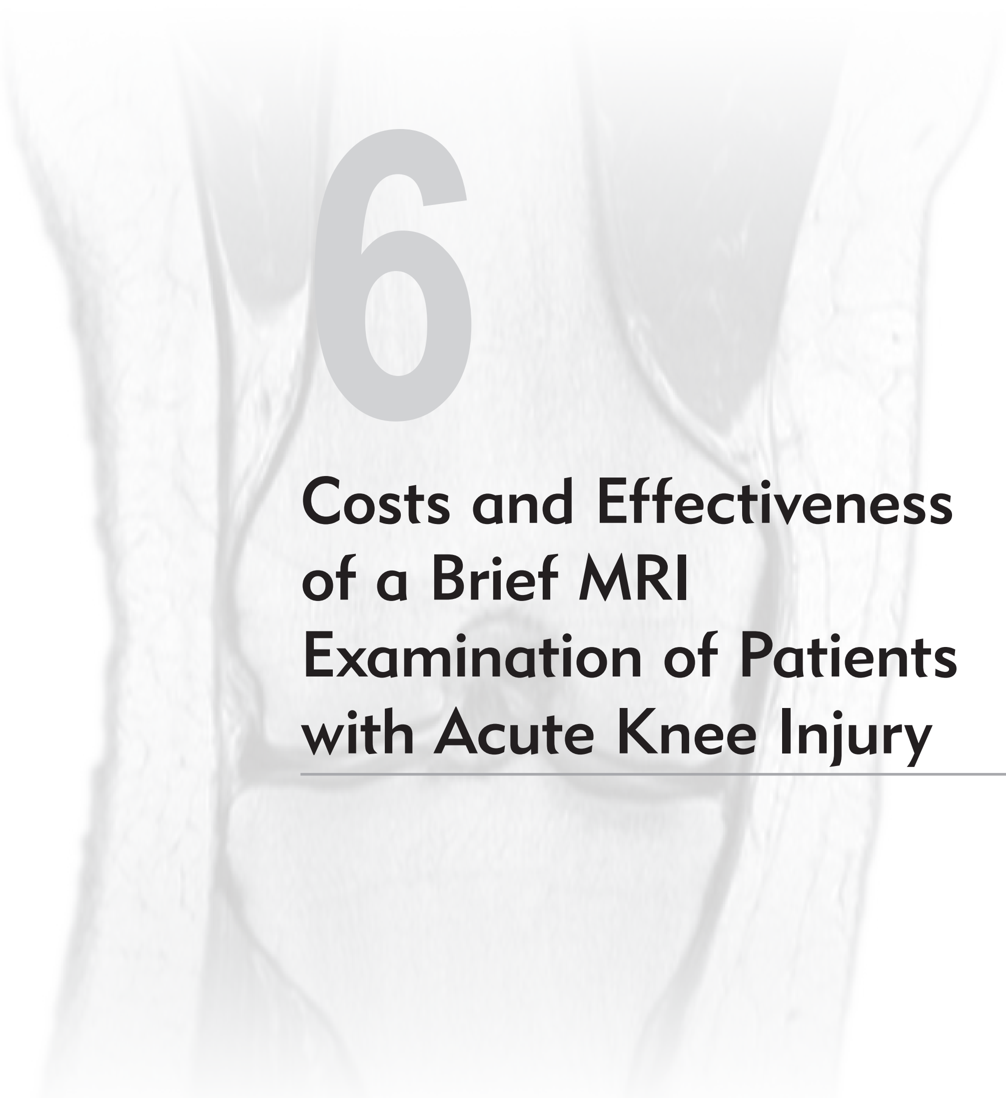
REFERENCES

1. Bretlau T, Christensen OM, Edstrom P, Thomsen HS, Lausten GS. Diagnosis of scaphoid fracture and dedicated extremity MRI. Acta Orthop Scand 1999;70:504–508.
2. Gabler C, Kukla C, Breitenseher MJ, Trattnig S, Vecsei V. Diagnosis of occult scaphoid fractures and other wrist injuries: are repeated clinical examinations and plain radiographs still state of the art? Langenbecks Arch Surg 2001;386:150–154.
3. Breitenseher MJ, Metz VM, Gilula LA, et al. Radiographically occult scaphoid fractures: value of MR imaging in detection. Radiology 1997;203:245–250.
4. Moss ML, Buongiorno PA, Clancy VA. Intranasal midazolam for claustrophobia in MRI. J Comput Assist Tomogr 1993;17:991–992.

5. Nikken JJ, Oei EHG, Ginai AZ, et al. Acute wrist trauma: value of a short dedicated extremity MR imaging examination in prediction of need for treatment. Radiology 2005;234:116–124.
6. Oei EHG, Nikken JJ, Ginai AZ, et al. Acute knee trauma: value of a short dedicated extremity MR imaging examination for prediction of subsequent treatment. Radiology 2005;234:125–133.
7. Nikken JJ, Oei EHG, Ginai AZ, et al. Acute ankle trauma: value of a short dedicated extremity MR imaging examination in prediction of need for treatment. Radiology 2005;234:134–142.
8. Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001;285:1987–1991.
9. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–483.
10. The EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.
11. Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53–72.
12. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35:1095–1108.
13. Oostenbrink JB, Koopmanschap MA, Rutten FFH. Handleiding voor kostenonderzoek, methoden en richtlijnprijzen voor economische evaluaties in de gezondheidszorg. Amstelveen, the Netherlands: College voor zorgverzekeringen, 2000.
14. Hunink MGM, Glasziou PP. Decision making in health and medicine: integrating evidence and values. Cambridge, England: Cambridge University Press, 2001.
15. Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in health and medicine. Oxford, England: Oxford University Press, 1996.
16. Koopmanschap MA, Rutten FF, van Ineveld BM, van Roijen L. The friction cost method for measuring indirect costs of disease. J Health Econ 1995;14:171–189.
17. Bryan S, Weatherburn G, Bungay H, et al. The cost-effectiveness of magnetic resonance imaging for investigation of the knee joint. Health Technol Assess 2001;5:1–95.
18. Dorsay TA, Major NM, Helms CA. Cost-effectiveness of immediate MR imaging versus traditional follow-up for revealing radiographically occult scaphoid fractures. AJR Am J Roentgenol 2001;177:1257–1263.
19. Raby N. Magnetic resonance imaging of suspected scaphoid fractures using a low field dedicated extremity MR system. Clin Radiol 2001;56:316–320.
20. Solomon DH, Simel DL, Bates DW, Katz JN, Schaffer JL. The rational clinical examination: does this patient have a torn meniscus or ligament of the knee?—value of the physical examination. JAMA 2001;286:1610–1620.
21. Becker A, Seitz R, Jacobi E, Leidl R. Cost evaluation by a patient questionnaire: pilot study of a weekly cost diary [in German]. Rehabilitation (Stuttg) 2001;40:12–20.

22. Biering-Sorensen F, Biering-Sorensen M. Sleep disturbances in the spinal cord injured: an epidemiological questionnaire investigation, including a normal population. Spinal Cord 2001;39:505–513.
23. Heath AC, Howells W, Kirk KM, et al. Predictors of non-response to a questionnaire survey of a volunteer twin panel: findings from the Australian 1989 twin cohort. Twin Res 2001;4:73–80.
24. Bakker E, Van Gool JD, Van Sprundel M, Van Der Auwera C, Wyndaele JJ. Results of a questionnaire evaluating the effects of different methods of toilet training on achieving bladder control. BJU Int 2002;90:456–461.
25. Hanneman MJ, Sprangers MA, De Mik EL, et al. Quality of life in patients with anorectal malformation or Hirschsprung's disease: development of a disease-specific questionnaire. Dis Colon Rectum 2001;44:1650–1660.
26. Campbell MJ, Waters WE. Does anonymity increase response rate in postal questionnaire surveys about sensitive subjects?: a randomised trial. J Epidemiol Community Health 1990;44:75–76.
27. Balen AH, Fleming C, Robinson A. Health needs of adolescents in secondary gynaecological care: results of a questionnaire survey and a review of current issues. Hum Fertil (Camb) 2002;5:127–132.
28. Lund E, Gram IT. Response rate according to title and length of questionnaire. Scand J Soc Med 1998;26:154–160.
29. Duffy DL, Martin NG. Increasing the response rate to a mailed questionnaire by including more stamps on the return envelope: a cotwin control study. Twin Res 2001;4:71–72.
30. Maconochie N, Doyle P, Davies G, et al. The study of reproductive outcome and the health of offspring of UK veterans of the Gulf War: methods and description of the study population. BMC Public Health 2003;3:4.
31. Hunink MG, Krestin GP. Study design for concurrent development, assessment, and implementation of new diagnostic imaging technology. Radiology 2002;222:604–614.
32. Nikken JJ, Ginai AZ, Krestin GP, Hunink MGM. Comparison of short and standard protocols in dedicated extremity MRI of wrist, knee, and ankle injury. In: Nikken JJ ed. MRI for the initial evaluation of acute wrist, knee, and ankle trauma. Rotterdam: Erasmus University; 2003; 41-50.



6

Costs and Effectiveness of a Brief MRI Examination of Patients with Acute Knee Injury

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ABSTRACT

The aim of this study was to assess the costs and effectiveness of selective short magnetic resonance imaging (MRI) in patients with acute knee injury. A model was developed to evaluate the selective use of MRI in patients with acute knee injury and no fracture on radiography based on the results of a trial in which 208 patients were randomized between radiography only and radiography plus MRI. We analyzed medical (diagnostic and therapeutic) costs, quality of life, duration of diagnostic workup, number of additional diagnostic examinations, time absent from work, and time to convalescence during a 6-month follow-up period. Quality of life was lowest (EuroQol at 6 weeks 0.61 (95% CI 0.54–0.67)); duration of diagnostic workup, absence from work, and time to convalescence were longest; and the number of diagnostic examinations was largest with radiography only. These outcomes were more favorable for both MRI strategies (EuroQol at 6 weeks 0.72 (95% CI 0.67–0.77) for both). Mean total costs were 2,593 euros (95% CI 1,815–3,372) with radiography only, 2,116 euros (95% CI 1,488–2,743) with radiography plus MRI, and 1,973 euros (95% CI 1,401–2,543) with selective MRI. The results suggest that selective use of a short MRI examination saves costs and potentially increases effectiveness in patients with acute knee injury without a fracture on radiography.

INTRODUCTION

Magnetic resonance imaging (MRI) is an established imaging tool in the evaluation of acute knee injuries. The main purpose of MRI for knee trauma is to determine if therapeutic arthroscopy is indicated, usually in the case of persisting symptoms. This application of MRI has been studied extensively (1–5). MRI is, however, rarely performed at initial presentation of a patient with an acute knee trauma, mainly because of the generally high costs, long examination duration, and limited availability in this clinical setting. Diagnostic information from MRI could be extremely valuable, however, since reliable physical examination shortly after a knee trauma is often hampered by swelling and pain (6,7). MRI, therefore, could play a significant role in the routine initial examination of patients with acute knee injury.

A requisite would be the easy availability of an MRI system, a relatively inexpensive MRI examination, and a short examination time. This can be achieved by using a low field dedicated extremity MRI system with a short data acquisition protocol (8,9). Although the low field strength and shortening of the MRI protocol reduce image quality compared with a standard MRI examination, it has been demonstrated that lower magnetic field strength does not substantially reduce the diagnostic performance for most traumatic knee abnormalities (1,10–12). The information obtained from MRI could be sufficient to reduce the time to completion of the diagnostic workup and to influence the treatment strategy. This information could influence the decision whether follow-up of the patient is warranted, whether treatment is indicated, or whether the patient can be sent home without the need for follow-up. Early detection of traumatic abnormalities could lead to earlier treatment of the patient and potentially to earlier recovery. This could lead to earlier resumption of work, resulting in a decrease of production losses, and thereby a decrease of costs to society.

To evaluate the use of MRI in this setting, we previously performed a randomized controlled trial (RCT) and cost-effectiveness analysis and found that a short dedicated extremity MRI examination in addition to radiography in all patients with acute knee injury improves prediction of the need for additional treatment (8), shortens the time to completion of diagnostic workup, reduces the number of additional diagnostic procedures, improves quality of life in the first 6 weeks compared with radiography alone, and reduces societal costs associated with lost productivity (although the last of these was nonsignificant (9)). In the previously published RCT, patients underwent MRI regardless of the radiography findings, although it can be argued that MRI in the examination of cases of knee trauma has limited added value for the initial treatment if a fracture has already been demonstrated on radiography.

Therefore, the aim of the present study was to assess the costs and effectiveness of performing a short MRI examination on a low field dedicated extremity MRI system in the evaluation of acute knee trauma selectively in patients without a fracture on radiography. This was compared with MRI in all patients and radiography only as initial diagnostic strategies.

MATERIALS AND METHODS

A model was developed to evaluate radiography followed by selective use of a short MRI examination if radiography showed no fracture in patients with acute knee injury. The model was based on the results of an RCT (9).

Study design

We performed a prospective, pragmatic RCT in a university hospital, including patients with a traumatic knee injury, which had occurred within the preceding 7 days before presentation. All patients were examined by an emergency physician, traumatologist, or orthopaedic surgeon and patients were included if radiography of the knee was ordered. Exclusion criteria were pre-existing knee complaints; compound fracture; substantial injury of the head, back, thorax, or abdomen; need for urgent treatment; and intoxication. The subjects were randomized between two diagnostic strategies consisting of plain radiography alone (strategy 1, reference strategy) and radiography followed by a short MRI examination (strategy 2). Since this was not one of the study arms of the RCT, we modeled a third strategy consisting of plain radiography, followed by a selective short MRI examination, only if no fracture was visible on the radiograph. Modeling was performed by using a composite of the results of patients from strategy 1 (no MRI examination) who showed a fracture on the radiograph, and patients from strategy 2 (radiography followed by MRI) who did not show a fracture on the radiograph. In this way the costs and effects of the third strategy could be obtained from the randomized patient groups.

Patients were randomized by drawing from consecutively numbered, sealed envelopes containing computer-generated random assignments. Block randomization was used with a block size of 20 to obtain equal numbers of patients in both strategies. Research staff and radiology technologists on service carried out the inclusion from 0800 to 2300 hours, 7 days a week. All patients were given written and oral information about the goal of the study, and all participating subjects gave informed consent. The study was approved by the institutional review board of Erasmus MC, University Medical Center, Rotterdam, The Netherlands. The results of the RCT are reported in accordance with the CONSORT statement (13).

Imaging technique and interpretation

All patients underwent anteroposterior and lateral radiography of the affected knee, and additional patellar or tunnel views if considered necessary. MRI was performed immediately following radiography using a 0.2-T dedicated extremity MRI system (Artoscan M, Esaote S.p.a., Genoa, Italy) with an MR protocol as described previously (8, 9). The average duration of MR data acquisition was 6 min and the total MR examination time, including MRI start-up and patient positioning was on average 15 min. The MRI was assessed by an experienced musculoskeletal radiologist (A.Z.G., 25 years of experience) or by a resident on service during evenings and weekends. The residents were in their second to fifth year of training. The result was reported to the treating physician immediately. Resident interpretations were re-read the next working day by the experienced musculoskeletal radiologist. In the case of a different interpretation the physician was informed.

Follow-up

Data were collected on utilization of medical resources, quality of life, and production losses caused by absence from work and time to convalescence. The follow-up period was 6 months. Although 6 months is relatively short for outcome assessment, we expected that this period would be long enough for relevant differences across the strategies to emerge. The effect of the availability of more diagnostic information in the initial stage is not likely to cause a significant difference in costs beyond 6 months after trauma. Questionnaires were mailed to all subjects 1 week, 6 weeks, 3 months, and 6 months after inclusion. These questionnaires included quality of life measuring instruments as well as questions about utilization of medical resources outside our hospital, out-of-pocket expenses, days off work, and time to convalescence. If questionnaires were not returned we interviewed the patient by telephone and urged them to return the quality of life questionnaires. In addition to the information from the questionnaires, data were obtained from patient records and from the computerized hospital information system.

Measurement of effectiveness

Quality of life was measured using the EuroQol (14,15) and the Short Form 36 Health Survey (SF-36) (16). Using the EuroQol it is possible to assign one preference-based score, which can be calculated using a regression equation (17). The SF-36 consists of 36 questions covering eight domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health). An algorithm is used to assign values to each domain.

From the moment a patient indicated on one of the four questionnaires that he or she did not have complaints of the injured knee anymore, we assumed that no further change in quality of life related to the initial trauma would occur, and the EuroQol and SF-36 scores measured at that point in time were extrapolated to the remaining questionnaires. If a person indicated that he/she did not have complaints anymore but did not fill in the quality of life questionnaires, mean values of all other complaint-free patients from the same randomized group were used, since it is well known that imputation of missing values results in less bias than analysis of complete cases only (18,19). We used linear regression analysis to analyze if these mean values were influenced by age and sex and adjusted accordingly.

The time to completion of the diagnostic workup was defined as the time from initial presentation to the last diagnostic examination. The number of additional diagnostic procedures was assessed by reviewing the hospital information system and by information from the questionnaires or telephone inquiry if the examinations had been performed outside our hospital. The number of days absent from work and the time to recovery were obtained from the questionnaires or, if the questionnaires were not returned, by telephone inquiry.

A patient was regarded to have recovered if he or she did not have daily complaints anymore.

Measurement of costs

All costs relevant from the societal perspective, including medical and nonmedical costs, were recorded during a follow-up period of 6 months. Medical costs consisted of costs of diagnostic procedures and treatment both inside and outside the hospital as well as patient travel costs. Costs of initial treatment as well as diagnostic procedures were calculated using a bottom-up approach (20), taking into account the initial investment of equipment, additional costs during use, maintenance, years of use, discounting and annuitization (21), number of procedures per year, personnel costs, materials used, room rent, housekeeping, administration, and overhead costs. Costs were discounted at a rate of 3% per annum (22). Estimated actual costs of hospital visits and hospital admissions were obtained from the Dutch Council for Care Insurance (20). For costs of operations we used reimbursement tariffs as established by the Dutch Central Organ for Tariffs in Healthcare.

Out-of-pocket expenses and patient time costs were recorded as direct nonmedical costs. Patient time costs were included in the cost analysis (22) in order to capture the gain in effectiveness obtained through a more expedient diagnostic workup in monetary units. Patient time costs were determined by multiplying the time spent on follow-up, diagnostic and therapeutic procedures (including travel time, and waiting time) by the average net income of subjects stratified for age (obtained from the Dutch Central Bureau for Statistics, data for both working and nonworking subjects in the Netherlands adjusted for the year 2007).

Costs associated with production losses were estimated using the 'friction cost method' as described by Koopmanschap et al. and recommended in guidelines for cost-effectiveness analysis (22,23). According to this method costs to society are only generated during the time it takes to replace a sick employee, which is called the friction period.

After the friction period no costs to society are generated, since the sick employee is replaced by someone drawn from the ranks of the unemployed. For short-term absence from work the loss of productivity may be low, because work may be performed by colleagues or work can be postponed and performed on return of the sick employee.

For long-term or permanent absence extra costs of maintaining production, costs of production loss, costs of filling the vacancy, and costs of training the new employee are incorporated.

The costs of lost productivity per day absent from work were calculated using friction cost data estimated for working people in the Netherlands in 1998, based on sex and age (20), adjusted for the year 2007. The friction period for the year 1998 was estimated to be 4 months (20), but because of increased shortage on the labor market we estimated the friction period in 2007 to be 6 months (personal communication, Koopmanschap). Costs were analyzed on an intention-to-diagnose-and-treat basis.

The effect of uncertainty of the involved parameters on the robustness of our results was studied in a sensitivity analysis. One-way sensitivity analysis was conducted by exploring a range from 50 to 200% for each parameter. Parameters that appeared sensitive in the one-way analysis were analyzed in a three-way sensitivity analysis.

The analyses were performed using Microsoft Excel 97 SR-2 (Microsoft Corp, Redmond, WA) and SPSS for Windows (release 10.0.0; SPSS Inc., Chicago, IL, USA) software packages. Because one of our strategies is a composite of the results of the other two, statistical testing for differences was not justified. We therefore chose to report 95% confidence intervals (CIs) instead of p values.

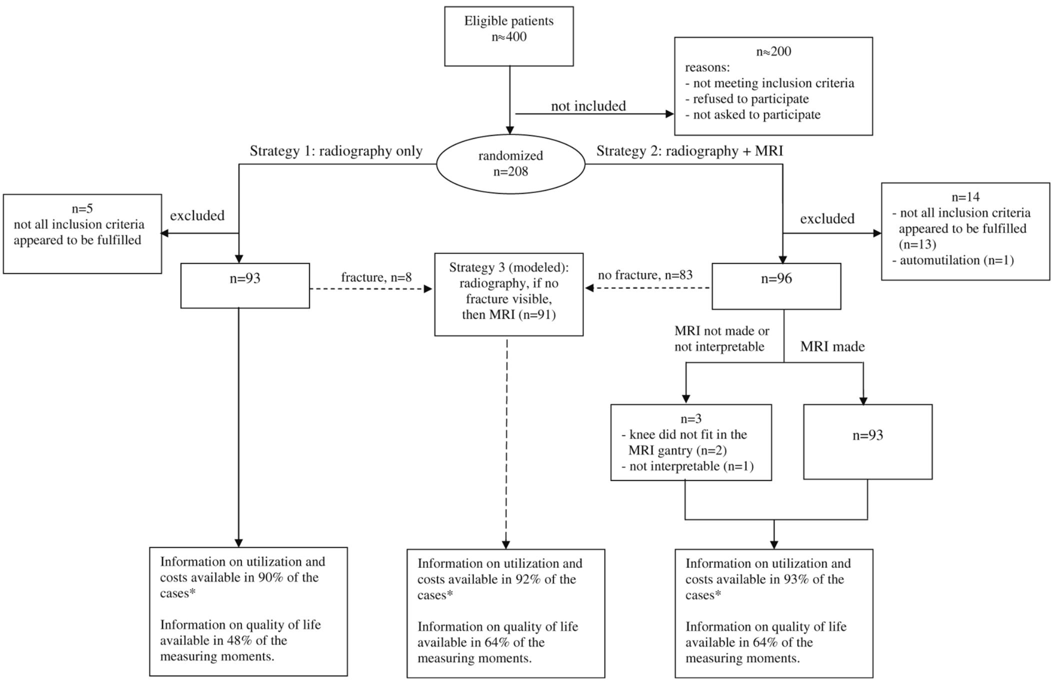

Figure 1. Flow diagram of subjects passing through the trial.
*The remaining percentage concerns patients that were not treated in our hospital, but information on possible treatment elsewhere is lacking

Table 1. Baseline characteristics of the patient groups in the three strategies

	Strategy 1 (n = 93)	Strategy 2 (n = 96)	Strategy 3 (n = 91)
Mean age (years)	34.7	32.2	33.7
Sex (percentage male)	68	62	63
Fracture visible on X-ray (number of patients)	8	13	8
Type of trauma (direct/indirect/unknown)	41/51/1	36/59/1	36/55/0

Strategy 1:
only radiography

Strategy 2:
radiography plus MRI

Strategy 3:
MRI if no fracture on radiography

Table 2. Final diagnoses in 189 patients with acute knee injury (one patient may have more than one diagnosis)

	Strategy 1	Strategy 2	Strategy 3
No abnormalities	0	2	2
Contusion	18	24	25
Distortion[a]	21	14	14
Fracture			
Patella	4	6	4
Tibial plateau	0	2	0
Fibula head avulsion	0	1	0
Avulsion at the MCL origin	0	1	0
Segond fracture	1	0	1
Osteochondral fracture	3	3	3
Quadriceps tendon rupture	1	0	0
Medial meniscus tear	8	11	11
Lateral meniscus tear	4	5	4
Cruciate ligament rupture			
ACL partial	5	3	3
ACL total	7	14	12
PCL partial	0	1	1
PCL total	1	0	0
ACL+PCL total	1	0	0
ACL+PCL partial	1	0	0
Collateral ligament rupture			
MCL partial	10	6	6
MCL total	3	4	3
LCL partial	0	1	1
LCL total	0	0	0
Prepatellar bursitis	0	1	1
Traumatized gonarthrosis	3	1	1
Unknown[b]	9	5	5

Strategy 1: only radiography
Strategy 2: radiography plus MRI
Strategy 3: MRI if no fracture on radiography
ACL anterior cruciate ligament, PCL posterior cruciate ligament, MCL medial collateral ligament, LCL lateral collateral ligament

[a]A distortion was defined as an indirect trauma (torsion, hyperextension, varus, or valgus) without signs of osseous, meniscal, or ligamentous injury during initial evaluation or follow-up

[b]Final diagnosis could not be established (e.g., patient had persistent pain, but did not seek medical attention)

RESULTS

From August 1999 to May 2001, 208 patients were included. A flow diagram of patients passing through the study is presented in Fig. 1. About half of the eligible patients were randomized: a few patients refused to participate, but the main reason for missing potential candidates was the fact that due to the inclusion time—including evenings and weekends—many radiology technologists were involved in asking the patients to participate, which was forgotten regularly. On review, 18 patients did not fulfill all inclusion criteria and one case was suspected of automutilation; these 19 patients were excluded from the analysis. Of the remaining 189 patients 96 patients were allocated to the MRI strategy and 93 patients to the reference strategy (i.e., strategy 1, only radiography). In two patients allocated to the MRI strategy, the MRI could not be made because the knee could not be positioned in the center of the magnet bore: one patient had a locked knee, and in one case the knee was too large to fit into the magnet. In one very obese patient the MRI was uninterpretable. In accordance with the intention-to-diagnose-and-treat principle, these three patients remained in the MRI strategy in the analyses. The baseline characteristics are described in Table 1. Eight patients in strategy 1 (only radiography) showed a fracture on the radiograph, and 83 patients in strategy 2 (radiography plus MRI) showed no fracture on the radiograph. These 91 patients formed the subject group for strategy 3 (MRI if no fracture on radiography). The final diagnoses as assessed using all information including follow-up are listed in Table 2.

Effectiveness

Linear regression analysis showed that the mean EuroQol and SF-36-domain scores of patients without complaints were not significantly influenced by age or sex, and therefore mean values of EuroQol and SF-36-domain values were used for imputation. The mean EuroQol scores per strategy are presented in Fig. 2. Patients in strategy 2 (radiography plus MRI in all patients) showed a higher EuroQol score at 1 and 6 weeks

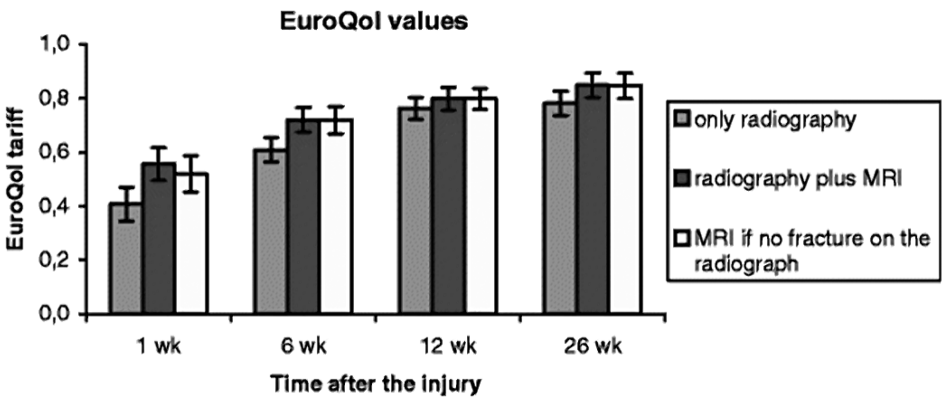

Figure 2. Mean EuroQol scores and 95% confidence intervals for the three strategies measured at four points in time after the initial injury

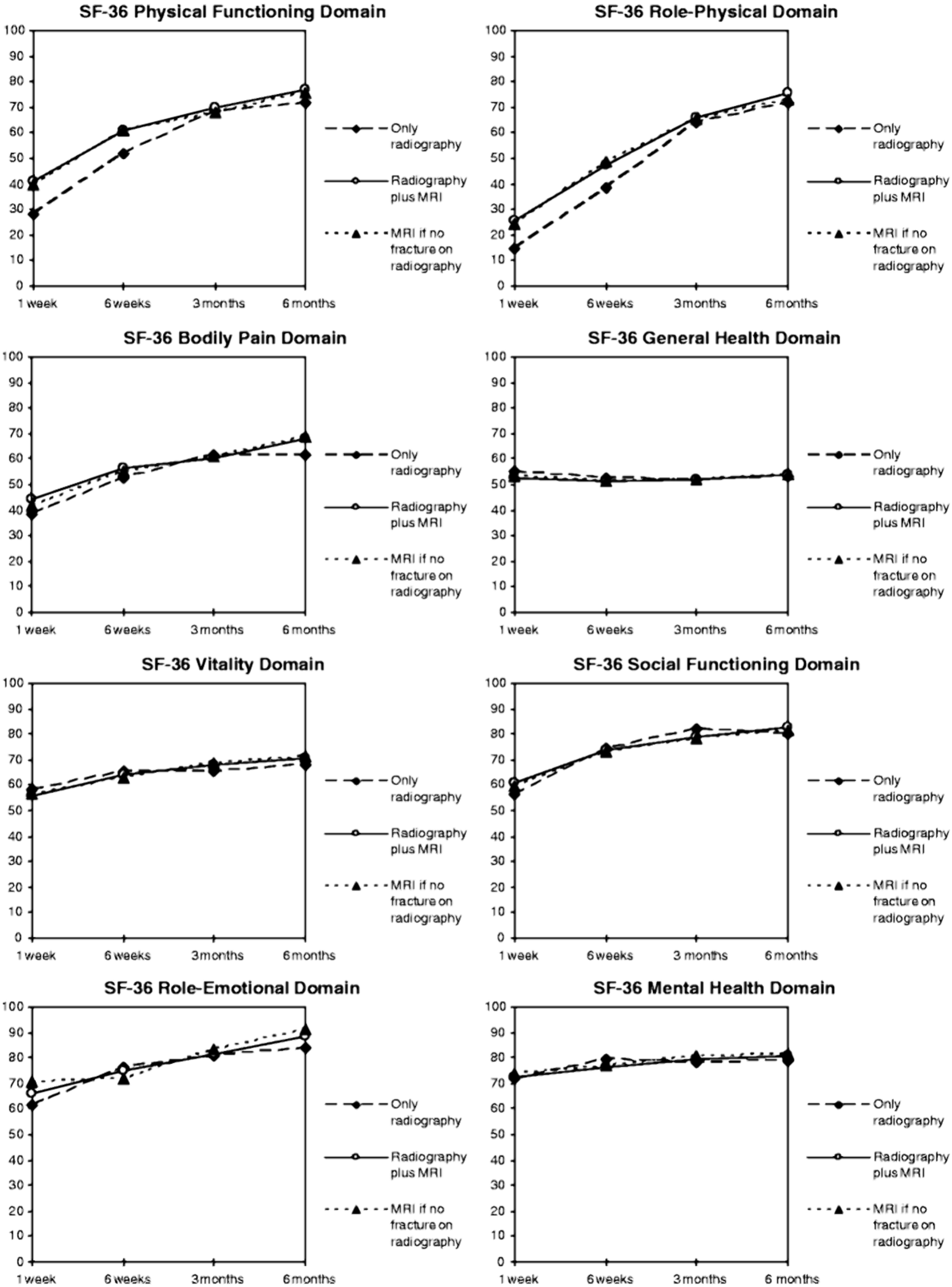

Figure 3. Mean SF-36 scores per domain for the three strategies at 1-week, 6-weeks, 3-months, and 6-months follow-up. A higher score implies a more favorable outcome

Table 3. Effectiveness results

	Strategy 1 (n = 93)	Strategy 2 (n = 96)	Strategy 3 (n = 91)
Mean time to last diagnostic procedure (days)	17.3 (9.3–25.2)	3.5 (0.0–7.6)	2.0 (0.0–4.1)
Number of additional diagnostic procedures	35	9	10
Mean duration of absence from work (days)	12.4 (7.5–17.3)	9.6 (5.9–13.2)	8.6 (5.0–12.3)
Mean time to convalescence (days)	76.6 (54.6–98.5)	66.2 (50.2–82.3)	60.4 (44.8–76.0)

95% confidence intervals are enclosed in parentheses
Strategy 1: only radiography
Strategy 2: radiography plus MRI
Strategy 3: MRI if no fracture on radiography

after the injury (EuroQol score 0.56 (95% CI 0.49–0.62) and 0.72 (95% CI 0.67–0.77), respectively) than patients in strategy 1 (only radiography; EuroQol score 0.41 (95% CI 0.33–0.48) and 0.61 (95% CI 0.54–0.67), respectively). In strategy 3 (MRI if no fracture visible on the radiograph) the EuroQol score at 1 week was slightly lower but similar (EuroQol score 0.52 (95% CI 0.45–0.59)) compared with strategy 2 (always MRI), whereas during follow-up the EuroQol scores of these two strategies were equivalent (EuroQol scores for strategies 2 and 3 were 0.72 (95% CI 0.67–0.77), 0.80 (95% CI 0.76–0.84), and 0.85 (95% CI 0.80–0.89) at 6 weeks, 3 months, and 6 months, respectively).

All the SF-36 domains, except for general health, demonstrated an increase in score over time (Fig. 3). The two MRI strategies demonstrated similar SF-36 scores across all domains at all points in time. After 1 and 6 weeks physical functioning and physical role functioning were higher in the MRI strategies compared with radiography alone. The scores of all the domains were very similar across the three strategies at all points in time.

The time to completion of the diagnostic workup, the duration of absence from work, and the time to convalescence were shortest in strategy 3 (Table 3). The number of additional procedures was almost the same in the two strategies with MRI, which was considerably shorter than in the strategy with only radiography.

Costs

Medical costs were highest in the strategy with MRI in all patients (strategy 2) and lowest if no MRI was performed at all (strategy 1) (Table 4). Travel costs were relatively low and similar across the three strategies. The friction costs constituted the largest cost factor in all strategies. Total costs were lowest if MRI was used selectively in patients without a fracture on the radiograph (strategy 3), mainly owing to a reduction in friction costs. Total costs were highest in the strategy with only radiography, which again was mainly attributable to high friction costs.

Sensitivity analysis

In a one-way sensitivity analysis the cost difference between the strategies including MRI (strategies 2 and 3) and the strategy with only radiography (strategy 1) was sensi-

Table 4. Mean costs associated with the initial knee injury

Cost	Strategy 1	Strategy 2	Strategy 3
Medical	704 (537–873)	803 (565–1,043)	744 (604–885)
Travel	19 (16–22)	20 (17–23)	21 (17–23)
Friction	1,755 (1,042–2,468)	1,154 (646–1,662)	1,097 (585–1,610)
Time	115 (67–163)	137 (34–242)	109 (66–153)
Total	2,593 (1,815–3,372)	2,116 (1,488–2,743)	1,973 (1,401–2,543)

Costs are in euros (adjusted to the year 2007 using consumer price indices); 95% confidence intervals are enclosed in parentheses
Strategy 1: only radiography
Strategy 2: radiography plus MRI
Strategy 3: MRI if no fracture on radiography

tive to the estimated friction costs per friction period, to the friction period itself, and to the costs of the short MRI examination (Table 5). Three-way sensitivity analysis of friction costs, friction period, and costs of the short MRI examination (Fig. 4) demonstrated that within plausible ranges of these variables the strategies that included MRI generated less costs than the strategy with only radiography. This conclusion was even more robust

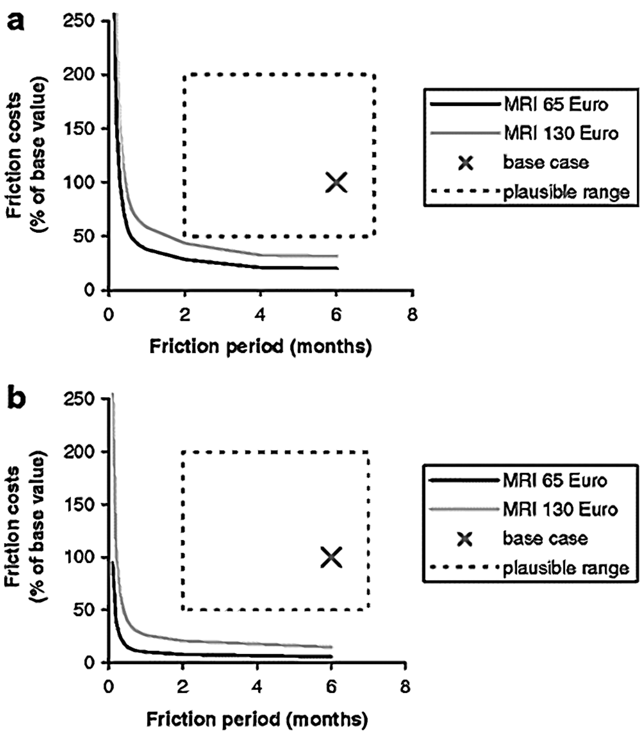

Figure 4. Three-way sensitivity analysis on friction costs and friction period for the base value of the short MRI examination (65 euros) and twice this base value. Radiography and MRI in all patients compared with radiography only (a); radiography in all patients followed by MRI if no fracture is visible on the radiograph compared with radiography only (b). In the area above the threshold lines the strategy that includes MRI generates less costs than the reference strategy. In the area below the threshold lines the strategy including MRI generates more costs than the reference strategy. A plausible range of friction costs and friction period is indicated

Table 5. One-way sensitivity analysis of the mean total cost difference between strategies

	Cost-savings with strategy 2 compared with strategy 1			Cost-savings with strategy 3 compared with strategy 1		
Value of variable	**50%**	**200%**	**Range**	**50%**	**200%**	**Range**
Baseline cost difference	479			621		
Friction costs	178	1080	902	293	1277	984
Friction period	307	479	172	432	621	189
Short MRI costs	511	413	98	651	561	90
Outpatient visit costs	494	448	46	635	594	41
Time costs	489	456	33	618	627	9
Costs per hospital day	486	463	23	601	661	60
Physiotherapy costs	484	467	17	634	597	37
Standard MRI costs	474	486	12	610	643	33
Operative therapy costs	477	482	5	617	629	12
Radiography costs	480	474	6	622	620	2

Cost-savings using strategy 2 and 3, respectively, compared with strategy 1 (reference strategy) for 50% and 200% of the variable value are presented. Only the most sensitive variables are presented. Costs are in euros
Strategy 1: only radiography
Strategy 2: radiography plus MRI
Strategy 3: MRI if no fracture on radiography

for strategy 3 (MRI if no fracture on radiography) (Fig. 4b) than for strategy 2 (MRI in all patients) (Fig. 4a).

DISCUSSION

MRI is seldom used as an initial diagnostic tool in acute knee injury because of the perceived high costs and long duration of the examination. We studied the costs and effectiveness of applying a short MRI examination in this setting. Two MRI strategies were analyzed and compared with the strategy of radiography alone, namely performing MRI in all patients and selective use of MRI if no fracture is demonstrated on the radiograph. The rationale behind the latter strategy is that we considered it plausible that the addition of MRI to radiography in patients who already show a fracture on the radiograph has limited value for the (initial) treatment: in most cases treatment will be determined by the fracture. This strategy was modeled, since it was not incorporated into the trial. Modeling created limitations in the comparison of the strategies, since differences between the modeled and the observed strategies could not be tested statistically. However, we chose to use a modeled strategy because it created the opportunity to analyze a realistic and relevant strategy beyond the scope of the original trial.

The selective application of MRI in patients without a fracture on the radiograph resulted in a slight improvement in quality of life during the first 6 weeks compared with using radiography only. The quality of life was almost identical for the two MRI strategies. Time to diagnosis, duration of absence from work, and time to convalescence were all slightly shorter compared with MRI in all patients and substantially shorter compared with only radiography.

Whilst performing this study we assumed that the early diagnostic information from MRI would result in a more appropriate and earlier treatment. Although this is true for many cases, we acknowledge that there is a potential danger of overtreatment. Some meniscal tears may heal or become symptomless without surgery (24). Still, if the short MRI examination leads to an overall reduction in costs without a reduction in quality of life as was demonstrated, the benefits of more accurate early diagnostic information outweighs the risk of overtreatment. On the other hand, we acknowledge that MRI should not be regarded as a substitute for thorough clinical history taking and examination, and that MRI may be unnecessary in certain patients. If there are obvious mechanical symptoms such as locking, arthroscopy is required regardless of MRI findings (25,26). In less equivocal cases, however, MRI may be useful, since physical examination is often unreliable if performed in the acute stage (6,7).

Medical costs were lowest if only radiography was performed. As expected, if an MRI was performed selectively in the absence of a fracture, medical costs were lower than if MRI was performed in all patients. Thus, the application of a short MRI examination did not lead to a reduction in costs of subsequent diagnostic and therapeutic procedures. The main reduction in costs was brought about by a reduction in lost productivity, which was similar for both MRI strategies. The difference in time costs was small across strategies because the mean time spent for diagnostic and therapeutic procedures was similar. Travel costs were similar and low for all groups. This is plausible in the Dutch situation, since the density of hospitals in the Netherlands is high, and travel distance to the nearest hospital is generally short.

Our conclusions were robust in sensitivity analysis. A three-way analysis of the most sensitive parameters (friction costs, friction period, and costs of the short MRI examination) did not influence our conclusions. Our results were, however, influenced by heterogeneity of the patient populations, expressed by the wide confidence intervals of the costs (Table 4). This heterogeneity within the patient groups was to be expected since we considered all patients with traumatic knee injury, ranging from a mild injury, without need for treatment to trauma with extensive internal derangement. Friction costs were especially subject to heterogeneity in the studied population. Since a short period off work may generate considerable costs, absenteeism caused high mean friction costs in spite of the fact that only a small number of patients were absent from work.

The low sensitivity of our results to variation in costs of the MRI examination suggests that a high field MRI system can also be used for the initial evaluation of knee trauma, still with a reduction in overall costs from the societal perspective. The examination costs will increase, but the better quality images may increase reliability of the examination result, with potential improvement in patient outcome.

A limitation of the study is the fact that a considerable percentage of the potentially eligible patients were not included, although inclusion was intended to be consecutive. The major reason why patients were not randomized was because the radiology technologist on service had forgotten to ask the patient to participate. We expect that the likelihood of selection bias in these cases of nonrandomized patients is low.

In many studies the response rate to mailed questionnaires is about 60–65% (27–34). In our study the response rate of patients that underwent both radiography and MRI was within that range, but the response rate of patients that only underwent radiography was lower, most likely because they were disappointed not to get an extra MRI examination during randomization and less willing to fill in the questionnaires. This may have biased the results on quality of life. For the data on costs we were much less dependent on the questionnaires, since we could obtain most of the data from the patient records and computerized hospital information system, sometimes complemented by telephone inquiry. In conclusion, our results suggest that the selective use of a short MRI examination following radiography in patients with acute knee injury without a fracture on the radiograph reduces costs to society and increases effectiveness compared with a strategy of using radiography alone. The results also indicate that, compared with MRI in all patients, selective MRI in patients without a fracture on the radiograph could reduce both medical costs and costs to society without affecting health outcomes. Because the results were in part obtained from a modeling analysis they should ideally be evaluated in a prospective trial.

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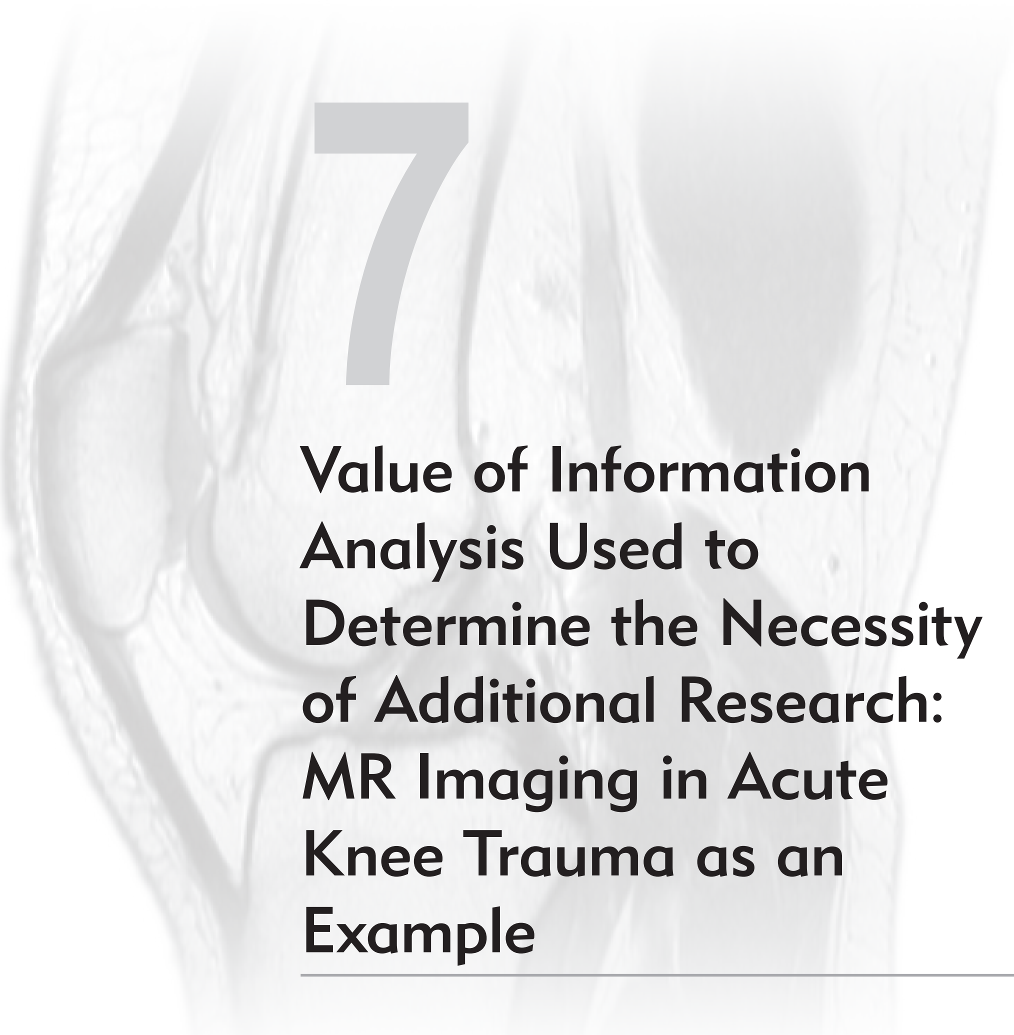
REFERENCES

1. Oei EH, Nikken JJ, Verstijnen AC, Ginai AZ, Hunink MG (2003) MR imaging of the menisci and cruciate ligaments: a systematic review. Radiology 226:837–848.
2. Elvenes J, Jerome CP, Reikeras O, Johansen O (2000) Magnetic resonance imaging as a screening procedure to avoid arthroscopy for meniscal tears. Arch Orthop Trauma Surg 120:14–16.
3. Munk B, Madsen F, Lundorf E et al (1998) Clinical magnetic resonance imaging and arthroscopic findings in knees: a comparative prospective study of meniscus anterior cruciate ligament and cartilage lesions. Arthroscopy 14:171–175.
4. Weinstabl R, Muellner T, Vecsei V, Kainberger F, Kramer M (1997) Economic considerations for the diagnosis and therapy of meniscal lesions: can magnetic resonance imaging help reduce the expense? World J Surg 21:363–368.
5. Vincken PW, ter Braak BP, van Erkel AR et al (2002) Effectiveness of MR imaging in selection of patients for arthroscopy of the knee. Radiology 223:739–746.
6. Hardaker WT Jr, Garrett WE Jr, Bassett FH 3rd (1990) Evaluation of acute traumatic hemarthrosis of the knee joint. South Med J 83:640–644.
7. Mitsou A, Vallianatos P (1988) Clinical diagnosis of ruptures of the anterior cruciate ligament: a comparison between the Lachman test and the anterior drawer sign. Injury 19:427–428.
8. Oei EH, Nikken JJ, Ginai AZ et al (2005) Acute knee trauma: value of a short dedicated extremity MR imaging examination for prediction of subsequent treatment. Radiology 234:125–133.
9. Nikken JJ, Oei EH, Ginai AZ et al (2005) Acute peripheral joint injury: cost and effectiveness of low-field-strength MR imaging–results of randomized controlled trial. Radiology 236:958–967.
10. Vellet AD, Lee DH, Munk PL et al (1995) Anterior cruciate ligament tear: prospective evaluation of diagnostic accuracy of middle- and high-field-strength MR imaging at 1.5 and 0.5 T. Radiology 197:826–830.
11. Rutt BK, Lee DH (1996) The impact of field strength on image quality in MRI. J Magn Reson Imaging 6:57–62.
12. Barnett MJ (1993) MR diagnosis of internal derangements of the knee: effect of field strength on efficacy. AJR Am J Roentgenol 161:115–118.
13. Moher D, Schulz KF, Altman D (2001) The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 285:1987–1991.
14. The EuroQol Group (1990) EuroQol–a new facility for the measurement of health-related quality of life. Health Policy 16:199–208.
15. Brooks R (1996) EuroQol: the current state of play. Health Policy 37:53–72.

16. Ware JE Jr, Sherbourne CD (1992) The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30:473–483.
17. Dolan P (1997) Modeling valuations for EuroQol health states. Med Care 35:1095–1108.
18. Schafer J (1997) Analysis of incomplete multivariate data. Chapman & Hall, London .
19. van der Heijden GJ, Donders AR, Stijnen T, Moons KG (2006) Imputation of missing values is superior to complete case analysis and the missing-indicator method in multivariable diagnostic research: a clinical example. J Clin Epidemiol 59:1102–1109.
20. Oostenbrink JB, Koopmanschap MA, Rutten FFH (2000) Handleiding voor kostenonderzoek, methoden en richtlijnprijzen voor economische evaluaties in de gezondheidszorg. College voor zorgverzekeringen, Amstelveen .
21. Hunink MGM, Glasziou PP (2001) Decision making in health and medicine - integrating evidence and values. Cambridge University Press, Cambridge.
22. Gold MR, Siegel JE, Russell LB, Weinstein MC (1996) Cost-effectiveness in health and medicine. Oxford University Press, Oxford.
23. Koopmanschap MA, Rutten FF, van Ineveld BM, van Roijen L (1995) The friction cost method for measuring indirect costs of disease. J Health Econ 14:171–189.
24. Solomon DH, Simel DL, Bates DW, Katz JN, Schaffer JL (2001) The rational clinical examination. Does this patient have a torn meniscus or ligament of the knee? Value of the physical examination. JAMA 286:1610–1620.
25. Dandy DJ (1997) Arthroscopy and MRI for the knee. J Bone Joint Surg Br 79:520.
26. Rose NE, Gold SM (1996) A comparison of accuracy between clinical examination and magnetic resonance imaging in the diagnosis of meniscal and anterior cruciate ligament tears. Arthroscopy 12:398–405.
27. Kotaniemi JT, Hassi J, Kataja M et al (2001) Does non-responder bias have a significant effect on the results in a postal questionnaire study? Eur J Epidemiol 17:809–817.
28. Becker A, Seitz R, Jacobi E, Leidl R (2001) (Cost evaluation by a patient questionnaire: pilot study of a weekly cost diary) Kostenmessung durch Patientenbefragung: Pilotstudie zu einem Kostenwochenbuch. Rehabilitation (Stuttg) 40:12–20.
29. Biering-Sorensen F, Biering-Sorensen M (2001) Sleep disturbances in the spinal cord injured: an epidemiological questionnaire investigation, including a normal population. Spinal Cord 39:505–513.
30. Heath AC, Howells W, Kirk KM et al (2001) Predictors of non-response to a questionnaire survey of a volunteer twin panel: findings from the Australian 1989 twin cohort. Twin Res 4:73–80.
31. Bakker E, Van Gool JD, Van Sprundel M, Van Der Auwera C, Wyndaele JJ (2002) Results of a questionnaire evaluating the effects of different methods of toilet training on achieving bladder control. BJU Int 90:456–461.

32. Campbell MJ, Waters WE (1990) Does anonymity increase response rate in postal questionnaire surveys about sensitive subjects? A randomised trial. J Epidemiol Community Health 44:75–76.
33. Lund E, Gram IT (1998) Response rate according to title and length of questionnaire. Scand J Soc Med 26:154–160.
34. Maconochie N, Doyle P, Davies G et al (2003) The study of reproductive outcome and the health of offspring of UK veterans of the Gulf War: methods and description of the study population. BMC Public Health 3:4.



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Value of Information Analysis Used to Determine the Necessity of Additional Research: MR Imaging in Acute Knee Trauma as an Example

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ABSTRACT

PURPOSE: To help guide future outcomes research regarding the use of magnetic resonance (MR) imaging in patients with acute knee trauma in an emergency department setting, with use of prospective data from a randomized clinical trial and value of information analysis.

MATERIALS AND METHODS: A total of 189 patients (123 male, 66 female; mean age, 33.4 years) were randomly assigned to undergo radiography alone (n = 93) or radiography and MR imaging (n = 96). Institutional review board approval and informed consent (parental consent for minors) were obtained. During 6 months of follow-up, data on quality of life and 39 cost parameters were collected. Value-of-information analysis was used to estimate the expected benefit of future research to eliminate the decision uncertainty that remained after trial completion. In addition, the parameters that were responsible for most of the decision uncertainty were identified, the expected benefits of various study designs were evaluated, and the optimal sample size was estimated.

RESULTS: Only three parameters were responsible for most of the decision uncertainty: number of quality-adjusted life-years, cost of an overnight hospital stay, and friction costs. A study in which data on these three parameters are gathered would have an optimal sample size of 3500 patients per arm and would be expected to result in a societal benefit of ¤5.6 million or 70 quality-adjusted life-years.

CONCLUSION: The optimal study design for use of MR imaging to evaluate acute knee trauma involves a trial in which there are 3500 patients per trial arm, and data on the number of quality-adjusted life-years, cost of an overnight hospital stay, and friction costs are collected.

INTRODUCTION

Patients who present to the emergency department with acute knee trauma may benefit from immediate magnetic resonance (MR) imaging. Moreover, the initial cost of MR imaging may be offset by a reduction in the subsequent medical and societal costs because the patient may be able to return to work sooner than if MR imaging had not been performed. In a randomized controlled trial, we assessed the additional value of MR imaging in patients with acute knee trauma (1). After 6-month follow-up of 189 patients, we found no significant difference in costs and a small transient significant difference in outcome. These results made us question whether a second larger trial, in which we would attempt to identify a difference in costs and a durable difference in patient outcome that may have remained undetected in our initial study, would be justified.

If study results show no significant differences between the primary outcomes, the researchers invariably conclude that more clinical research is needed to reduce decision uncertainty (2). Uncertainty could result in the adoption of suboptimal medical interventions, which could harm patients or result in inefficient allocation of limited health care funds. More research—for example, another clinical trial—is expected to decrease this uncertainty and benefit patients, save money, or both. However, research is costly, and money spent on one research project cannot be spent on another. Furthermore, while additional research is being performed, a potentially cost-effective intervention is being withheld from patients. These problems raise the question of whether more research regarding an uncertain decision is a good value for the money. More clinical research is justified only if the expected benefit of this research exceeds the expected cost. Value-of-information analysis is a method that expands on cost-effectiveness analysis and can be used to determine if more research is justified regarding a medical decision. This method is used to estimate the expected benefit of a proposed study given the currently available evidence. In addition, value-of-information analysis can be used to identify the optimal study design and sample size. Use of value-of-information analysis has been embraced and recommended by the National Institute for Clinical Excellence in the United Kingdom as a framework for setting research priorities in health care (3).

The purpose of this study was to help guide future outcomes research regarding the use of MR imaging in patients with acute knee trauma in an emergency department setting, with use of prospective data from a randomized clinical trial and value-of-information analysis.

MATERIALS AND METHODS

Randomized Controlled Trial

In a previously published diagnostic randomized controlled trial (1), we (E.H.O., J.J.N.) enrolled 189 consecutive patients (123 male [mean age, 31.9 years; age range, 12.6–74.6 years], 66 female [mean age, 36.1 years; age range, 16.6–72.9 years]) with a mean age of 33.4 years between August 1999 and May 2001. These patients had recent knee trauma and were referred to the radiology department for conventional radiography (1). Patients were randomly assigned to undergo radiography alone (n = 93) or conventional radiography followed by a short dedicated MR examination (n = 96). Institutional review board approval and informed consent (parental consent for minors) were obtained for the randomized study.

During 6 months of follow-up, quality of life was measured four times with a valuative device (EuroQol). All relevant societal costs were recorded during the follow-up period. These costs included medical and nonmedical costs. Medical costs consisted of costs of diagnostic procedures and treatment both inside and outside the hospital and were estimated with 36 resource-use parameters for each strategy. Nonmedical costs were estimated with three parameters: patient travel costs, patient time cost, and friction costs. The latter was an estimate of societal production losses. In total, 40 parameters (39 cost parameters and quality of life) were sampled for each strategy. Mean values and 95% confidence intervals were calculated for costs and effects of both strategies. (See the original article [1] for more details on study design and analysis.)

Cost-effectiveness Analysis

To perform cost-effectiveness analysis, we (B.G.K., J.J.N.) converted Euroqol values into utility values (4). For each patient, an author (B.G.K.) calculated the overall number of quality-adjusted life-years during the study period as the effect parameter (5).

A choice of one of the two strategies that is based on both cost and effect can be made only if a trade-off between cost and effect is made by placing a monetary value on health. We used a societal willingness-to-pay threshold of ¤80 000 per quality-adjusted life-year, as recently recommended by a Dutch governmental institute (6). Subsequently, we (B.G.K., T.S.) combined cost and effect into one outcome, which we termed net (monetary) benefit (7). Net benefit was calculated by multiplying effect by willingness to pay and subtracting cost. The strategy with the maximum net benefit is the strategy that is preferred.

Value-of-Information Analysis

We (B.G.K., T.S.) applied value-of-information analysis, as described in the literature (8–12). First, we estimated the total expected value of perfect information (EVPI) per patient. This is the value of collecting data about the effect parameter and all cost parameters in an infinitely large study. In other words, it is the value of removing all uncertainty related to the decision problem.

Subsequently, we estimated the expected value for the entire patient population that can potentially benefit from more research (population EVPI). To calculate the population EVPI, we (B.G.K., M.G.M.H.) estimated the effective lifetime of the technology to be 10 years. Benefits to future patients were discounted at a rate of 3% per year (5). For the Netherlands perspective, we estimated the annual population that could potentially benefit from the results of a future study to be 20 000 patients. We performed additional analysis for the European Union perspective. By extrapolating the annual population of 20 000 patients to the European Union, we determined that an annual population of 561 000 patients could benefit from more research. If the population EVPI is substantial, it is of interest to estimate the EVPI for individual parameters or sets of parameters. We termed this the partial EVPI. Partial EVPI is used to identify the parameters that have the highest informational value regarding decision uncertainty.

If the total EVPI is substantial, we are interested to learn the expected benefit of reducing uncertainty by obtaining information from a future study with a finite sample size. This is referred to as the total expected value of sample information (EVSI). Moreover, we can assess the expected benefit of future studies with a finite sample size that is used to collect information on a limited set of parameters. This is referred to as the partial EVSI. An author (B.G.K.) estimated the partial EVSI for several sets of parameters to assess various study designs.

Comparing the EVSI with the cost of performing research enables us to determine whether an additional study is justified given the cost. Subtracting the cost of research from the EVSI results in the expected net benefit of sampling (ENBS). The optimal sample size is determined by calculating the sample size that maximizes the ENBS.

For a future multicenter trial with a 3-year duration (assuming the study requires two full-time equivalent junior researchers and a senior researcher with 0.4 full-time-equivalent responsibility), we (B.G.K., M.G.M.H.) assumed a fixed cost of ¤500 000 and a variable cost of ¤500 per patient if all parameters in the initial trial were to be measured. If data on only three parameters (friction cost, overnight hospital stay, and quality-adjusted life-years) were to be collected, we assumed a fixed cost of ¤250 000 and a variable cost of ¤250 per patient. These cost estimates were based on our current expenses for similar studies.

Technical Details and Analysis

To allow for value-of-information analysis, we (B.G.K., T.S.) represented the joint uncertainty about the mean values of all parameters by using a multivariable normal distribution, with variances equal to the estimated squared standard errors of the mean and correlations between the different parameters calculated from the dataset. The central limit theorem justified the normality assumption.

An author (B.G.K.) performed 10 million simulations for each analysis, resulting in standard errors in our estimates of about 1%. Nested simulations were not required to estimate partial EVPI and EVSI because the relationship between the net benefit and each parameter was linear and because the multivariable normal distribution allowed us to calculate conditional mean values (8,13). To estimate EVSI, an author (B.G.K.) derived posterior normal distributions for the sampled parameters by using Bayesian updating of the prior normal distributions (14). We (B.G.K., T.S.) assumed that the standard deviations and correlations between parameters in future research would be the same as those in the initial trial. All analyses were performed with R software (version 1.7.1; R Foundation for Statistical Computing, Vienna, Austria) that can be accessed at http://www.r-project.org.

RESULTS

Cost-effectiveness Analysis

The combination of radiography and MR imaging was more effective (that is, it resulted in more quality-adjusted life-years during the study period), was less costly, and had a higher net benefit than radiography alone (Table). The differences in effect and net benefit were significant, but the difference in costs was not.

Population EVPI: Overall Importance of Uncertainty

We found a total EVPI of ¤2.1 per patient. The resulting population EVPI was ¤365 000 for the Netherlands and ¤10.2 million for the European Union. These values have an equivalent benefit of 5 quality-adjusted life-years for the Netherlands and 128 quality-adjusted life-years for the European Union. An effective lifetime for the technology of 5 years instead of 10 years would reduce these benefits by approximately half.

Partial EVPI: Important Parameters

In the initial study, only two of the 40 collected data parameters had a nonzero partial EVPI. The partial EVPI of the quality-adjusted life-year was ¤1.0 per patient, and the partial EVPI of the friction cost was ¤0.01 per patient. These two parameters had a synergistic effect, and together they had a partial EVPI of ¤1.9 per patient. This synergistic effect was augmented by considering the cost of an overnight hospital stay. A future study in which data on the number of quality-adjusted life-years, the cost of an overnight hospital stay, and the friction costs per patient would be gathered would have a partial EVPI of ¤2.0 per patient, which would be nearly equal to the total EVPI.

Total EVSI and ENBS: Optimal Sample Size

We first considered the optimal sample size for a future study to be identical to that in our

Table. Cost, Effect, and Net Benefit

Cost-effectiveness characteristic	Radiography only	Radiography and MR imaging	Difference between strategies
Cost (€)	2231 (1561, 2901)	1815 (1277, 2353)	-416 (-1275, 443)
Effect (QALY)	0.35 (0.34, 0.36)	0.38 (0.36, 0.39)	0.03 (0.01, 0.04)
Net benefit (€) *	25848 (24696, 27000)	28315 (27399, 29,231)	2467 (515, 4419)

Note.—Data are mean values. Data in parentheses are 95% confidence intervals. QALY = quality-adjusted life-year.
* Mean net benefit was calculated by multiplying effect by willingness to pay and subtracting cost, with willingness to pay set at a ratio of ¤80 000 per quality-adjusted life-year.

previous study, enabling us to collect data on all parameters. The population EVSI for a study from the perspective of the Netherlands did not exceed the study costs for any sample size. This meant that more research was not justified. The population EVSI for a study from the perspective of the European Union increased as the sample size increased until a plateau was reached; this plateau was equivalent to the population EVPI (Fig 1). The study costs increased linearly as the sample size increased. The maximum ENBS of ¤3.8 million was reached at a sample size of 2500 patients per trial arm. One should note, however, that there was a decreasing marginal gain in the ENBS: A study with 1500 patients per trial arm was expected to reach a net benefit of ¤3.4 million.

Partial EVSI and ENBS: Optimal Sample Size

To calculate partial EVSI, we considered a study that would enable us to collect data on only the three most important parameters: quality-adjusted life-years, cost of an overnight hospital stay, and friction cost per patient. The population (partial) EVSI for a study from the perspective of the Netherlands did not exceed the study cost for any sample size. The same study from the perspective of the European Union had a slightly lower population EVSI and substantially lower study costs compared with the study in which data were collected for all parameters (Fig 2). Therefore, the ENBS was higher when only the three most important parameters were sampled. The optimal sample size was 3500 patients per trial arm, resulting in an ENBS of ¤5.6 million or 70

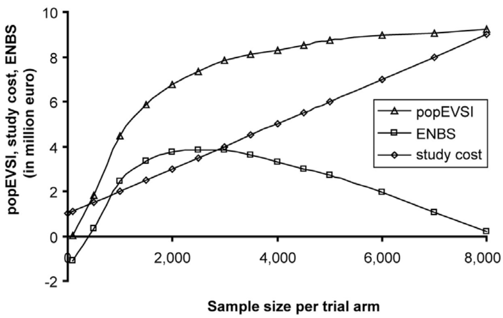

Figure 1. Population EVSI (popEVSI) for all parameters, study costs, and ENBS. The ENBS curve reaches a maximum value (¤3.8 million) when the sample size is 2500 patients per trial arm.

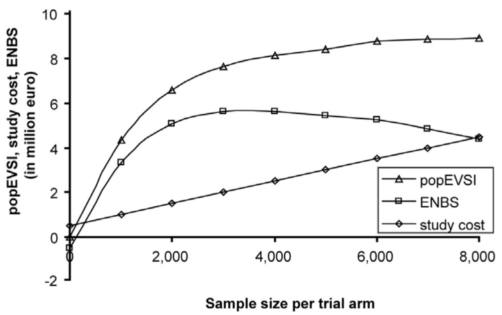

Figure 2. Population EVSI (popEVSI) for three parameters (friction cost, overnight hospital stay, and quality-adjusted life-years), study costs, and ENBS. The ENBS curve reaches a maximum value (¤5.6 million) when the sample size is 3500 patients per trial arm.

quality-adjusted life-years. Again, because of the decreasing marginal gain, we found an ENBS of ¤5.1 million for a study with 2000 patients.

DISCUSSION

We found a population EVPI of ¤10.2 million for a study from the perspective of the European Union regarding the decision of whether to add MR imaging to the current initial work-up of patients with acute knee trauma. This indicates that if we would eliminate all uncertainty regarding this decision, we could expect a societal financial benefit of ¤10.2 million, which is equivalent to a societal health benefit of 128 quality-adjusted life-years. Only three parameters were responsible for the decision uncertainty: the number of quality-adjusted life-years, cost of an overnight hospital stay, and friction costs per patient. Collecting data on the other 37 cost parameters has almost no additional benefit. A study in which data on these three parameters were gathered would have an optimal sample size of 3500 patients in each trial arm, and it would be expected to result in a societal benefit of ¤5.6 million or 70 quality-adjusted life-years. From the perspective of the Netherlands, however, more research was not justified.

It is important to realize that the calculated societal benefit of ¤5.6 million or 70 quality-adjusted life-years is an expected net benefit: It is a probability-weighted average over all possible outcomes of a future study. We learn the actual benefit of a study only after we have initiated the study, collected the data, and analyzed the actual results. Often, there is no actual benefit. The findings of the future study are more likely than not to confirm that the strategy that we believe to be optimal is indeed optimal. If a future study results in a change in the optimal strategy, the benefit may be a reduction in cost, an increase in quality-adjusted life-years, or a combination of these benefits.

The expected societal benefit of ¤5.6 million should be compared with the expected societal benefit of other unrelated proposed clinical research projects to set research priorities. The decision uncertainty regarding imaging for patients with acute knee trauma turns out to be relatively small in comparison with other clinical problems that have been addressed in value of information analyses (15). More research regarding MR imaging in patients with acute knee trauma is justified, but other clinical studies are expected to result in up to a 100-fold higher benefit. The prioritization of research studies will ultimately depend on the portfolio of potential studies submitted to a funding agency, their corresponding expected value of information, and the available research budget.

Our results were sensitive to the uncertain magnitude of the population expected to benefit from reducing decision uncertainty. This is, by definition, true for all value-of-information analyses; however, it is not a drawback but rather inherent to the assessment of the expected benefit of future research. Both the annual population that can potentially benefit from the research and the effective lifetime of the technology are influential and uncertain. The annual population that can benefit from research depends on the perspective of the policy maker: For example, is it the perspective of the hospital, the state, the country, or something even larger? When research proposals are compared, they need to be judged and compared from one perspective. Furthermore, the effective lifetime of the technology is uncertain because we do not know when improvements in diagnosis and treatment will come about and how they will influence decision uncertainty.

A few limitations pertain specifically to our study. We applied Dutch medical and non-medical costs to the entire European Union. This may have biased our results. Moreover, we assumed that medical care in the entire European Union was similar to that in the Netherlands. In addition, in our analyses we assumed that the intervention has no effect on costs and effects after the 6-month follow-up period. Although these limitations may affect the precise figure that results from the calculations, they are unlikely to have a substantial effect on our conclusions.

Our results imply that a Dutch funding agency seeking to maximize future health in the Netherlands should not fund more research regarding the value of MR imaging in patients with acute knee trauma. A European agency, however, should consider funding a multicenter trial with about 3500 patients in each trial arm in which the friction costs, the cost of an overnight hospital stay, and the number of quality-adjusted life-years are measured. However, other unrelated research proposals with a higher expected benefit should receive priority.

Value-of-information analysis is an analytic tool that can help researchers decide whether more clinical research regarding an uncertain medical decision is justified. It is a logical initial step when clinical research is considered regarding a medical decision or when the results of a randomized clinical trial are inconclusive. Value-of-information analysis can be used to determine whether the decision uncertainty justifies the cost of research. Decision uncertainty can be modeled by using all available evidence in the literature (5). Alternatively, the results of a previous clinical study or meta-analysis can be used for value-of-information analysis, as in the current study. Ideally, the analysis should involve all competing strategies to include all decision uncertainty. If the expected benefit of more research is substantial, value-of-information analysis can be used to identify key parameters, evaluate various study designs, and estimate optimal sample sizes. Claxton et al (15,16) demonstrated the feasibility of value-of-information analysis to help guide the research priority setting of the National Health Service in the United Kingdom. Although the mathematics are relatively simple, we realize that it takes time to understand the concepts of value-of-information analysis. To our knowledge, this is the only method with a theoretically sound basis; therefore, we foresee an important role for value of information analysis in guiding future research. The budget for clinical research is limited, and money should be spent where the expected benefits are greatest. Moreover, more clinical research is justified only if the expected benefit of more research exceeds the expected research costs.

REFERENCES

1. Nikken JJ, Oei EH, Ginai AZ, et al. Acute peripheral joint injury: cost and effectiveness of low-field-strength MR imaging—results of randomized controlled trial. Radiology 2005;236:958–967.
2. Phillips CV. The economics of "more research is needed". Int J Epidemiol 2001;30:771–776.
3. Claxton K, Sculpher M, Drummond M. A rational framework for decision making by the National Institute for Clinical Excellence (NICE). Lancet 2002;360:711–715.
4. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35:1095–1108.
5. Hunink MGM, Glasziou P. Decision making in health and medicine. Cambridge, England: Cambridge University Press, 2001.
6. Van Rijen, AJG. Zinnige en duurzame zorg. Zoetermeer, the Netherlands: Raad voor de Volksgezondheid en Zorg, 2006.
7. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. Med Decis Making 1998;18(2 suppl):S68–S80.
8. Ades AE, Lu G, Claxton K. Expected value of sample information calculations in medical decision modeling. Med Decis Making 2004;24:207–227.
9. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. J Health Econ 1999;18:341–364.
10. Brennan A, Chilcott J, Kharroubi S, O'Hagan A. A two level Monte Carlo approach to calculating expected value of perfect information: resolution of the uncertainty in methods [abstr]. Med Decis Making 2002;22(suppl):552.
11. Felli JC, Hazen GB. Sensitivity analysis and the expected value of perfect information. Med Decis Making 1998;18:95–109.
12. Groot Koerkamp B, Hunink MGM, Stijnen T, Weinstein MC. Identifying key parameters in cost-effectiveness analysis using value of information: a comparison of methods. Health Econ 2006;15:383–392.
13. Anderson TW. An introduction to multivariate statistical analysis. Hoboken, NJ: Wiley-Interscience, 1984.
14. Gelman A, Carlin JG, Stern HS, Rubin DB. Bayesian data analysis. London, England: Chapman & Hall, 1995.
15. Claxton K, Ginnelly L, Sculpher M, Philips Z, Palmer S. A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme. Health Technol Assess 2004;8(31):1–103, III.
16. Claxton K, Eggington S, Ginnelly L, et al. A pilot study of value of information analysis to support research recommendations for NICE. York, England: Centre for Health Economics, 2005.

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MRI Follow-Up of Conservatively Treated Meniscal Knee Lesions in General Practice

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ABSTRACT

PURPOSE: To evaluate the natural course of meniscal lesions on follow-up MRI, prognostic factors for meniscal status change after one year, and the association with clinical outcome.

MATERIALS AND METHODS: We analyzed 403 meniscal horns in 101 conservatively treated patients (59 male, mean age 40 years) in general practice who underwent initial MRI of the knee within 5 weeks after knee trauma. We used univariable and multivariable ordinal logistic regression analysis to analyze prognostic factures, including demographics and initial MRI findings, for meniscal status change on follow-up MRI after one year, and we assessed the association with clinical outcome.

RESULTS: On follow-up MRI we found 49 deteriorated and 18 improved meniscal horns. 9 new tears and 27 new degenerative lesions were seen. In the multivariable analysis, age (OR 1.3/decade, 95% CI 1.1-1.7), body weight (OR 1.2/10 kilograms, 95% CI 1.0-1.5), a total anterior cruciate ligament (ACL) rupture on initial MRI (OR 2.4, 95% CI 1.1-4.8), location in the posterior horn of the medial meniscus (OR 3.0, 95% CI 1.2-7.4), and a meniscal lesion on initial MRI (OR 0.3, 95% CI 0.1-0.7) were statistically significant predictors of meniscal MRI appearance change after one year. Change on MRI was not statistically significantly associated with clinical outcome.

CONCLUSION: In conservatively treated patients, meniscal deterioration on follow-up MRI one year after trauma is predicted by higher age and body weight, initial total ACL rupture, and location in the posterior horn of the medial meniscus. Change of MRI appearance is not associated with clinical outcome.

INTRODUCTION

Traumatic knee injury is a frequently encountered condition with a reported incidence of 5.3 per 1000 patients in Dutch general practice annually (1). In our country, approximately 75% of patients with traumatic knee injury are diagnosed and treated conservatively by general practitioners. The majority of these patients recover without the need for referral to a specialist or surgery (2).

Magnetic resonance imaging (MRI) is a well-established and accurate diagnostic imaging modality for evaluation of the knee joint (3, 4). In most cases, MRI is performed in the diagnostic work-up of persistent traumatic knee complaints in search of treatable lesions, in particular meniscal tears. MRI, therefore, is usually applied as a triage test for targeted therapeutic arthroscopy (5-7).
Little is known about the appearance of meniscal lesions on follow-up MRI after conservative treatment and its correlation with clinical outcome. Several previous studies have reported on follow-up MRI after surgical meniscal repair (8-10), but in a recent systematic review of the literature, Boks et al. (11) found only one small study on the natural course of meniscal lesions evaluated by sequential MRI (12).

The purpose of this study was to evaluate the natural course of meniscal lesions on structured follow-up MRI in the general practice population, to identify prognostic factors at baseline for meniscal status change after one year, and to assess the association of follow-up MRI findings with clinical outcome.

MATERIALS AND METHODS

Patient selection and study design

We studied a subgroup of the prospective observational HONEUR knee cohort study into acute and chronic knee complaints in primary care in which 1068 adult and adolescent patients were included. The study design of this cohort was described in detail by Heintjes et al. in a previous paper (13). The subgroup consisted of consecutively included patients aged 18 to 65 years who visited the general practitioner because of acute knee trauma within the preceding 5 weeks (14). Exclusion criteria were: severe trauma necessitating immediate hospital referral, a fracture demonstrated radiographically, and MRI contra-indications. The study was approved by the institutional review board of Maasstad Ziekenhuis, Rotterdam, The Netherlands, and each patient provided written informed consent.

Patients underwent initial MRI within 3 to 6 weeks after trauma and follow-up MRI after approximately 12 months. Immediately following both MRI examinations, an experienced physiotherapist (HW) performed standardized physical examination, blinded for MRI findings, which included specific meniscal provocation tests.

At baseline and 12 months after trauma self-reported questionnaires were completed, recording a pain score measured on an 11-point numeric rating scale ranging from 0 (no pain) to 10 (unbearable pain) (15), Lysholm knee function score (16), specialist referral, and whether an operation had been performed. At 12 months we also recorded perceived recovery measured on a 7-point Likert scale, ranging from 'completely recovered' to 'worse than ever'.

MRI technique and interpretation

MRI examinations were performed on a 1.0 Tesla whole-body MRI unit (Signa Horizon LX, GE Medical Systems, Milwaukee, USA) and a dedicated knee coil. We performed sagittal T1-, T2-, and proton density-weighted fast spin-echo, coronal T1-weighted gradient echo and fat-suppressed T2-weighted fast spin-echo, and axial proton-density weighted fast spin-echo sequences.

The anterior and posterior horns of both menisci were scored separately for tears or degenerative lesions using the grading system listed in Table 1. We also assessed the presence or absence of coexistent cruciate ligament lesions. Two independent readers (one senior radiology resident (SB) and one experienced musculoskeletal radiologist (DV)) assessed the initial MRI examinations and three independent readers (two senior radiology residents (EHGO and IMK) and one experienced musculoskeletal radiologist (JHH)) evaluated the follow-up MRI using a standardized case report form. In case of discrepancies, consensus was reached through discussion or the majority opinion was used for analysis. MRI readers were blinded to findings on physical examination, pain scores, and functional scores as reported on the questionnaires, but to reflect clinical practice, the initial MRI examination was available for comparison on follow-up MRI interpretation. Unless there were abnormalities that required immediate attention (e.g. fractures or tumors), initial MRI findings were not reported to the general practitioner. Hence, the treatment strategy was not influenced by the MRI findings. In case of referral to a specialist, the specialist was able to request the initial MRI report so as to avoid unnecessary repetition of an MRI examination.

Table 1. Grading system of meniscal lesions

Grading system of meniscal lesions	
Grade 0	Normal meniscal horn
Grade 1	Focal increased signal intensity within the meniscus
Grade 2	Linear band of increased signal intensity not extending to the articular surface
Grade 3	Horizontal meniscal tear
Grade 4	Longitudinal or vertical meniscal tear
Grade 5	Complex meniscal tear with a combination of multiple cleavage planes

Note: Grade 1 and 2 lesions represent degenerative abnormalities.

Data analysis

Patients who underwent an operation during the follow-up period were excluded from the analysis. We performed per-meniscal horn univariable and multivariable ordinal logistic regression analysis using Stata/SE 10.0 for Windows (StataCorp, College Station, Texas, USA) with the separately available user-written Gologit2 macro (17). As the three possible ordinal outcomes, we defined an improved, unchanged, and deteriorated meniscal appearance as reflected by the grading difference on follow-up versus initial MRI. Performing ordinal logistic regression analysis with three possible outcomes, two regression equations are estimated with two regression coefficients per independent variable. The first coefficient contrasted an unchanged or deteriorated with an improved meniscal appearance, and the second coefficient indicated a deteriorated versus an unchanged or improved meniscal appearance. For each independent variable, we evaluated the applicability of the proportional odds assumption using the Brant test in the univariable analyses and Gologit2's 'autofit' option in the multivariable analyses. If the proportional odds assumption was fulfilled, the same regression coefficient was estimated across equations, whereas different regression coefficients for the two regression equations were computed if the assumption was violated. In the multivariable analysis, we specified per variable whether or not the proportional odds assumption was to be applied. In this way, we obtained partial proportional odds models, with two identical regression coefficients for variables meeting the proportional odds assumption and two different coefficients for those that violated the assumption.

The following independent variables were analyzed: age (continuous and dichotomized at age 40), sex, physique as measured by body weight and body mass index (continuous and dichotomized at 25 and 30 kilograms/m^2), sports injury as the trauma mechanism, baseline pain score (continuous and dichotomized at 6 points), Lysholm knee function score (continuous and dichotomized at 50 points), presence of a degenerative or traumatic meniscal lesion on baseline MRI, a complete ACL rupture on the initial MRI, and three dummy variables to code the four meniscal horns so as to assess the effect of location. We also evaluated pain at passive flexion during initial physical examination, since this was the only variable from physical examination to show an association with meniscal tears in a previous study (18).

Variables with a p-value of less than 0.10 in the univariable analysis were included in the multivariable analysis. In the multivariable analysis, a p-value of less than 0.05 was considered statistically significant.

We used the mean values of the other patients to impute missing data on baseline pain score and Lysholm knee function score in 3 patients, and on pain score and perceived recovery in 7 and 1 patients respectively. Since sports injury was strongly correlated with age and sex, we performed a logistic regression analysis with these variables to impute missing data on sports injury in 6 patients. It has been demonstrated that imputation of missing data reduces the risk of bias and is preferable over complete case analysis (19,20).

We assessed the association between change of meniscal MRI appearance and clinical outcome, as indicated by perceived recovery and change in pain score at 12 months versus baseline. Since these variables were recorded on a patient level, we first created an overall variable, reflecting per patient whether or not meniscal deterioration was seen in any of the horns on follow-up. We assumed that rating of clinical outcome is determined by the meniscal horn with the least favorable change. Thus, a patient with improvement of one meniscal horn and deterioration of another horn on follow-up MRI was coded as deteriorated in the overall variable. Subsequently, we analyzed the association between meniscal deterioration on a per-patient level and perceived recovery and change in pain score using Fisher's exact test.

Because the exact procedure and effect on meniscal MRI appearance was unknown in some patients that underwent surgery, and to explore the effect of possible selection bias, we performed a sensitivity analysis including the operated patients.

Since four meniscal horns per patient were analyzed separately, we corrected for the clustered nature of the data using bootstrapping when testing for statistical significance. Bootstrapping was performed by creating 1000 replications of the dataset using sampling with replacement and treating all of a patient's observations as a cluster (implying an independent identical distribution at the patient level) (21). Bias-corrected 95% confidence intervals are reported.

RESULTS

134 of 263 potentially eligible patients fulfilled the inclusion criteria and agreed to undergo additional MRI and physical examination at baseline. Follow-up MRI and physical examination were performed in 117 patients. 17 patients were not followed up because they refused follow-up MRI and physical examination, or because they had moved and we were unable to contact them. A diagram indicating the patient selection and flow through the study is presented in Figure 1. 15 patients were excluded from the analysis because they reported to have undergone surgery (14 arthroscopies and one ACL reconstruction) during follow-up. The exact type of arthroscopic procedure, however, was not always known. Another patient was excluded because post-operative findings associated with a partial meniscectomy of the anterior horn of the lateral meniscus were unequivocally present on follow-up MRI, although data on the procedure was missing on the questionnaires. In one patient, only the posterior horn of the medial meniscus was excluded because of partial meniscectomy prior the start of the study. Thus, a total of 403 meniscal horns in 101 patients (59 male, 42 female;mean age 40, range 18-63 years) were analyzed. Mean time between MRI examinations was

Figure 1. Flow diagram indicating the selection of subjects and the flow of patients through the study.

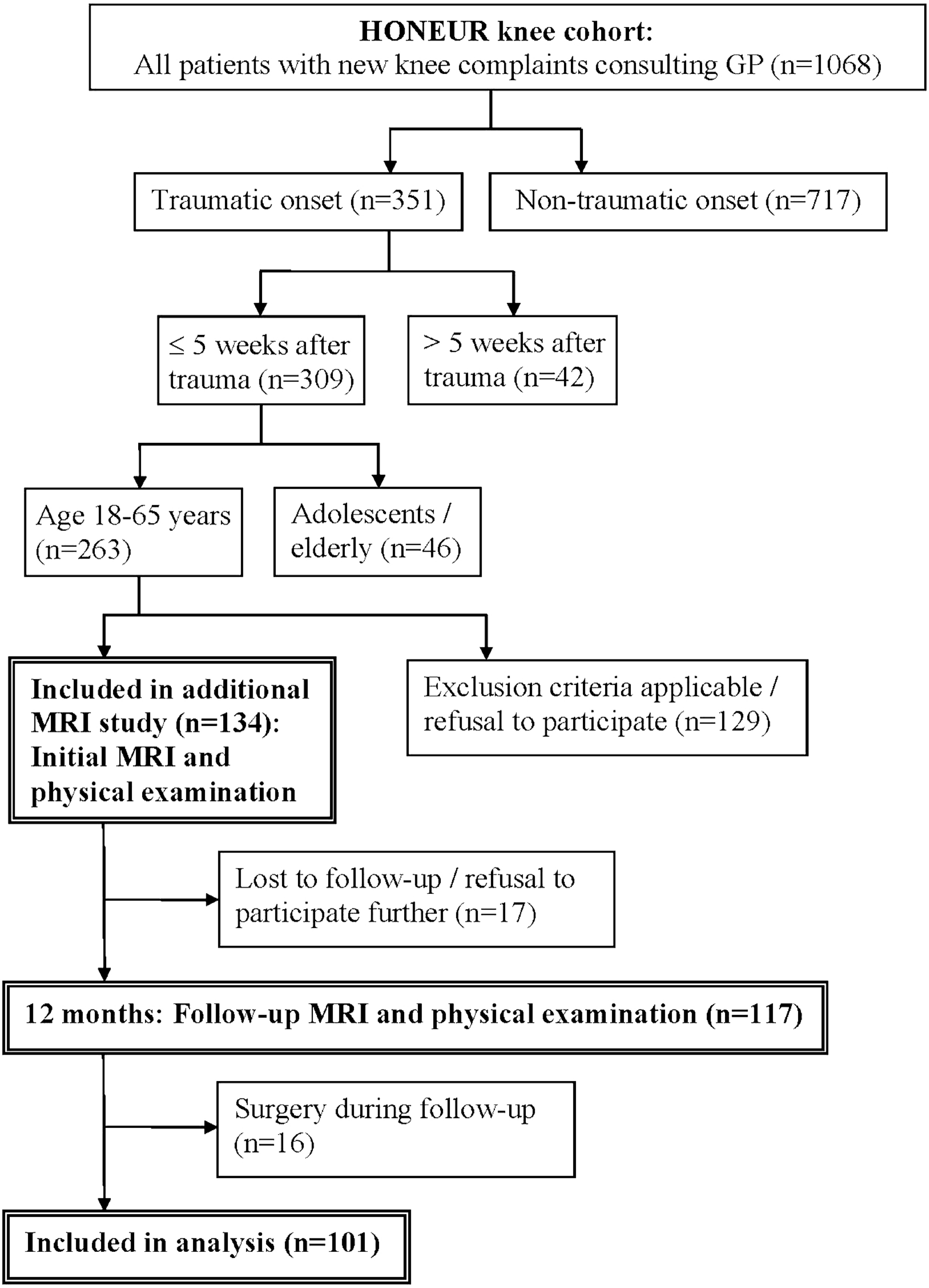

Table 2. Change in meniscal appearance on follow-up MRI compared to initial MRI

	Lateral meniscus anterior horn (n=101)	Lateral meniscus posterior horn (n=101)	Medial meniscus anterior horn (n=101)	Medial meniscus posterior horn (n=100)	Total (n=403)
Unchanged					
Normal to Normal	56	71	85	19	231
Grade 1 to Grade 1	12	9	5	24	50
Grade 2 to Grade 2	1	0	3	16	20
Horizontal tear to Horizontal tear	5	6	2	10	23
Vertical tear to Vertical tear	3	0	1	7	11
Complex tear to Complex tear	1	0	0	0	1
New degenerative lesions and tears					
Normal to Grade 1 (new)	11	7	2	5	25
Normal to Grade 2 (new)	2	0	0	0	2
Normal to Horizontal tear	2	0	0	1	3
Progression of lesion complexity					
Grade 1 to Grade 2	0	1	0	4	5
Grade 1 to Horizontal tear	1	0	0	0	1
Grade 2 to Horizontal tear	1	0	0	4	5
Horizontal tear to Complex tear	0	3	0	2	5
Vertical tear to Complex tear	3	0	0	0	3
Improvement of lesion complexity					
Grade 2 to Grade 1	0	1	1	1	3
Horizontal tear to Grade 2	1	0	0	1	2
Vertical tear to Grade 1	0	0	0	1	1
Vertical tear to Grade 2	0	0	0	2	2
Complex tear to Horizontal tear	0	0	0	1	1
Normalization of lesions					
Grade 1 to Normal	2	2	1	1	6
Grade 2 to Normal	0	0	1	1	2
Horizontal tear to Normal	0	1	0	0	1

Note: combinations that are not listed in the table were not observed in our study.

404 days (standard deviation 59.1, range 315-675 days).

At baseline, there were 50 tears and 122 degenerative lesions in 403 meniscal horns, most frequently in the posterior horn of the medial meniscus. The change of meniscal MRI appearance after one year follow-up is presented in Table 2. 336 meniscal horns (of which 231 were normal) remained unchanged after one year. 27 initially normal meniscal horns showed progression to a degenerative lesion, but not into a tear. 6 initially degenerative lesions were scored as frank tears on follow-up MRI, all of which were horizontal. 3 new meniscal tears, also exclusively of the horizontal type, were seen on follow-up MRI without preexisting abnormalities initially. 8 meniscal tears showed progression and developed into complex ruptures. In contrast, 8 degenerative lesions and 1 horizontal tear on initial MRI were classified as normal on follow-up MRI. 5 initial meniscal tears no longer extended to the articular surface on follow-up MRI and were thus classified as a degenerative lesion. 2 initially complex meniscal tears showed improved morphology on follow-up.

Table 3 presents the results of the univariable ordinal logistic regression analysis. Age (both continuous and dichotomized at 40

Table 3. Results of the univariable ordinal logistic regression analysis

Covariable	Observed frequency in study population of 101 patients (percentage) §	Odds ratio (95% confidence interval)		P-value
Age (continuous)	40.0 years (11.8, 18-63) §	1.02/yr	(1.00-1.04)	0.03
Age > 40 years	48 (48)	2.09	(1.16-3.76)	0.01
Male sex	59 (58)	0.93	(0.58-1.50)	0.78
Body weight	82.2 kg (16.0, 40-129) §	1.01/kg	(1.00-1.03)	0.10
Body mass index (continuous)	26.1 kg/m² (4.2, 17-40) §	1.04	(0.98-1.09)	0.20
Body mass index > 25 kg/m²	58 (57)	1.45	(0.89-2.36)	0.13
Body mass index > 30 kg/m²	18 (18)	1.35	(0.74-2.48)	0.33
Sports injury *	53 (52)	0.81	(0.50-1.30)	0.38
Baseline pain score continuous #	4.4 (2.2, 0-10) §	0.93	(0.85-1.03)	0.17
Baseline pain score > 6 points #	34 (34)	0.62	(0.36-1.06)	0.08
Baseline Lysholm score continuous #	66.8 (18.1, 18-100) §	1.00	(0.98-1.01)	0.53
Baseline Lysholm score > 50 #	79 (78)	1.07	(0.64-1.80)	0.79
Pain at passive flexion during physical exam	62 (61)	1.16	(0.73-1.84)	0.53
Meniscal lesion on initial MRI	142/403 horns (35)	0.48	(0.23-0.98)	0.05
Total ACL rupture on initial MRI	9 (9)	1.89	(1.12-3.21)	0.02
Location in posterior horn medial meniscus	100 (99)	0.39	(0.14-1.07)	0.07

§ For continuous variables, we report mean (standard deviation, range).
* 6 missing values were imputed .
# 3 missing values were imputed.

years), baseline pain score 6 points or higher, a meniscal lesion on initial MRI, complete ACL rupture on initial MRI, and location in the posterior horn of the medial meniscus were statistically significant predictors of change of meniscal appearance after one year, and were included in the multivariable ordinal logistic regression analysis. We also included body weight (continuous) since it was of borderline significance when analyzed univariably (p=0.10). Baseline pain score was no longer statistically significant when controlling for the other variables, and was therefore excluded from the final multivariable model (Table 4). In the sensitivity analysis of 117 patients including the 16 operated patients, we identified the same significant variables as above with similar odds ratios and confidence intervals (results not tabulated).

Correlation with clinical outcome

Regarding perceived recovery at one year, 28 and 67 patients reported complete recovery and improvement respectively, whereas 2 patients experienced some deterioration. There were no patients reporting substantial deterioration or a condition worse than ever. Table 5 presents a crosstabulation of perceived recovery and meniscal MRI appearance change. 42 patients with meniscal deterioration on follow-up MRI reported improvement of clinical outcome. Meniscal deterioration was not statistically significantly associated with clinical deterioration measured by perceived recovery (Fisher's exact test p-value 0.50). Similarly, no statistically significant association was found between meniscal deterioration and an increased pain score at 12 months follow-up (Fisher's exact test p-value 1.0, results not tabulated).

Table 4. Results of the multivariable ordinal logistic regression analysis

Covariable	Odds ratio	95% Confidence interval	P-value
No change and deterioration versus improvement			
Age (continuous, per decade)	1.33	1.07-1.68	0.01
Body weight (continuous, per 10 kg)	0.85	0.63-1.15	0.29
Presence of meniscal lesion on initial MRI	0.30	0.12-0.72	0.01
Presence of total ACL rupture on initial MRI	2.35	1.14-4.82	0.02
Location in posterior horn medial meniscus	0.74	0.16-3.46	0.70
Deterioration versus no change and improvement			
Age (continuous, per decade)	1.33	1.07-1.68	0.01
Body weight (continuous, per 10 kg)	1.22	1.01-1.49	0.04
Presence of meniscal lesion on initial MRI	0.30	0.12-0.72	0.01
Presence of total ACL rupture on initial MRI	2.35	1.14-4.82	0.02
Location in posterior horn medial meniscus	2.98	1.20-7.40	0.02

Table 5. Perceived recovery and overall per-patient change in meniscal appearance on follow-up MRI

	Perceived recovery					
	Complete recovery	Strong improvement	Some improvement	Unchanged	Some deterioration	Total
MRI appearance improved or unchanged	12	35	6	2	2	57
MRI appearance deteriorated	16	22	4	2	0	44
Total	28	57	10	4	2	101

Note: table displays number of patients.

DISCUSSION

We studied the natural course of meniscal knee lesions and prognostic factors for meniscal appearance change on follow-up MRI one year after trauma. Unlike the majority of published studies on meniscal pathology we studied a general practice population, because in our country most patients with traumatic knee injury are managed in primary care. We found a variable meniscal MRI appearance after one year follow-up. Higher age and body weight, an initial total ACL rupture, and location in the posterior horn of the medial meniscus were found to be significant predictors of meniscal deterioration.

In a recent systematic review by Boks et al. (11) only one previous article on the natural course of peripheral meniscal lesions was found, reporting on a limited number of 6 patients (12). To our knowledge, our study is the first to evaluate the natural course of meniscal pathology using MRI follow-up in a large study population in primary care.

The majority of meniscal horns (57.3%) were initially normal and remained normal on follow-up, reflecting the primary care setting of this study. It is possible that the proportion of normal menisci was larger than in a hospital setting. We found that new degenerative meniscal lesions may develop within one year after trauma. Conversely, in a number of menisci initially scored as degenerative, we no longer observed abnormal signal intensity on follow-up, suggesting that smaller areas of intrameniscal signal abnormality may be transient. All new meniscal tears were of the horizontal type, and the majority of these were degenerative lesions initially. This finding is consistent with previous studies suggesting that horizontal tears are usually a manifestation of degenerative disease rather than trauma (22,23). It is likely that the new horizontal meniscal tears that were not associated with previous abnormalities developed gradually from normal to a degenerative lesion and subsequently to a degenerative tear over the course of one year.

Apart from progression of lesion complexity, we also found improvement of meniscal tear morphology in several patients. In a number of patients extension to the articular surface was no longer visible on follow-up MRI. Although the number of these cases is relatively small, the findings suggest that natural healing is possible. The natural healing potential of menisci after conservative treatment was also reported previously by Ihara et al. (24), but in this study arthroscopy was used instead of MRI to assess the menisci.

In the multivariable ordinal logistic regression analysis, deterioration of meniscal appearance after one year was significantly predicted by higher age and body weight, location in the posterior horn of the medial meniscus, and a total ACL rupture on initial MRI. The latter finding is consistent with previous studies demonstrating a higher incidence of meniscal tears in ACL-deficient unstable knees (25,26). Presence of a meniscal lesion on initial MRI was also statistically significant, but with an odds ratio smaller than 1, indicating improvement if a meniscal lesion was present initially, and suggesting a natural healing potential for meniscal lesions. The natural healing tendency is, however, nullified if other predictive factors for deterioration with an odds ratio greater than 1 are present.

Since the HONEUR knee cohort was not aimed at assessing treatment options for knee lesions, the management of our patient population was not documented in detail. Consequently, in some of the 14 patients who underwent arthroscopy, it was unknown what procedure was performed. Although most of these patients probably underwent partial meniscectomy, the most common procedure in the setting of meniscal pathology, we were not completely certain which component of MRI appearance change could be attributable to surgery. To overcome this problem and to obtain a homogenous study population, we only analyzed conservatively treated patients. To explore the possible effect of selection bias that may have been introduced because the more severe cases necessitating surgery were not analyzed, we performed a sensitivity analysis including the operated patients. This resulted in an identical multivariable model with similar odds ratios.

We also studied the association between change in meniscal MRI appearance and clinical outcome. We found no statistically significant association between meniscal deterioration on follow-up MRI and worse clinical outcome, as reflected by perceived recovery or change in pain score. Many patients with deteriorated meniscal MRI appearance still reported strong improvement or even complete recovery. Analogously, poor association was found between change in pain score and meniscal MRI appearance. Our results are consistent with those of Deutsch et al. (12), indicating that meniscal appearance on follow-up MRI does not correlate with clinical outcome, and suggesting that it is not useful to perform follow-up MRI of the menisci to explain clinical deterioration.

We used a 1.0 Tesla MRI unit, but it has been shown that lower magnetic field strength does not significantly reduce diagnostic performance for meniscal tears (3). Moreover, since we studied meniscal lesions over time rather than the diagnostic accuracy of the MRI technique, we expect that this did not influence our results. We cannot completely exclude the possibility of misinterpretation of meniscal appearance change due to slight differences in scan plane orientation, but in our view the likelihood of misclassification is low because identical pulse sequences were used for initial and follow-up MRI, and in most cases the presence of a meniscal tear was confirmed on multiple contiguous images.

We conclude that the MRI appearance of meniscal lesions one year after trauma is variable. In conservatively treated patients, higher age and body weight, total ACL rupture, and location in the posterior horn of the medial meniscus predict meniscal deterioration on follow-up MRI after one year, and if present, these factors nullify the natural healing potential suggested by our results. There is no association between change in meniscal MRI appearance and clinical outcome, and in many clinically recovered or strongly improved patients, persistent abnormal or deteriorated meniscal appearance is seen.

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REFERENCES

1. Van der Linden MW, Westert GP, de Bakker DH, et al. Tweede nationale studie naar ziekten en verrichtingen in de huisartspraktijk: klachten en aandoeningen in de bevolking en in de huisartspraktijk. Utrecht, Bilthoven: NIVEL, Rijksinstituut voor volksgezondheid en milieu., 2004.
2. Cardol M, van Dijk L, de Jong JD, et al. Tweede Nationale Studie naar ziekten en verrichtingen in de huisartspraktijk. Huisartsenzorg: wat doet de poortwachter ? Utrecht, Bilthoven: NIVEL/RIVM, 2004.
3. Oei EHG, Nikken JJ, Verstijnen AC, Ginai AZ, Hunink MGM. MR imaging of the menisci and cruciate ligaments: a systematic review. Radiology 2003; 226:837-848.
4. Mackenzie R, Palmer CR, Lomas DJ, Dixon AK. Magnetic resonance imaging of the knee: diagnostic performance studies. Clin Radiol 1996; 51:251-257.
5. Ruwe PA, Wright J, Randall RL, Lynch JK, Jokl P, McCarthy S. Can MR imaging effectively replace diagnostic arthroscopy? Radiology 1992; 183:335-339.
6. Vincken PW, ter Braak BP, van Erkel AR, et al. Effectiveness of MR imaging in selection of patients for arthroscopy of the knee. Radiology 2002; 223:739-746.
7. Vincken PW, ter Braak AP, van Erkel AR, et al. MR imaging: effectiveness and costs at triage of patients with nonacute knee symptoms. Radiology 2007; 242:85-93.

8. Hantes ME, Zachos VC, Zibis AH, et al. Evaluation of meniscal repair with serial magnetic resonance imaging: a comparative study between conventional MRI and indirect MR arthrography. Eur J Radiol 2004; 50:231-237.
9. Mustonen AO, Tielinen L, Lindahl J, Hirvensalo E, Kiuru M, Koskinen SK. MRI of menisci repaired with bioabsorbable arrows. Skeletal Radiol 2006; 35:515-521.
10. Steenbrugge F, Verstraete K, Verdonk R. Magnetic reasonance imaging of the surgically repaired meniscus: a 13-year follow-up study of 13 knees. Acta Orthop Scand 2004; 75:323-327.
11. Boks SS, Vroegindeweij D, Koes BW, Hunink MG, Bierma-Zeinstra SM. Follow-up of posttraumatic ligamentous and meniscal knee lesions detected at MR imaging: systematic review. Radiology 2006; 238:863-871.
12. Deutsch AL, Mink JH, Fox JM, et al. Peripheral meniscal tears: MR findings after conservative treatment or arthroscopic repair. Radiology 1990; 176:485-488.
13. Heintjes EM, Berger MY, Koes BW, Bierma-Zeinstra SM. Knee disorders in primary care: design and patient selection of the HONEUR knee cohort. BMC Musculoskelet Disord 2005; 6:45.
14. Boks SS, Vroegindeweij D, Koes BW, Hunink MGM, Bierma-Zeinstra SM. Magnetic resonance imaging abnormalities in symptomatic and contralateral knees: prevalence and associations with traumatic history in general practice. Am J Sports Med 2006; 34:1984-1991.
15. Herr KA, Spratt K, Mobily PR, Richardson G. Pain intensity assessment in older adults: use of experimental pain to compare psychometric properties and usability of selected pain scales with younger adults. Clin J Pain 2004; 20:207-219.
16. Briggs KK, Kocher MS, Rodkey WG, Steadman JR. Reliability, validity, and responsiveness of the Lysholm knee score and Tegner activity scale for patients with meniscal injury of the knee. J Bone Joint Surg Am 2006; 88:698-705.
17. Williams R. Generalized Ordered Logit/Partial Proportional Odds Models for Ordinal Dependent Variables. In:The Stata Journal, 2006; 58-82.
18. Wagemakers HP, Heintjes EM, Boks SS, et al. Diagnostic value of history-taking and physical examination for assessing meniscal tears of the knee in general practice. Clin J Sport Med 2008; 18:24-30.
19. Van der Heijden GJ, Donders AR, Stijnen T, Moons KG. Imputation of missing values is superior to complete case analysis and the missing-indicator method in multivariable diagnostic research: a clinical example. J Clin Epidemiol 2006; 59:1102-1109.
20. Schafer J. Analysis of incomplete multivariate data. London: Chapman & Hall, 1997.
21. Efron B, Tibshirani RJ. An introduction to the bootstrap. New York, NY: Chapman & Hall, 1993.

22. Bhattacharyya T, Gale D, Dewire P, et al. The clinical importance of meniscal tears demonstrated by magnetic resonance imaging in osteoarthritis of the knee. J Bone Joint Surg Am 2003; 85-A:4-9.
23. Lange AK, Fiatarone Singh MA, Smith RM, et al. Degenerative meniscus tears and mobility impairment in women with knee osteoarthritis. Osteoarthritis Cartilage 2007; 15:701-708.
24. Ihara H, Miwa M, Takayanagi K, Nakayama A. Acute torn meniscus combined with acute cruciate ligament injury. Second look arthroscopy after 3-month conservative treatment. Clin Orthop Relat Res 1994:146-154.
25. Daniel DM, Stone ML, Dobson BE, Fithian DC, Rossman DJ, Kaufman KR. Fate of the ACL-injured patient. A prospective outcome study. Am J Sports Med 1994; 22:632-644.
26. Nebelung W, Wuschech H. Thirty-five years of follow-up of anterior cruciate ligament-deficient knees in high-level athletes. Arthroscopy 2005; 21:696-702.

9

Predictive Factors for New Onset or Progression of Osteoarthritis in the Knee Joint One Year after Trauma; MRI Follow-Up in General Practice

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Submitted

ABSTRACT

PURPOSE: To prospectively evaluate prognostic factors for new onset or progression of degenerative change on follow-up MRI one year after traumatic knee injury and to evaluate the association with clinical outcome.

MATERIALS AND METHODS: We studied 117 patients (67 male, 50 female; mean age 41, range 18-63 years) in general practice who underwent initial knee MRI 3-6 weeks after acute trauma, and follow-up MRI after one year. Degenerative femorotibial change on both MRI examinations was graded using the adapted Kellgren and Lawrence scale. We used univariable and multivariable logistic regression analysis to analyze the prognostic value of demographics, trauma mechanism, pain score, Lysholm functional knee score, and initial MRI findings on development of new degenerative change or progression of pre-existing osteoarthritis. We also studied the association between new or progressive degenerative change and clinical outcome, as reflected by perceived recovery.

RESULTS: On initial MRI, 33 knees showed degenerative abnormalities. On follow-up MRI, 22 of 84 initially normal knees demonstrated new degenerative change, and in 5 knees with pre-existing osteoarthritis, progression was seen. In the univariable analysis, age above 50 years and body mass index greater than 25 kg/m^2 were significant predictors of new or progressive degenerative change ($p<0.10$). The most significant predictor, however, was bone marrow edema on initial MRI, and this remained the only significant prognostic variable in the multivariable analysis (OR 5.29 (95% CI 1.64-17.1), $p=0.005$). A significant association between new or progressive degenerative change and clinical outcome was found ($p=0.003$).

CONCLUSION: Presence of bone marrow edema on MRI for acute knee injury is strongly predictive for new onset or progression of degenerative change of the femorotibial joint on follow-up MRI one year after trauma, which is reflected in clinical outcome.

INTRODUCTION

Osteoarthritis (OA) of the knee is a common cause of functional impairment and pain in the general population. Although the pathogenesis and etiology of OA is not fully understood, it is regarded as a generalized degenerative process involving all tissues of the affected joint (1). Besides demographic factors such as age and sex, obesity and knee trauma are established risk factors for the development of OA of the knee (2-4). With a reported incidence of 5.3 per 1000 patients annually, traumatic knee injury is a frequently encountered condition in general practice (5).

Meniscal lesions and anterior cruciate ligament (ACL) injuries constitute a large proportion of traumatic knee injury, and evidence exists that traumatic meniscal lesions are associated with progression of OA of the knee (6,7). ACL injuries most commonly occur in young- to middle-aged physically active people, and in a previous study it was found that approximately 50% of this population develop OA of the knee 10-20 years after the injury (8). It has also been suggested that bone marrow edema is a risk factor for structural deterioration and progression of knee OA (9,10).

Detection of early OA changes in the knee by radiographs alone is limited and the correlation between radiographic findings and clinical symptoms is poor (11-13). With magnetic resonance imaging (MRI) it is possible to separately evaluate bone, cartilage, ligaments, meniscus and soft- tissue abnormalities, allowing an in-depth whole organ assessment rather than an indirect radiographic projection of intra-articular damage. Therefore, MRI has been advocated as the best currently available imaging modality for the detection of early osteoarthritic changes (6,14,15).

The extent to which traumatic knee abnormalities predict the development of OA within the first years after trauma has only been sparsely documented. We performed a study in the general practice population to prospectively evaluate prognostic factors, including initial MRI findings, for new onset or progression of OA of the femorotibial joint, assessed by follow-up MRI one year after trauma, and to evaluate the association with clinical outcome.

MATERIALS AND METHODS

Patient selection and study design

We performed a subgroup study within the HONEUR knee cohort, a prospective observational cohort study in general practice, in which patients were included if they consulted their general practitioner for the first time because of acute or chronic knee complaints. The study design of this general cohort, in which a total of 1068 patients were included, has been previously described in detail by Heintjes et al. (16). The subgroup under investigation in the present study consisted of consecutively included patients aged 18 to 65 years consulting one of the 47 collaborating general practitioners because of an acute knee trauma within the preceding 5 weeks (17). Patients were excluded in case of severe injury requiring immediate hospital referral, if a fracture was demonstrated in those referred for conventional radiography, or if there were contra-indications for MRI. The study was approved by the institutional review board of the Maasstad Ziekenhuis, Rotterdam, The Netherlands, and written informed consent was obtained from each patient.

MRI technique and interpretation

MRI was performed within 3 to 6 weeks after trauma and repeated after approximately 1 year follow-up. For both examinations, we applied the same technique and pulse sequences, using a 1.0 Tesla whole-body MRI unit (Signa Horizon LX, GE Medical Systems, Milwaukee, USA) and a dedicated knee coil. The scan protocol consisted of sagittal T1-, T2-, and proton density-weighted fast spin-echo sequences, coronal T1-weighted gradient echo and fat-suppressed T2-weighted fast spin-echo sequences, and an axial proton-density weighted fast spin-echo sequence.

The initial and follow-up MRI examinations were evaluated for the presence of degenerative abnormalities of the femorotibial joint. For this purpose, we used the adapted Kellgren and Lawrence scoring system, which was originally developed for grading osteoarthritic change on conventional radiography (18). Using this grading system, each femorotibial joint was scored as follows: grade 0: no degenerative abnormalities; grade 1: minimal osteophyte of unknown significance; grade 2: osteophytes without joint space narrowing; grade 3: moderate joint space narrowing; grade 4: severe joint space narrowing with sclerosis of subchondral bone. In addition to degenerative abnormalities, we assessed the presence of meniscal and ligamentous lesions, as well as bone marrow edema on the initial MRI. Findings were documented on a standardized report form.

Two independent readers (one senior radiology resident (SB) and one experienced musculoskeletal radiologist (DV)) evaluated the initial MRI examination, and in case of discrepancies, consensus was reached through discussion. The follow-up MRI exams were assessed by three independent readers (two senior radiology residents (EHGO and IMK) and one experienced musculoskeletal radiologist (JHH)), and in case of discrepancies the majority opinion was used for analysis.

To reflect clinical practice, both the reports and the images of the initial MRI examination were available on follow-up MRI evaluation. In this observational cohort study, the treating general practitioner was not informed of the findings on the initial MRI unless findings required immediate treatment. Hence, the treatment strategy was not influenced by the MRI findings. If a patient was referred to a medical specialist, the initial MRI report was provided on request, so as to avoid unnecessary repetition of an MRI examination.

Self-reported questionnaires

Self-reported questionnaires were completed at baseline and 12 months after trauma. On the questionnaires, we recorded a pain score measured on an 11-point numeric rating scale ranging from 0 (no pain) to 10 (unbearable pain) (19), the Lysholm knee function score (20), referral to a medical specialist, and whether an operation had been performed. At 12 months we also scored perceived recovery as rated by the patient and measured on a 7-point Likert scale, ranging from 'completely recovered' to 'worse than ever'. Both the initial and follow-up MRI readers were blinded to the reported scores on the questionnaires.

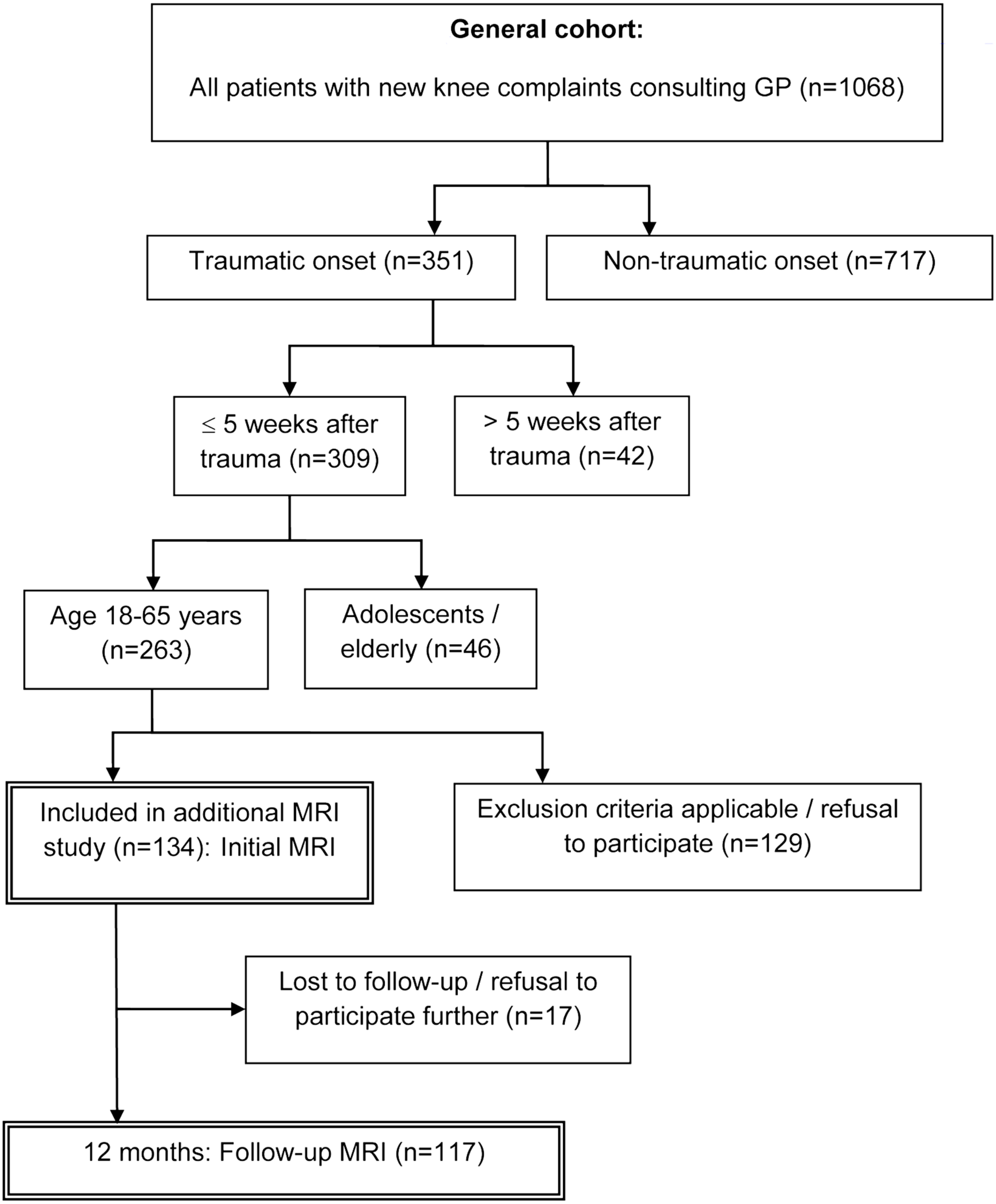
Data analysis

Univariable and multivariable binary logistic regression analysis was performed using SPSS 11.0 for Windows. As the binary outcome, we defined any increase on the Kellgren and Lawrence scale on follow-up MRI compared to initial MRI. Therefore, this could either be new degenerative change in a previously unaffected knee or deterioration of pre-existing osteoarthritis.

We analyzed the following independent variables: age (both continuous and dichotomized at age 50 years), sex, physique as measured by body weight and body mass index (both continuous and dichotomized at 25 and 30 kg/m^2), a sports injury as the setting of knee trauma, baseline pain score as measured by the 11-point numeric rating scale (continuous and dichotomized at 6 points or higher), Lysholm knee function score (continuous and dichotomized at 50 points). The prognostic value of the following knee lesions on initial MRI was also evaluated: meniscal lesion (degenerative, tear, or combined; lateral and medial meniscus analyzed separately or in combination), anterior cruciate ligament rupture (partial, total, or combined), bone marrow edema in the distal femur or proximal tibia (medial and lateral femorotibial joint compartments analyzed separately and combined). Since there were relatively few total PCL and collateral ligament ruptures, we combined these lesions with a total ACL rupture, resulting in a combined variable indicating any total rupture of either cruciate of collateral ligament. In the univariable analysis, we regarded variables as statistically significant if they had a p-value of less than 0.10. In the multivariable analysis, we used a threshold p-value of 0.05 to determine statistical significance.

We missed data on sports injury in 6 patients and since the association with a sports injury was strongly correlated with age and sex, we used these variables in a logistic regression analysis to impute the missing data on sports injury. Data on baseline pain score and Lysholm knee function score were missing in 3 patients, and the pain score and perceived recovery data after 12 months follow-up were lacking in 7 and 1 patients respectively. We imputed these data with the mean values of the other patients, since it has been demonstrated that imputation of missing data reduces the risk of bias and is preferable over complete case analysis (21,22).

Figure 1. Flow diagram indicating the selection of subjects and the flow of patients through the study.



16 patients underwent surgery during follow-up, which consisted of arthroscopy in 15 patients and an ACL reconstruction in one patient. Since this study was not aimed at assessing therapy for meniscal injury, the exact type of surgical or arthroscopic procedures was not known in every operated patient. To explore the possible effect of surgery on the result of the analysis, we performed a sensitivity analysis from which the operated patients were exluded.

Table 1. Crosstabulation of femorotibial Kellgren and Lawrence score on initial versus follow-up MRI

		Kellgren and Lawrence score on initial MRI					
		Grade 0 (normal)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Kellgren and Lawrence score on follow-up MRI	**Grade 0 (normal)**	62	-	-	-	-	62
	Grade 1	18	16	-	-	-	34
	Grade 2	4	1	5	-	-	10
	Grade 3	-	2	-	4	-	6
	Grade 4	-	-	-	2	3	5
	Total	84	19	5	6	3	117

Note: Table presents number of patients.
Kellgren and Lawrence Score:
Grade 0: no degenerative abnormalities
Grade 1: minimal osteophyte of unknown significance
Grade 2: osteophytes without joint space narrowing
Grade 3: moderate joint space narrowing
Grade 4: severe joint space narrowing with sclerosis of subchondral bone

Perceived recovery measured on the self-reported questionnaire at 12 months follow-up was regarded as an indicator of clinical outcome. The expected course of recovery one year after knee trauma was complete recovery or at least strong improvement. Following dichotomization of this variable into complete recovery or strong improvement versus some improvement, unchanged or deteriorated, we analyzed the association between OA progression on the Kellgren and Lawrence score and the clinical outcome using Fisher's exact test.

RESULTS

134 patients (67 male, 50 female; mean age 45 years, standard deviation 12.2 years, range 18-63 years) were included and underwent MRI at baseline. 17 patients were not followed up because they refused participation or because they had moved and we were unable to contact them. Thus, follow-up MRI was performed in 117 patients. The mean time between MRI examinations was 403 days (standard deviation 57.8 days, range 315-675 days). A flow diagram indicating the selection of subjects and the flow of patients through the study is presented in Figure 1.

A cross-tabulation of the Kellgren and Lawrence score on initial versus follow-up MRI is listed in Table 1. At baseline, there were 84 knees without femorotibial degenerative change (Kellgren and Lawrence grade 0) and 33 knees with osteoarthritic change. At one year follow-up, a total of 27 knees showed an increase on the Kellgren and Lawrence scale. 22 of these were initially normal and developed grade 1 or 2 abnor-

Table 2. Results of the univariable logistic regression analysis

Covariable	Frequency in study population of 117 patients (percentage) §	Odds ratio (95% confidence interval)	P-value
Age (continuous)	41.0 years (12.2, 18-63) §	1.03/yr (0.99-1.07)	0.10
Age > 50 years	30 (26)	2.57 (1.02-6.44)	0.04
Male sex	67 (57)	0.74 (0.30-1.78)	0.50
Body weight	82.6 kg (15.6, 40-129) §	1.01/kg (0.98-1.04)	0.41
Body mass index (continuous)	26.3 kg/m^2 (4.1, 17-40) §	1.07 (0.97-1.19)	0.18
Body mass index > 25 kg/m^2	69 (59)	2.39 (0.92-6.21)	0.07
Body mass index > 30 kg/m^2	20 (17)	1.55 (0.53-4.53)	0.42
Sports injury *	59 (50)	1.08 (0.46-2.55)	0.87
Baseline pain score continuous #	4.6 (2.3, 0-10) §	1.01 (0.84-1.22)	0.92
Baseline pain score > 6 points #	44 (38)	0.79 (0.32-1.94)	0.60
Baseline Lysholm score continuous #	65.1 (18.8, 16-100) §	0.99 (0.97-1.01)	0.25
Baseline Lysholm score > 50 #	88 (75)	0.72 (0.28-1.89)	0.51
Lesions on initial MRI			
Total ACL rupture	12 (10)	1.13 (0.28-4.49)	0.87
Total or partial ACL rupture	21 (18)	1.90 (0.68-5.33)	0.22
Total cruciate or collateral ligament rupture	14 (12)	2.05 (0.62-6.73)	0.24
Lateral meniscal tear	24 (21)	0.85 (0.28-2.54)	0.77
Lateral meniscus degenerative lesion or tear	47 (40)	0.84 (0.35-2.05)	0.71
Medial meniscal tear	32 (27)	1.82 (0.73-4.55)	0.20
Medial meniscus degenerative lesion or tear	91 (78)	1.34 (0.45-3.97)	0.60
Lateral or medial meniscal tear	43 (37)	1.52 (0.64-3.65)	0.35
Lateral or medial meniscus degenerative lesion or tear	95 (81)	1.03 (0.34-3.09)	0.97
Bone marrow edema in lateral compartment	45 (39)	3.06 (1.26-7.42)	0.01
Bone marrow edema in medial compartment	53 (45)	3.14 (1.27-7.77)	0.01
Bone marrow edema in lateral or medial compartment	67 (57)	6.01 (1.92-18.8)	0.002

Note:
§ For continuous variables, we report mean (standard deviation, range).
* 6 missing values were imputed.
# 3 missing values were imputed.

malities after one year follow-up. The other 5 patients demonstrated deterioration of pre-existing degenerative change.

The results of the univariable logistic regression analysis are presented in Table 2. Age above 50 years, body mass index greater than 25 kg/m^2, and the presence of bone

Table 3. Perceived recovery after 12 months and progression of degenerative change on follow-up MRI

	Perceived recovery					
	Complete recovery	Strong improvement	Some improvement	Unchanged	Some deterioration	Total
Unchanged absent or pre-existing degenerative change	23	57	6	3	1	90
New or progressive degenerative change	7	10	7	1	2	27
Total	30	67	13	4	3	117

Note: table displays number of patients.

marrow edema on initial MRI (both for the medial and lateral compartments separately and combined) were significant predictors of increased Kellgren and Lawrence score after one year follow-up when analyzed univariably. Sex, sports injury, baseline pain score, Lysholm knee function score, degenerative lesions or tears of the menisci (analyzed separately or combined), ACL rupture (partial, total, or combined), and the combined variable of total cruciate or collateral ligament ruptures were not statistically significant.

We included age above 50 years, body mass index greater than 25 kg/m^2, and bone marrow edema (medial and lateral compartments combined) in the multivariable logistic regression analysis. Although age and body mass index both were no longer statistically significant when controlling for bone marrow edema (OR 1.51 (95% CI 0.56-4.12), p=0.42 and OR 2.07 (95% CI 0.75-5.73), p=0.16 respectively), we kept these variables in the model, since these are established risk factors for osteoarthritis. Thus, in the final multivariable model medial and/or lateral femorotibial bone marrow edema on initial MRI was the only statistically significant predictor of increased Kellgren and Lawrence score on follow-up MRI after one year (OR 5.29 (95% CI 1.64- 17.1), p=0.005).

In the sensitivity analysis of 101 conservatively treated patients excluding the 16 patients that had undergone surgery during follow-up, we identified the same statistically significant variables in the univariable logistic regression analysis (results not tabulated). Similarly, femorotibial bone marrow edema was the only statistically significant variable in the multivariable analysis (OR 5.38 (95% CI 1.67-17.3), p=0.005).

A crosstabulation of perceived recovery versus stable or progressive degenerative change on follow-up MRI is shown in Table 3. 97 patients reported complete recovery or strong improvement after 12 months follow-up, whereas 3 patients experienced some deterioration. There were no patients that reported a substantial deterioration or a condition worse than ever. 17 of the 27 patients with new or progressive osteoarthritic change reported complete recovery or strong improvement in terms of perceived recovery versus 80 of the 90 patients with absent or unchanged OA. There was a statistically significant association between new or progressive osteoarthritic change on follow-up MRI and perceived recovery (Fisher's exact test p-value 0.003).

DISCUSSION

We evaluated prognostic factors, including initial MRI findings after knee trauma, for new onset or progression of OA of the femorotibial joint, as assessed by follow-up MRI after one year. Unlike previously published studies on this subject, we conducted this study in the general practice population as most patients with traumatic knee injury are managed in a primary care setting in our country. In the univariable logistic regression analysis, higher age (>50 years), higher body mass index (>25 kg/m^2), and bone marrow edema were associated with new or progressive osteoarthritic changes of the femorotibial joint one year after trauma. In the multivariable logistic regression analysis, however, only bone marrow edema was statistically significant and it was found to be a strong predictor. Whereas previously published studies focused on the long-term (2 years and more) risk of developing OA after knee injury, we focused on the risk of developing MRI signs of OA during the first year following trauma (7,8,23).

Both higher age and higher body mass index were identified as risk factors for progression of OA of the knee in previous case control studies and population based studies (2,4,24). Although we only found this association in the univariable logistic regression analysis, we kept these variables in the model, since these are established risk factors for osteoarthritis. It is possible that the number of patients was too small to demonstrate significance. Apparently bone marrow edema is more important in the onset or progression of OA of the knee than the other two risk factors.

Our findings are consistent with other reports on bone marrow edema. In the Pond-Nuki dog model of OA, bone marrow lesions were considered a very early sign of OA (10). In a longitudinal study by Felson et al. bone marrow edema was suggested to be a powerful predictor of disease progression in non-traumatically injured patients with symptomatic OA of the knee (9). Histopathologically, bone marrow edema after traumatic injury of the knee (also referred to as bone bruise) is thought to be the result of micro fractures and hemorrhage in the subcortical trabecular bone. Bone bruise related cartilage changes are reported to be the result of chondrocyte degeneration with proteoglycan loss and increased levels of cartilage oligomeric matrix protein (COMP) in the superficial cartilage matrix and in the synovial fluid (25). As damage to the articular cartilage is thought to be an important factor in the development of OA, this may explain the relationship between traumatic bone marrow edema and early progression of OA. In a previous study, we found that the median healing time of post-traumatic bone bruises in our study group was 42.1 weeks (26). The present study suggests that although the bone bruise itself may have healed within a year, a long term effect may be initiated by this lesion, i.e. the development of osteoarthritic change of the knee joint.

Our study has several limitations. We only evaluated the femorotibial joint because there were too few patients (n=4) with new onset or progressive patellofemoral OA to justify a separate logistic regression analysis. We considered that pooling these joints would be meaningless, because the pathogenesis of femorotibial and patellofemoral OA is probably not identical, and the effect of trauma may differ for the two joints. In recent MRI based studies on OA, the Whole Organ Magnetic Resonance Imaging Score (WORMS) and Knee Osteoarthritis Scoring System (KOSS) have been used to grade the severity of degenerative change (15,27). At the time of the baseline MRI performed in our study (2002-2003), however, these scoring systems had not been introduced, and the adapted Kellgren and Lawrence scale was used instead. For reasons of comparability and to avoid interfering with the prospective study design, we continued using the same grading system for the evaluation of progression of OA on the 1-year follow-up MRI (18). The outcome was defined as any increase on the Kellgren and Lawrence scale. We acknowledge that this refers to a heterogeneous group of patients including those with new onset OA and those with progression of pre-existing osteoarthritic changes. The majority of patients with progression of OA on MRI, however, had no OA initially, indicating that the results of this study were largely based on patients who developed new onset degenerative change within one year after trauma. Most of these patients developed mild degenerative change of Kellgren and Lawrence grade 1 severity.

Since the contralateral knee was not imaged, we cannot exclude that degeneration as part of the natural history explains part of our findings. Furthermore, which proportion of osteoarthritic change is attributable to trauma is unknown, but whether or not the OA is attributable to the trauma, although interesting pathophysiologically, is clinically less relevant. The important point is that in a patient with knee injury, bone marrow edema predicts the development of early OA.

We performed our study in the primary care setting, and consequently patients with more severe traumatic injuries of the knee were not included because they were referred to secondary care immediately. This may explain the relative limited number of meniscal injuries and cruciate ligament injuries in our patient population, which implied a limited power to demonstrate a statistically significant association between these lesions and early progression of OA. The true extent to which meniscal damage and cruciate ligament injuries predict early progression of OA may be underestimated in our study, as both type of lesions have been reported to be risk factors for progression of OA (6-8).

Since it was not the aim of the study to evaluate treatment for traumatic knee lesions, we did not record in detail what procedure was performed in the operated patients. To explore the consequences of this limitation, we performed a sensitivity analysis excluding the operated patients. The same prognostic factor with a similar odds ratio was found, indicating that the results of the analysis were not influenced by the type of treatment, underscoring the robustness of the model.

We found a significant association between new onset or progression of femorotibial OA at follow-up MRI and clinical outcome as measured by perceived recovery. All patients in our study sustained a knee injury resulting in acute trauma- related symptoms. One year after trauma the expected natural healing course would be complete recovery or at least strong improvement. Since the disabling symptoms in the initial stage after trauma are no longer present one year after trauma, a perceived recovery less than "strong improvement" in all likelihood reflects the effect of new onset or progressive OA. In light of our results, this stresses the importance of identifying those patients with bone bruise in the initial stage after trauma and those with no or minor improvement of clinical outcome after trauma, since these patients are at high risk of developing new onset OA. In the future these patients may benefit from the development of novel treatment strategies targeting bone bruises.

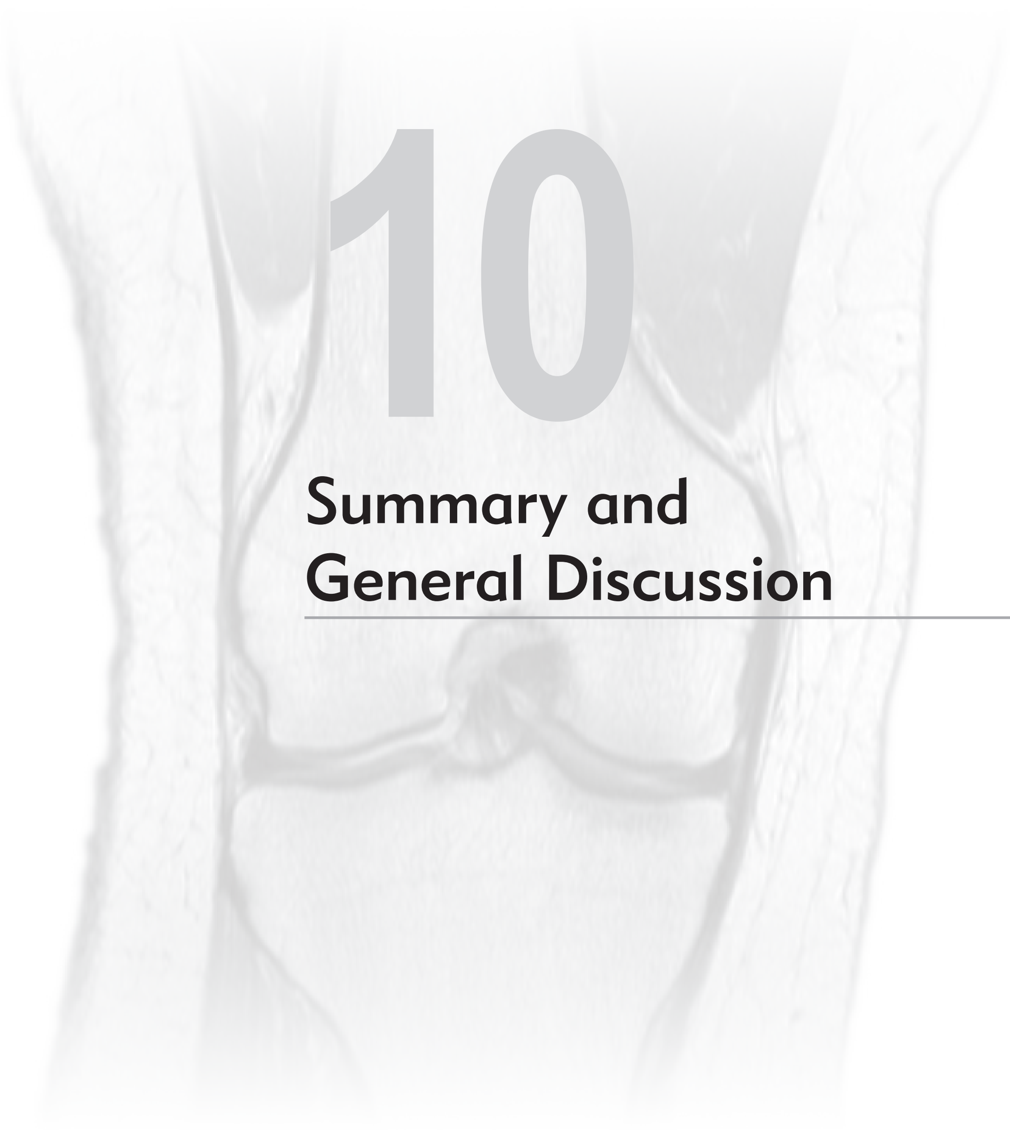
In conclusion, the results of this study demonstrate that bone marrow edema on initial MRI after knee trauma is a strong predictor, and in multivariable analysis the only predictor, for new onset and progression of osteoarthritic change of the knee joint on 1-year follow-up MRI, which is reflected in clinical outcome.

REFERENCES

1. Peterfy CG. Imaging of the disease process. Curr Opin Rheumatol 2002; 14:590-596.
2. Spector TD, Hart DJ, Doyle DV. Incidence and progression of osteoarthritis in women with unilateral knee disease in the general population: the effect of obesity. Ann Rheum Dis 1994; 53:565-568.
3. Roos EM. Joint injury causes knee osteoarthritis in young adults. Curr Opin Rheumatol 2005; 17:195-200.
4. Reijman M, Pols HA, Bergink AP, et al. Body mass index associated with onset and progression of osteoarthritis of the knee but not of the hip: the Rotterdam Study. Ann Rheum Dis 2007; 66:158-162.
5. Van der Linden MW, Westert GP, de Bakker DH, et a. Tweede nationale studie naar ziekten en verrichtingen in de huisartspraktijk: klachten en aandoeningen in de bevolking en in de huisartspraktijk. Utrecht, Bilthoven: NIVEL, Rijksinstituut voor volksgezondheid en milieu, 2004.

6. Berthiaume MJ, Raynauld JP, Martel-Pelletier J, et al. Meniscal tear and extrusion are strongly associated with progression of symptomatic knee osteoarthritis as assessed by quantitative magnetic resonance imaging. Ann Rheum Dis 2005; 64:556-563.
7. Sharma L, Eckstein F, Song J, et al. Relationship of meniscal damage, meniscal extrusion, malalignment, and joint laxity to subsequent cartilage loss in osteoarthritic knees. Arthritis Rheum 2008; 58:1716-1726.
8. Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. Am J Sports Med 2007; 35:1756-1769.
9. Felson DT, McLaughlin S, Goggins J, et al. Bone marrow edema and its relation to progression of knee osteoarthritis. Ann Intern Med 2003; 139:330-336.
10. Libicher M, Ivancic M, Hoffmann M, Wenz W. Early changes in experimental osteoarthritis using the Pond-Nuki dog model: technical procedure and initial results of in vivo MR imaging. Eur Radiol 2005; 15:390-394.
11. Spector TD, Hart DJ, Huskisson EC. The use of radiographs in assessing the severity of knee osteoarthritis. J Rheumatol Suppl 1991; 27:38-39.
12. Lawrence JS, Bremner JM, Bier F. Osteo-arthrosis. Prevalence in the population and relationship between symptoms and x-ray changes. Ann Rheum Dis 1966; 25:1-24.
13. Kijowski R, Blankenbaker DG, Stanton PT, Fine JP, De Smet AA. Radiographic findings of osteoarthritis versus arthroscopic findings of articular cartilage degeneration in the tibiofemoral joint. Radiology 2006; 239:818-824.
14. Link TM, Steinbach LS, Ghosh S, et al. Osteoarthritis: MR imaging findings in different stages of disease and correlation with clinical findings. Radiology 2003; 226:373-381.
15. Peterfy CG, Guermazi A, Zaim S, et al. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage 2004; 12:177-190.
16. Heintjes EM, Berger MY, Koes BW, Bierma-Zeinstra SM. Knee disorders in primary care: design and patient selection of the HONEUR knee cohort. BMC Musculoskelet Disord 2005; 6:45.
17. Boks SS, Vroegindeweij D, Koes BW, Hunink MGM, Bierma-Zeinstra SM. Magnetic resonance imaging abnormalities in symptomatic and contralateral knees: prevalence and associations with traumatic history in general practice. Am J Sports Med 2006; 34:1984-1991.
18. Petersson IF, Boegard T, Saxne T, Silman AJ, Svensson B. Radiographic osteoarthritis of the knee classified by the Ahlback and Kellgren & Lawrence systems for the tibiofemoral joint in people aged 35-54 years with chronic knee pain. Ann Rheum Dis 1997; 56:493-496.
19. Herr KA, Spratt K, Mobily PR, Richardson G. Pain intensity assessment in older adults: use of experimental pain to compare psychometric properties and usability of selected pain scales with younger adults. Clin J Pain 2004; 20:207-219.

20. Briggs KK, Kocher MS, Rodkey WG, Steadman JR. Reliability, validity, and responsiveness of the Lysholm knee score and Tegner activity scale for patients with meniscal injury of the knee. J Bone Joint Surg Am 2006; 88:698-705.
21. Van der Heijden GJ, Donders AR, Stijnen T, Moons KG. Imputation of missing values is superior to complete case analysis and the missing-indicator method in multivariable diagnostic research: a clinical example. J Clin Epidemiol 2006; 59:1102-1109.
22. Schafer J. Analysis of incomplete multivariate data. London: Chapman & Hall, 1997.
23. Cooper C, Snow S, McAlindon TE, et al. Risk factors for the incidence and progression of radiographic knee osteoarthritis. Arthritis Rheum 2000; 43:995-1000.
24. Hochberg MC, Lethbridge-Cejku M, Scott WW, Jr., Reichle R, Plato CC, Tobin JD. The association of body weight, body fatness and body fat distribution with osteoarthritis of the knee: data from the Baltimore Longitudinal Study of Aging. J Rheumatol 1995; 22:488-493.
25. Thiryayi WA, Thiryayi SA, Freemont AJ. Histopathological perspective on bone marrow edema, reactive bone change and haemorrhage. Eur J Radiol 2008; 67:62-67.
26. Boks SS, Vroegindeweij D, Koes BW, Bernsen RM, Hunink MG, Bierma-Zeinstra SM. MRI follow-up of posttraumatic bone bruises of the knee in general practice. AJR Am J Roentgenol 2007; 189:556-562.
27. Kornaat PR, Ceulemans RY, Kroon HM, et al. MRI assessment of knee osteoarthritis: Knee Osteoarthritis Scoring System (KOSS)--inter-observer and intra-observer reproducibility of a compartment-based scoring system. Skeletal Radiol 2005; 34:95-102.



10

Summary and General Discussion

Traumatic knee injury is a very common condition that is frequently encountered both in general practice and in the hospital setting. In the Netherlands, most patients with knee trauma are evaluated and treated by the general practitioner (1). Although MRI has been established as a reliable non-invasive method for assessing traumatic intra-articular pathology of the knee joint, such as ligamentous and meniscal tears, it is usually applied at a later stage in case of persisting symptoms, to determine if therapeutic arthroscopy is necessary (2-5). Because of its accuracy, it has largely replaced diagnostic arthroscopy in current clinical practice. The reported diagnostic performance is variable, however, especially for MRI systems with low magnetic field strengths.

In the initial stage after knee trauma, the evaluation usually consists of clinical history taking and physical examination, sometimes supplemented by radiography if a fracture is suspected (6). The accuracy of thorough physical examination in the acute stage, however, is notoriously low because of joint swelling, pain, and guarding (7,8). Moreover, only the bony structures can be assessed on radiography. This raised the question whether MRI could play a role in the initial assessment after traumatic knee injury.

In this thesis, various aspects of MRI for traumatic knee injury were described. Following a review of the MRI interpretation of the most frequent traumatic knee abnormalities and a systematic review of the diagnostic performance of MRI for meniscal and cruciate ligament injury, two prospective studies on MRI after knee trauma were presented. Both studies featured a different patient population and study design: a randomized clinical trial was performed in the hospital emergency department setting and a prospective cohort study with MRI follow-up was conducted in the general practice population.

Review studies on MRI for traumatic knee injury

In **chapter 2** we reviewed the current application of MRI for traumatic knee injury. After a brief discussion on indications for MRI in the setting of knee trauma and the most commonly used MRI techniques, we reviewed and illustrated the MRI appearance and classification of the most frequent traumatic knee lesions, followed by an overview of the most common pitfalls in the interpretation of knee MRI.

We subsequently performed a systematic review and meta-analysis on the diagnostic performance of MRI for cruciate ligament ruptures and meniscal tears, described in **chapter 3**. In a an analysis of 29 articles published between 1991 and 2000, we found that the pooled weighted sensitivity was higher for medial than for lateral meniscal tears (93.3% [95% CI 91.7-95.0] versus 79.3% [95% CI 74.3-84.2] respectively), but that the pooled weighted specificity was lower for medial compared with lateral meniscal tears (88.4% [95% CI 85.4-91.4] versus 95.7% [95% CI 94.6-96.8] respectively). No statistically significant difference in pooled weighted sensitivity for tears of both cruciate ligaments was observed, but pooled weighted specificity for the posterior cruciate ligament was higher than that for the anterior cruciate ligament (99.4% [95% CI 98.9-99.9] versus 94.3% [95% CI 92.7-95.5] respectively). The objective of this study was also to identify factors that influence diagnostic performance, in particular study design characteristics and the magnetic field strength of the MRI system. In a summary operating characteristics analysis, we found that several study design characteristics influence diagnostic performance. In particular, the presence of verification bias substantially increased reported diagnostic performance for posterior cruciate ligament tears. A modest effect of magnetic field strength was observed, although this was only statistically significant for anterior cruciate ligament tears.

Randomized controlled clinical trial in the hospital emergency department

To study the application of MRI routinely in the acute setting after trauma, we performed a randomized controlled clinical trial in the emergency department of our hospital. We included patients if they had sustained an acute knee trauma in the preceding week and if a radiograph was ordered by the examining physician. Patients were randomized between two diagnostic strategies, i.e. the current diagnostic work-up consisting of only radiography and a diagnostic strategy in which radiography was immediately followed by a short MRI examination on a dedicated extremity MRI scanner (Figure 1). This type of scanner has been specifically designed for extremity imaging and offers certain advantages over usual high-field strength whole body MRI units: the costs of purchasing, installing, and maintaining the system and costs per examination are lower because of the compact design and the low-field strength permanent magnet. Moreover, because of the dedicated extremity design, this type of scanner may be more readily available for emergency use than whole body imagers, which are in most centers often heavily used for imaging of scheduled patients. We assumed that these advantages may overcome the constraints that have traditionally prevented the use of MRI as a routine screening tool in the emergency setting. Since MRI in this setting can only be feasible if the examination time is relatively short, we developed a scanning protocol with an average acquisition time of 6 minutes. The whole examination, including system start-up, and patient positioning, could therefore be performed in less than 15 minutes. We acknowledge that shortening of the MRI protocol inevitably resulted in loss of image quality, but in a pilot study we found that our imaging protocol was of sufficient quality to detect most abnormalities (9), and as stated above, it was demonstrated in our systematic review that lower field strength of the MRI system does not substantially reduce diagnostic performance for most traumatic knee abnormalities.

In **chapter 4** we described a prediction rule for identifying patients who require additional treatment versus those who do not and can be discharged without the need of follow-up. We studied whether the short

Figure 1. Design of the Artoscan M (Esaote Biomedica, Genoa, Italy) low-field dedicated extremity MRI scanner.

MRI examination, performed in addition to or instead of radiography aids in the prediction whether specific treatment is required. To this end, we performed univariable and multivariable logistic regression analysis to evaluate the predictive performance of sex, age, trauma mechanism, radiography result, and MRI result for specific treatment within 6 months follow-up. We created four models for the different diagnostic strategies and we assesssed differences in model performance by means of Akaike's information criterion and ROC analysis. Treatment was required in 109 of the 189 patients, and age above 30 years, an indirect trauma mechanism, and radiography results were significant predictors of the need for treatment in the multivariable analyses ($p<0.05$). Regarding MRI, only abnormal results were a statistically significant predictor of treatment required and only when MRI replaced radiography (OR 2.61, 95% CI 1.12-6.06). The model with both radiography and MRI results did, however, demonstrate better performance ($p=0.04$) than the model with radiography only. The results indicated that the implementation of a short MRI examination in addition to or instead of radiography improves the prediction of the need for specific treatment, but that it does not significantly aid in identifying those patients that can be discharged without follow-up.

In **chapter 5** we assessed the costs and effectiveness of implementing a short MRI examination in the initial evaluation of knee trauma. Apart from the knee, we also studied the cost-effectiveness of MRI for the initial evaluation of wrist or ankle trauma. Costs were analyzed from a societal perspective because we hypothesized that implementation of MRI in the initial stage after trauma may result in more timely diagnosis and treatment, earlier recovery, and shorter absence from work, thereby reducing those costs to society that are associated with loss of productivity (10,11). As measures of effectiveness, we collected data on quality of life, time to completion of the diagnostic work-up, number of additional diagnostic studies, time absent from work, and time to convalescence. Quality of life was recorded on self-reported questionnares sent at 1 week, 6 weeks, 3 months, and 12 months after inclusion. We found that for the knee joint (189 patients analyzed), quality of life measured with the EuroQol index was significantly higher in the MRI strategy, but only at 1 and 6 weeks follow-up. In addition, in knee injured patients the number of diagnostic procedures was significantly lower and the time to completion of the diagnostic work-up in patients after knee injury was significantly shorter in the MRI strategy versus the strategy with radiography only. For the other joints (87 wrists and 196 ankles analyzed) there was no statistically significant difference in any of the effectiveness measures between the two diagnostic strategies. For the knee joint, the mean costs were lower for the MRI strategy (€1820) versus the strategy with radiography only (€2231), largely because of a reduction in costs of lost productivity. For the wrist joint costs were higher with the use of MRI and for the ankle joint the costs were similar. For all three joints, however, the costs differences were not statistically significant. We concluded that MRI in patients with acute wrist and ankle trauma is neither cost saving nor effective in improving quality of life or expediting diagnostic work-up. For the knee joint, use of MRI in all patients after trauma improves quality of life in the first 6 weeks, shortens the diagnostic work-up, reduces the number of additional diagnostic studies, and may reduce costs to society, although the latter was not statistically significant.

The results of the cost-effectiveness analysis led us to further explore the costs and effectiveness of implementing a short MRI examination in the initial evaluation after knee injury, as described in **chapter 6**. Since it can be argued that MRI in this setting has limited added value if a fracture has already been demonstrated on radiography, we introduced a third diagnostic strategy in which radiography was followed by selective MRI only if no fracture was demonstrated radiographically. Since this diagnostic strategy was not one of the study arms of the RCT, it was modeled by using a composite of the results of patients from the strategy with radiography only who showed a fracture on the radiograph, and patients from the strategy with radiography plus MRI who did not show a fracture on the radiograph. We used the same methods and measures of effectiveness as described in chapter 5 to analyze the three diagnostic strategies, but we adjusted all costs to the year 2007 using consumer price indices. Throughout the follow-up period quality of life was equivalent for both MRI strategies. Especially at 1 and 6 weeks follow-up, the EuroQol score was more favorable for the MRI strategies (0.72, 95% CI 0.67-0.77 at 6 weeks for both) compared to the strategy with radiography alone (0.61, 95% CI 0.54-0.67 at 6 weeks). Time to diagnosis, duration of absence from work, and time to convalescence were shorter, and total costs were lower if MRI was applied selectively compared to MRI in all patients, but differences were not statistically significant. Total costs were, however, substantially lower with selective use of MRI (€1973, 95% CI 1401-2543) compared to radiography only (€2593, 95% CI 1815-3372). The results suggested that in patients with acute knee injury, implementation of a selective short MRI examination if radiography shows no fracture reduces costs to society and potentially increases effectiveness.

Because we found no significant differences in costs and only small and transient differences in effectiveness in our RCT, we wondered whether a larger RCT would demonstrate a statistically significant cost difference and durable difference in effectiveness. To evaluate this, we performed a value of information analysis (**chapter 7**) with the use of data from our RCT. With value of information analysis, one can estimate the expected benefit of future research to eliminate the decision uncertainty that remains if a trial shows no significant differences. In addition, it is possible to identify the parameters that influence this uncertainty the most, and to determine the optimal study design and sample size required (12-14). This is important, because additional research is costly and inefficient allocation of health care funds should be avoided. We found that the number of quality-adjusted life years, cost of an overnight hospital stay, and friction costs (an estimate of costs to society due to production losses) were responsible for most of the decision uncertainty, indicating that a future study should mainly focus on these parameters. Ideally such a study should be performed as an international multicenter trial from the perspective of the European Union with a sample size of 3500 patients per study arm. This would result in an expected societal benefit of €5.6 million or 70 quality-adjusted life years. The results also showed that more research into MRI for acute knee trauma in an emergency department setting is not justified from the perspective of the Netherlands because the population and partial expected value of sample information does not exceed the study cost for any sample size.

Limitations of our RCT mainly relate to the inclusion of patients and follow-up. Although inclusion was intended to be consecutive, a considerable percentage of potentially eligible patients were not asked to participate in the study. This may have caused a selection bias if patients who were not invited to participate differed from those who were included, particularly in terms of demographics or disease severity. Although we expect that the likelihood of selection bias is low, we could not verify this, since we were unable to trace most of the unincluded patients. The response rate to the mailed questionnaires was low, especially in patients that were assigned to undergo radiography only. These patients were probably less willing to fill in the questionnaires because they were disappointed not to get the additional MRI. As a result, we cannot exclude that the results on quality of life were biased, but for the data on costs we were less dependent on the questionnaires. Data on costs were largely obtained from the patient records and computerized hospital information system.

In conclusion, the results of our RCT indicate that it is not useful to perform a short dedicated extremity MRI examination instead of or in addition to radiography in the acute stage after knee injury in all patients. If implemented unselectively in all patients, MRI in the initial evaluation of knee trauma has limited added value in predicting the need for specific treatment, and it does not help identifying those patients that do not require treatment. In addition, we could not demonstrate a statistically significant reduction in costs from a societal perspective by performing such an early MRI examination in every patient. If performed selectively in patients without a fracture on the radiograph, however, an additional MRI examination potentially increases effectiveness and may save costs to society, mainly because of a reduction in costs associated with lost productivity. Further research on this application of MRI is warranted only if conducted as a large multicenter trial.

MRI follow-up study in general practice

We performed a subgroup study within the HONEUR knee cohort, which was a prospective observational cohort study of 1068 patients with acute or chronic knee complaints conducted in general practice (15). The subgroup consisted of 134 adult patients who visited their general practitioner because of acute knee trauma. These patients underwent initial MRI within 3 to 6 weeks after trauma and a follow-up MRI after one year. In addition, a standardized physical examination was performed immediately following each MRI examination, and self-reported questionnaires regarding pain, Lysholm functional knee score, and perceived recovery were completed at baseline and after one year follow-up. The results of this MRI follow-up study were presented in the final part of this thesis.

In **chapter 8** we assessed how the meniscal appearance changes on one year follow-up MRI compared to the initial MRI after trauma, because in a previously published systematic review it was found that little is known about the natural course of meniscal lesions (16). In 101 conservatively treated patients, traumatic and degenerative meniscal abnormalities on initial and follow-up MRI were scored for the anterior and posterior horns of both menisci separately, using a 6 point grading system. We evaluated the predictive value of demographics, trauma mechanism, pain score, Lysholm functional knee score (17), and initial MRI findings on deterioration or improvement of meniscal MRI appearance using univariable and multivariable ordinal logistic regression analysis per meniscal horn. The association with clinical outcome, reflected by perceived recovery and change in pain score after one year, was also studied. On initial MRI, we diagnosed 50 meniscal tears and 122 degenerative lesions in 403 meniscal horns. On follow-up MRI, we observed deterioration of meniscal MRI appearance in 49 meniscal horns and improvement in 18 horns. In the multivariable logistic regression analysis, age (OR 1.3/decade, 95% CI 1.1-1.7), body weight (OR 1.2/10 kilograms weight increase, 95% CI 1.0-1.5), the presence of a total anterior cruciate ligament rupture on initial MRI (OR 2.4, 95% CI 1.1-4.8), and location in the posterior horn of the medial meniscus (OR 3.0, 95% CI 1.2-7.4) were statistically significant predictors of unfavorable change of meniscal MRI appearance after one year. The presence of a meniscal lesion on initial MRI was also a significant predictor (OR 0.3, 95% CI 0.1-0.7), but with an odds radio smaller than one, suggesting a natural healing potential for some meniscal lesions. Meniscal status change on MRI was not significantly associated with clinical outcome, indicating that it is not useful to perform a follow-up MRI examination of the meniscus to explain clinical deterioration.

In another study, presented in **chapter 9**, we assessed the prognostic factors for development of new onset or worsening of pre-existing degenerative change (osteoarthritis) during the one year follow-up. The presence and severity of femorotibial osteoarthritic change on follow-up MRI was compared with that on the initial MRI examination using the adapted Kellgren and Lawrence scale (18). Univariable and multivariable logistic regression analysis was performed to assess the prognostic value of the same independent variables as used in chapter 8 on development of new degenerative change or progression of pre-existing osteoarthritis. We also evaluated the association with clinical outcome, as reflected by perceived recovery. 117 patients were analyzed including those who had undergone surgery during follow-up. 33 knees showed degenerative abnormalities on the initial MRI. On follow-up MRI, 22 of 84 initially normal knees demonstrated new osteoarthritis, and progression was noted in 5 knees with pre-existing degenerative change. In the univariable analysis, age above 50 years and a body mass index greater than 25 kg/m^2 significantly predicted new or progressive osteoarthritis ($p<0.10$). The most significant predictor, however, was the presence of bone marrow edema (also referred to as bone bruise) on the initial MRI, and this was the only statistically significant prognostic factor in the multivariable analysis (OR 5.29, 95% CI 1.64-17.1). Because we found a significant association between new or progressive degenerative change and clinical outcome, we concluded that the presence of bone marrow edema on MRI performed for acute knee injury is a strong predictor of new onset or progressive femorotibial osteoarthritis on follow-up MRI after one year, which is reflected in a clinical outcome.

There were several limitations of this MRI follow-up study. 17 of the 134 patients (13%) were lost to follow-up or refused to participate further, but we believe that this percentage is low compared to other studies (19,20). For logistic reasons, it was impossible to have the follow-up MRI studies interpreted by the same radiologists that had read the initial MRI examination. Therefore, the initial and follow-up MRI examinations were interpreted by different readers, which may have biased the results. We believe, however, that the amount of bias is limited because well-defined criteria for interpreting meniscal lesions and degenerative abnormalities were used by all readers (18,21,22). Since the objective of the HONEUR knee cohort was not to evaluate treatment options for traumatic knee lesions, the management of the patients in the cohort was not documented in detail. As a result, it was unknown which procedure was performed in the 15 patients that underwent arthroscopy. We believed that lack of such information precludes a reliable interpretation of the post-operative meniscus, and therefore decided to exclude the operated patients from the analysis on the natural course of meniscal lesions, but included them in a sensitivity analysis. In the analysis of new-onset or progressive degenerative change, we included the patients that had undergone surgery during follow-up, but we performed a sensitivity analysis with those patients excluded. Both sensitivity analyses did not change the results. To grade the severity of osteoarthritis, we used the adapted Kellgren and Lawrence scale, which was originally developed for radiographic purposes. In recent studies, the Whole Organ Magnetic Resonance Imaging Score (WORMS) (23) and the Knee Osteoarthritis Scoring System (KOSS) (24) have been used to grade osteoarthritis on MRI, but these MRI specific scoring systems had not been introduced at the time of the initial MRI in our study (2002-2003). We continued to use the Kellgren and Lawrence scale for assessing the follow-up MRI for reasons of comparability and to avoid interfering with the prospective study design.

The two clinical studies described in this thesis not only differed in study design and setting. When comparing the patient population, the mean patient age in our RCT in the emergency department turned out to be lower (33.4 years versus 40.8 years (25) in our study in general practice). A male predominance was noted in our RCT (123 male, 66 female), while in the HONEUR subgroup study in general practice the male-to-female ratio was more balanced (74 male, 60 female). We compared the frequency of traumatic knee abnormalities in both studies, and in our study conducted in the emergency department setting, we observed 16 medial meniscal tears (17%), 10 lateral meniscal tears (11%), 17 total anterior cruciate ligament ruptures (18%), and no total posterior cruciate ligament ruptures (0%) in the 93 patients that were randomized to the MRI strategy. In the 134 patients in the HONEUR cohort that underwent initial MRI after trauma, there were 35 medial meniscal tears (26%), 26 lateral meniscal tears (19%), 14 total anterior cruciate ligament ruptures (10%), and 2 total posterior cruciate ligament ruptures (1%). The higher frequency of meniscal tears in the general practice study was contrary to what we expected, but it may be explained by the higher mean age of patients and the fact that the largest proportion of meniscal tears was of the horizontal type, which is in most patients considered of degenerative rather than traumatic origin. The larger proportion of patients with a total anterior cruciate ligament rupture in our hospital-based trial suggests that patients who experience knee instability are more likely to visit a hospital emergency department than their general practitioner. The different timing of the MRI examination (within one week versus 3 to 6 weeks after trauma) is in our opinion unlikely to explain the differences in lesion frequencies.

Future research

Although the role of MRI in the diagnostic work-up of knee disorders has been established, the technique continues to evolve and will further improve in the future. In the coming years, research will be mainly focused on 3.0 Tesla knee MRI, particularly in relation to cartilage imaging and molecular imaging. 3.0 Tesla MRI offers a substantial improvement of signal-to-noise ratio, but is also challenging because it is more prone to artifacts (26,27). Novel MRI sequences continue to be developed, also for more conventional MRI field strenghts (28). For this reason, an update of the systematic review should be performed including the articles that were published after the year 2000. Studies on 3.0 Tesla knee MRI should be included to further explore the effect of magnetic field strength on diagnostic performance. Since there has been an improvement of MRI for the knee cartilage (including quantification with various mapping techniques) in recent years (29), an updated systematic review may also include cartilage abnormalities. The increased interest in cartilage imaging, both in the context of traumatic chondral lesions and degenerative osteoarthritic change, was triggered by new therapeutic treatment options for cartilage abnormalities, such as autologous chondrocyte transplantation. In order to plan and monitor such treatments, detailed imaging information about the cartilage is required (30). All these recently developed techniques need to be evaluated in prospective studies to assess the value for daily patient care.

The follow-up period of one year in our subgroup study of the HONEUR knee cohort in general practice was relatively short. To further assess the longer term natural course of traumatic knee abnormalities, in particular meniscal tears, it is intended to perform a second follow-up MRI scan in our patients after approximately 6 years.

It has been discussed extensively in this thesis whether another cost-effectiveness study should be conducted on the use of MRI in the initial stage after trauma: this is only justified from the perspective of the European Union. The European Union perspective is, in these days, however, no longer a theoretical point of view, since more and more processes are controlled under the regulations of the European Union. In the future, this may to a certain extent also involve health care and funding, and it is imaginable that cost-effectiveness studies from a European Union perspective, funded by a European agency, will be initiated in the coming years.

REFERENCES

1. Cardol M, van Dijk L, de Jong JD, et al. Tweede Nationale Studie naar ziekten en verrichtingen in de huisartspraktijk. Huisartsenzorg: wat doet de poortwachter ? Utrecht, Bilthoven: NIVEL/RIVM, 2004.
2. Elvenes J, Jerome CP, Reikeras O, Johansen O. Magnetic resonance imaging as a screening procedure to avoid arthroscopy for meniscal tears. Arch Orthop Trauma Surg 2000; 120:14-16.
3. Weinstabl R, Muellner T, Vecsei V, Kainberger F, Kramer M. Economic considerations for the diagnosis and therapy of meniscal lesions: can magnetic resonance imaging help reduce the expense? World J Surg 1997; 21:363-368.
4. Vincken PW, ter Braak BP, van Erkel AR, et al. Effectiveness of MR imaging in selection of patients for arthroscopy of the knee. Radiology 2002; 223:739-746.
5. Carrino JA, Schweitzer ME. Imaging of sports-related knee injuries. Radiol Clin North Am 2002; 40:181-202.
6. Stiell IG, Greenberg GH, Wells GA, et al. Derivation of a decision rule for the use of radiography in acute knee injuries. Ann Emerg Med 1995; 26:405-413.
7. Hardaker WT, Jr., Garrett WE, Jr., Bassett FH, 3rd. Evaluation of acute traumatic hemarthrosis of the knee joint. South Med J 1990; 83:640-644.
8. Mitsou A, Vallianatos P. Clinical diagnosis of ruptures of the anterior cruciate ligament: a comparison between the Lachman test and the anterior drawer sign. Injury 1988; 19:427-428.
9. Nikken JJ. MRI for the initial evaluation of acute wrist, knee, and ankle trauma. Erasmus MC, Rotterdam, 2003 (Thesis).
10. Oostenbrink JB, Koopmanschap MA, Rutten FFH. Handleiding voor kostenonderzoek, methoden en richtlijnprijzen voor economische evaluaties in de gezondheidszorg. Amstelveen: College voor zorgverzekeringen, 2000.
11. Hunink MGM, Glasziou PP. Decision making in health and medicine - integrating evidence and values. Cambrige: Cambridge University Press, 2001.
12. Ades AE, Lu G, Claxton K. Expected value of sample information calculations in medical decision modeling. Med Decis Making 2004; 24:207-227.
13. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. J Health Econ 1999; 18:341-364.
14. Groot Koerkamp B, Hunink MGM, Stijnen T, Weinstein MC. Identifying key parameters in cost-effectiveness analysis using value of information: a comparison of methods. Health Econ 2006; 15:383-392.
15. Heintjes EM, Berger MY, Koes BW, Bierma-Zeinstra SM. Knee disorders in primary care: design and patient selection of the HONEUR knee cohort. BMC Musculoskelet Disord 2005; 6:45.

16. Boks SS, Vroegindeweij D, Koes BW, Hunink MG, Bierma-Zeinstra SM. Follow-up of posttraumatic ligamentous and meniscal knee lesions detected at MR imaging: systematic review. Radiology 2006; 238:863-871.
17. Briggs KK, Kocher MS, Rodkey WG, Steadman JR. Reliability, validity, and responsiveness of the Lysholm knee score and Tegner activity scale for patients with meniscal injury of the knee. J Bone Joint Surg Am 2006; 88:698-705.
18. Petersson IF, Boegard T, Saxne T, Silman AJ, Svensson B. Radiographic osteoarthritis of the knee classified by the Ahlback and Kellgren & Lawrence systems for the tibiofemoral joint in people aged 35-54 years with chronic knee pain. Ann Rheum Dis 1997; 56:493-496.
19. Ihara H, Miwa M, Deya K, Torisu K. MRI of anterior cruciate ligament healing. J Comput Assist Tomogr 1996; 20:317-321.
20. Zugaro L, Catalucci A, Barile A, Di Cesare E, Masciocchi C. Anterior cruciate ligament tears in athletes: assessment and clinico-diagnostic control with a dedicated system [Italian]. Radiol Med (Torino) 1998; 96:198-203.
21. Reicher MA, Hartzman S, Duckwiler GR, Bassett LW, Anderson LJ, Gold RH. Meniscal injuries: detection using MR imaging. Radiology 1986; 159:753-757.
22. Crues JV, 3rd, Mink J, Levy TL, Lotysch M, Stoller DW. Meniscal tears of the knee: accuracy of MR imaging. Radiology 1987; 164:445-448.
23. Peterfy CG, Guermazi A, Zaim S, et al. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage 2004; 12:177-190.
24. Kornaat PR, Ceulemans RY, Kroon HM, et al. MRI assessment of knee osteoarthritis: Knee Osteoarthritis Scoring System (KOSS)--inter-observer and intra-observer reproducibility of a compartment-based scoring system. Skeletal Radiol 2005; 34:95-102.
25. Boks SS, Vroegindeweij D, Koes BW, Hunink MGM, Bierma-Zeinstra SM. Magnetic resonance imaging abnormalities in symptomatic and contralateral knees: prevalence and associations with traumatic history in general practice. Am J Sports Med 2006; 34:1984-1991.
26. Craig JG, Go L, Blechinger J, et al. Three-tesla imaging of the knee: initial experience. Skeletal Radiol 2005; 34:453-461.
27. Sampson MJ, Jackson MP, Moran CJ, Moran R, Eustace SJ, Shine S. Three Tesla MRI for the diagnosis of meniscal and anterior cruciate ligament pathology: a comparison to arthroscopic findings. Clin Radiol 2008; 63:1106-1111.
28. Gold GE, Reeder SB, Yu H, et al. Articular cartilage of the knee: rapid three-dimensional MR imaging at 3.0 T with IDEAL balanced steady-state free precession--initial experience. Radiology 2006; 240:546-551.
29. Pai A, Li X, Majumdar S. A comparative study at 3 T of sequence dependence of T(2) quantitation in the knee. Magn Reson Imaging 2008.
30. James SL, Connell DA, Saifuddin A, Skinner JA, Briggs TW. MR imaging of autologous chondrocyte implantation of the knee. Eur Radiol 2006; 16:1022-1030.

Samenvatting en Discussie

Traumatisch knieletsel komt veelvuldig voor en wordt zowel in de huisarts- als ziekenhuispraktijk met grote regelmaat gezien. In Nederland worden de meeste patiënten met acuut knieletsel onderzocht en behandeld door de huisarts (1). Magnetische resonantie beeldvorming (MRI) is een bewezen betrouwbare techniek voor de beoordeling van traumatische intra-articulaire letsels van de knie, zoals scheuren van het bandapparaat en menisci, maar wordt meestal pas in een later stadium verricht bij aanhoudende klachten om te bepalen of therapeutische arthroscopie noodzakelijk is (2-5). Vanwege de hoge diagnostische accuratesse heeft MRI de diagnostische arthroscopie in de huidige klinische praktijk grotendeels vervangen. Deze gerapporteerde diagnostische accuratesse is echter variabel, in het bijzonder voor MRI scanners met een lagere magnetische veldsterkte.

De beoordeling van de knie in het acute stadium na trauma bestaat meestal uit de anamnese en lichamelijk onderzoek, soms aangevuld met een röntgenfoto bij verdenking op een fractuur (6). Grondig lichamelijk onderzoek in het acute stadium is echter meestal onbetrouwbaar ten gevolge van gewrichtszwelling, pijn en spierverzet (7,8). Bovendien kunnen op een röntgenfoto alleen de botstructuren worden beoordeeld. Dit wierp de vraag op of MRI van aanvullende waarde kan zijn bij de eerste beoordeling na traumatisch knieletsel.

In dit proefschrift werden diverse aspecten van MRI bij traumatisch knieletsel beschreven, waarbij allereerst een overzicht over de beoordeling van de meest voorkomende traumatische knieletsels op MRI en een systematische review naar de diagnostische accuratesse van MRI voor meniscus- en kruisbandscheuren werden gepresenteerd, gevolgd door twee prospectieve studies met betrekking tot MRI na knieletsel. Bij deze beide klinische studies was sprake van een verschillende soort patiëntenpopulatie en studieopzet: een gerandomiseerde klinische trial werd verricht op de afdeling spoedeisende hulp van ons ziekenhuis en een prospectieve cohortstudie vond plaats in de huisartspraktijk.

Reviewstudies met betrekking tot MRI bij traumatisch knieletsel

In **hoofdstuk 2** toonden wij een overzicht van de huidige toepassing van MRI bij traumatisch knieletsel. Na een korte introductie over de indicaties voor MRI na knieletsel en de meest gebruikte MRI technieken, werd het MRI-beeld en de classificatie van de meest frequente traumatische knieletsels besproken en geïllustreerd. Tevens werden de meest voorkomende valkuilen bij de beoordeling van MRI van de knie belicht.

Vervolgens werd een systematische review en meta-analyse verricht naar de diagnostische accuratesse van MRI voor kruisband- en meniscusscheuren, beschreven in **hoofdstuk 3**. In een analyse van 29 artikelen gepubliceerd tussen 1991 en 2000 bleek dat de gepoolde gewogen sensitiviteit voor mediale meniscusscheuren hoger was dan voor laterale meniscusscheuren (respectievelijk 93.3% [95% CI 91.7-95.0] en 79.3% [95% CI 74.3-84.2]), maar bleek de gepoolde gewogen specificiteit voor mediale meniscusscheuren lager dan voor laterale meniscusscheuren (respectievelijk 88.4% [95% CI 85.4-91.4] en 95.7% [95% CI 94.6-96.8]). Het verschil in gepoolde gewogen sensitiviteit voor scheuren van beide kruisbanden was statistisch niet significant, maar de gepoolde gewogen specificiteit voor de achterste kruisband was hoger dan voor de voorste kruisband (respectievelijk 99.4% [95% CI 98.9-99.9] en 94.3% [95% CI 92.7-95.5]). In deze studie analyseerden wij ook de factoren die van invloed zijn op de diagnostische accuratesse, in het bijzonder factoren met betrekking tot de studieopzet en de magnetische veldsterkte van de MRI-scanner. Met behulp van een summary receiver operating characteristics analyse vonden wij dat de diagnostische accuratesse inderdaad wordt beïnvloed door diverse factoren gerelateerd aan de studieopzet. Zo was de gerapporteerde diagnostische accuratesse voor de achterste kruisband beduidend beter indien er sprake was van verificatie bias. Wij toonden een geringe invloed van de magnetische veldsterkte aan, maar deze was slechts statistisch significant voor voorste kruisbandrupturen.

Gerandomiseerde klinische trial op de spoedeisende hulp van het ziekenhuis

Wij verrichtten een gerandomiseerde klinische trial (RCT) op de afdeling spoedeisende hulp van ons ziekenhuis met als doel de routinematige toepassing van MRI in het acute stadium na knieletsel te onderzoeken. Patienten werden in deze studie geïncludeerd indien zij in de voorafgaande week een acuut knieletsel hadden doorgemaakt en er door de onderzoekend arts om deze reden een röntgenfoto werd aangevraagd. Geïncludeerde patiënten werden gerandomiseerd tussen twee diagnostische strategieën, te weten de huidige diagnostische work-up bestaande uit alleen een röntgenfoto en een diagnostische strategie waarbij onmiddellijk na de röntgenfoto aanvullend een korte MRI scan werd verricht op een "dedicated extremity" MRI-scanner (hoofdstuk 10, figuur 1). Dit type scanner is specifiek ontworpen voor beeldvorming van de extremiteiten en biedt enkele voordelen ten opzichte van de gebruikelijke whole-body MRI-scanners met hoge magnetische veldsterkte: vanwege de compacte afmeting en de permanente magneet met lage veldsterkte zijn de kosten van aanschaf, installatie en onderhoud en de kosten per onderzoek lager. Bovendien is een dergelijke scanner mogelijk beter beschikbaar voor acute extremiteitstoepassingen dan whole-body scanners, welke in de meeste centra vaak zijn volgepland met reguliere patiënten. Wij veronderstelden dat deze voordelen mogelijk een oplossing bieden voor de beperkingen die het routinematige gebruik van MRI bij acute patiënten traditioneel in de weg hebben gestaan. Omdat MRI in het acute stadium alleen haalbaar is indien de duur van het onderzoek relatief kort is, ontwikkelden wij een kort scanprotocol met een gemiddelde scanduur van 6 minuten. Het gehele onderzoek, inclusief opstarten van de scanner en positioneren van de patiënt, duurde derhalve minder dan 15 minuten. Verkorting van het scanprotocol resulteert onvermijdelijk in een verlies van beeldkwaliteit, maar in een pilotstudie toonden wij aan dat ons protocol van voldoende kwaliteit was om de meeste afwijkingen te detecteren (9). Bovendien was, zoals reeds genoemd, uit onze systematische review gebleken dat een lagere veldsterkte van de MRI scanner niet leidt tot een substantiële reductie in diagnostische accuratesse voor de meeste knieletsels.

In **hoofdstuk 4** beschreven wij een predictieregel met als doel patiënten die aanvullende behandeling behoeven te onderscheiden van hen bij wie behandeling en controle onnodig zijn. Wij onderzochten of de korte MRI-scan in aanvulling op of in plaats van een röntgenfoto behulpzaam is bij deze voorspelling of specifieke therapie noodzakelijk is. Univariabele en multivariabele logistische regressieanalyse werd verricht om de voorspellende waarde te bepalen van geslacht, leeftijd, traumamechanisme, uitslag van röntgenfoto en MRI-scan voor specifieke behandeling binnen 6 maanden na het letsel. Wij creëerden vier regressiemodellen voor de verschillende diagnostische strategieën en evalueerden de onderlinge verschillen door middel van Akaike's information criterion en ROC-analyse. Bij 109 van de 189 patienten was behandeling noodzakelijk. In de multivariabele analyse waren leeftijd boven 30 jaar, indirect traumamechanisme en de bevindingen op de röntgenfoto statistisch significante voorspellers voor noodzakelijke behandeling ($p<0.05$). Met betrekking tot MRI was alleen een abnormale uitslag significant voorspellend voor noodzakelijke behandeling en bovendien alleen als MRI werd toegepast in plaats van een röntgenfoto (OR 2.61, 95% CI 1.12-6.06). Het model met zowel een röntgenfoto als MRI was uit statistisch oogpunt echter robuuster dan het model met alleen een röntgenfoto ($p=0.04$). Uit de resultaten bleek dat de toepassing van een kort MRI-onderzoek in aanvulling op of in plaats van een röntgenfoto weliswaar de voorspelling van noodzaak tot behandeling verbetert, maar dat dit niet significant helpt bij de identificatie van patiënten die kunnen worden ontslagen zonder verdere follow-up.

In **hoofdstuk 5** onderzochten wij de kosten en effectiviteit van de implementatie van een kort MRI-onderzoek bij de initiële beoordeling na knieletsel. Ook werd deze toepassing van MRI voor pols- en enkelletsels bestudeerd. Wij analyseerden de kosten vanuit een maatschappelijk perspectief, omdat wij veronderstelden dat de toepassing van MRI in de acute fase na trauma mogelijk leidt tot een eerdere diagnose en behandeling, sneller herstel en korter arbeidsverzuim. Dit levert vanwege de lagere kosten gerelateerd aan productiviteitsverlies mogelijk een maatschappelijke kostenbesparing op (10,11). Als effectiviteitsmaten verzamelden wij gegevens met betrekking tot kwaliteit van leven, tijd tot afronding van het diagnostische proces, aantal aanvullende diagnostische onderzoeken, duur van arbeidsverzuim en tijd tot herstel. Kwaliteit van leven werd gemeten op vragenlijsten welke werden verstuurd 1 week, 6 weken, 3 maanden en 12 maanden na inclusie. Wij vonden met betrekking tot de knie (189 patiënten) dat de kwaliteit van leven gemeten met de Euro-Qol index alleen na 1 en 6 weken follow-up significant beter was voor de diagnostische strategie met MRI. In de strategie met MRI was het aantal diagnostische onderzoeken significant lager en de tijdsduur van het diagnostische proces significant korter ten opzichte van de strategie met alleen een röntgenfoto. Voor de overige gewrichten (87 polsen en 198 enkels) werd voor geen van de effectiviteitsmaten een significant verschil tussen de diagnostische strategieën gevonden. Voor de knie waren de gemiddelde kosten lager voor de MRI-strategie (€1820) ten opzichte van de strategie met alleen een röntgenfoto (€2231). Dit werd voornamelijk veroorzaakt door lagere kosten gerelateerd aan productiviteitsverlies. Voor de pols waren de kosten met gebruik van MRI hoger en voor het enkel waren de kosten met en zonder MRI vergelijkbaar. Voor alle drie gewrichten waren de kostenverschillen echter niet statistisch significant. Wij concludeerden dat MRI bij patiënten met acuut pols- of enkelletsel noch kostenbesparend noch effectief is. Voor de knie leidt de toepassing van MRI bij alle patiënten na trauma tot een verbetering van kwaliteit van leven in de eerste 6 weken, verkorting van het diagnostische traject, vermindering van het aantal aanvullende diagnostische onderzoeken en mogelijk tot een maatschappelijke kostenbesparing, hoewel dit laatste statistisch niet significant was.

De bovengenoemde resultaten waren aanleiding om de kosten en effectiviteit van de implementatie van een kort MRI-onderzoek in de initiële evaluatie van traumatisch knieletsel verder te onderzoeken, zoals beschreven in **hoofdstuk 6**. Omdat MRI waarschijnlijk een beperkte aanvullende waarde heeft indien er op een röntgenfoto reeds een fractuur is aangetoond, introduceerden wij een derde diagnostische strategie waarbij MRI selectief werd toegepast alleen als de röntgenfoto geen fractuur toonde. Omdat deze strategie niet een van de studiearmen van onze trial betrof, werd deze gemodelleerd door de resultaten van de patiënten uit de strategie met alleen een röntgenfoto waarbij een fractuur zichtbaar was te combineren met die van de patiënten uit de strategie met zowel röntgenfoto als MRI waarbij geen fractuur was aangetoond. Na adjustering van alle kosten voor het jaar 2007 middels consumenten prijs indices analyseerden wij de drie diagnostische strategieën met gebruik van dezelfde methoden en effectiviteitsmaten zoals beschreven in hoofdstuk 5. Gedurende de follow-up periode bleek de kwaliteit van leven voor beide strategieën met MRI gelijkwaardig. Met name na 1 en 6 weken follow-up was de EuroQol score gunstiger voor beide MRI strategieën (0.72, 95% CI 0.67-0.77 na 6 weken voor beide strategieën) vergeleken met de strategie met alleen een röntgenfoto (0.61, 95% CI 0.54-0.67 na 6 weken). Bij selectieve toepassing van MRI bleken de tijd tot diagnose, duur van arbeidsverzuim en tijd tot herstel korter en de totale kosten lager vergeleken met MRI bij alle patiënten, maar deze verschillen waren niet statistisch significant. De totale kosten waren echter substantieel lager met gebruik van selectieve MRI (€1973, 95% CI 1401-2543) vergeleken met alleen een röntgenfoto (€2593, 95% CI 1815-3372). Uit de resultaten kwam naar voren dat de implementatie van een selectieve korte MRI-scan bij patiënten met acuut knieletsel bij wie op de röntgenfoto geen fractuur zichtbaar is, leidt tot een maatschappelijke kostenbesparing en potentieel tot een hogere effectiviteit.

Omdat wij in onze RCT geen significante kostenverschillen en slechts een klein en voorbijgaand verschil in effectiviteit vonden, vroegen wij ons af of een grotere trial wél significante en duurzame verschillen zou kunnen aantonen. Om dit te onderzoeken verrichtten wij een zogenaamde "value of information" analyse (**hoofdstuk 7**), gebruikmakend van de gegevens uit onze RCT. Met behulp van "value of information" analyse is het mogelijk de verwachte meerwaarde van toekomstig onderzoek te bepalen om zo de besliskundige onzekerheid weg te nemen die voortbestaat wanneer een trial geen significante verschillen aantoont. Bovendien is het met deze methode mogelijk om de factoren te identificeren die de meeste invloed hebben op deze onzekerheid, om de optimale studieopzet te bepalen en om de benodigde studieomvang te berekenen (12-14). Dit is van belang omdat meer onderzoek kostbaar is en inefficiënte inzet van de beperkte financiële middelen in de gezondheidszorg vermeden dient te worden. Wij vonden dat het aantal kwaliteits-geadjusteerde levensjaren, de kosten per nacht ziekenhuisopname en de frictiekosten (een schatting van de maatschappelijke kosten gerelateerd aan arbeidsverzuim en productieverlies) van grootste invloed waren op de besliskundige onzekerheid, hetgeen suggereert dat een toekomstige studie zich vooral op deze factoren moet richten. Idealiter dienst een dergelijke studie te worden verricht als een internationale multicentrische trial vanuit het perspectief van de Europese Unie met een omvang van 3500 patiënten per randomisatie-arm. Dit zou leiden tot een verwachte opbrengst voor de maatschappij van €5.6 miljoen of 70 kwaliteits-geadjusteerde levensjaren. Uit de resultaten bleek tevens dat verder onderzoek naar MRI voor acuut knieletsel in een spoedeisende hulpsetting van een ziekenhuis niet gerechtvaardigd is vanuit het Nederlandse perspectief, omdat de verwachte opbrengst niet opweegt tegen de kosten van een dergelijke studie, ongeacht de omvang.

De beperkingen van onze RCT zijn voornamelijk gerelateerd aan de patiënteninclusie en follow-up. Hoewel het de bedoeling was om patiënten opeenvolgend te includeren, werd een substantieel aantal potentieel geschikte patiënten niet gevraagd in de studie te participeren. Een selectiebias zou mogelijk kunnen zijn ontstaan indien de patiënten die niet werden uitgenodigd mee te doen systematisch verschilden van patiënten die wel werden geïncludeerd met name met betrekking tot demografie of ernst van het letsel. Hoewel wij de kans hierop klein achten, kunnen wij dit niet nagaan omdat de meeste niet-geïncludeerde patiënten naderhand niet traceerbaar waren. Er was een laag responspercentage op de vragenlijsten, vooral onder de patiënten bij wie alleen een röntgenfoto werd gemaakt. Waarschijnlijk waren deze patiënten minder bereid om de vragenlijsten in te vullen omdat zij teleurgesteld waren dat er bij hen geen aanvullende MRI werd verricht. Hierdoor kunnen wij de mogelijkheid van bias met betrekking tot de resultaten van kwaliteit van leven niet uitsluiten. Voor de kostengegevens waren wij minder afhankelijk van de vragenlijsten, omdat deze grotendeels werden verzameld uit de patiëntendossiers en het ziekenhuis informatie systeem.

Concluderend tonen de resultaten van onze RCT aan dat het niet nuttig is om in de acute fase na knietrauma bij alle patiënten een korte MRI-scan te verrichten in plaats van of in aanvulling op een röntgenfoto. Deze niet-selectieve toepassing van MRI heeft namelijk een beperkte toegevoegde waarde bij de voorspelling of specifieke behandeling noodzakelijk is en is niet behulpzaam bij het identificeren van patiënten die geen behandeling behoeven. Bovendien konden wij bij een dergelijk gebruik van MRI geen statistisch significant verschil aantonen in de kosten vanuit een maatschappelijk perspectief. Indien MRI selectief wordt toegepast bij patiënten zonder een fractuur op de röntgenfoto, leidt dit echter tot een potentieel hogere effectiviteit en mogelijk tot een maatschappelijke kostenbesparing, voornamelijk als gevolg van lagere kosten gerelateerd aan productiviteitsverlies. Nader onderzoek met betrekking tot deze toepassing van MRI is alleen gerechtvaardigd indien dit een grote multicentrische studie betreft.

MRI follow-up studie in de huisartspraktijk

Wij verrichten een subgroepstudie binnen het HONEUR knie cohort, een prospectieve observationele cohortstudie in de huisartspopulatie waarin 1068 patiënten met acute of chronische knieklachten werden geïncludeerd (15). De subgroep bestond uit 134 volwassen patiënten die hun huisarts bezochten vanwege een acuut traumatisch knieletsel. Bij deze patiënten werd een initiële MRI-scan 3 tot 6 weken na trauma verricht, evenals een follow-up MRI-scan na een jaar. Ook werd na ieder MRI-onderzoek een gestandaardiseerd lichamelijk onderzoek verricht en werden zowel na het letsel als na een jaar follow-up vragenlijsten afgenomen met betrekking tot pijnscore, Lysholm functionele kniescore en ervaren herstel. De resultaten van deze MRI follow-up studie werden gepresenteerd in het laatste deel van dit proefschrift.

In **hoofdstuk 8** bestudeerden wij hoe het aspect van de meniscus verandert op de follow-up MRI in vergelijking met de initiële MRI na trauma. Uit een eerder gepubliceerde systematische review was namelijk gebleken dat er weinig bekend is over het natuurlijke beloop van meniscuslaesies (16). Bij 101 conservatief behandelde patiënten werden de voorhoorn en achterhoorn van beide menisci op de initiële en follow-up MRI separaat beoordeeld op traumatische of degeneratieve afwijkingen met behulp van een 6-punten schaal. Wij evalueerden de voorspellende waarde van demografische variabelen, traumamechanisme, Lysholm functionele kniescore (17) en initiële MRI-bevindingen voor verbetering of verslechtering van het aspect van de meniscus op follow-up MRI. Hiertoe werd een univariabele en multivariabele ordinale logistische regressieanalyse verricht per meniscushoorn. Wij onderzochten ook de associatie met klinische uitkomst, uitgedrukt als ervaren herstel en verandering in de pijnscore na een jaar. Op de initiële MRI-scans diagnosticeerden wij 50 meniscusscheuren en 122 degeneratieve afwijkingen in 403 meniscushoornen. Op de follow-up MRI-scans zagen wij een verslechtering van het MRI-beeld bij 49 meniscushoornen en verbetering bij 18 hoornen. In de multivariabele logistische regressieanalyse bleken leeftijd

(OR 1.3/decade, 95% CI 1.1-1.7), lichaamsgewicht (OR 1.2/10 kg gewichtstoename, 95% CI 1.0-1.5), de aanwezigheid van een totale voorste kruisbandruptuur op de initiële MRI (OR 2.4, 95% CI 1.1-4.8) en locatie in de achterhoorn van de mediale meniscus (OR 3.0, 95% CI 1.2-7.4) statistisch significante voorspellers van een verslechtering van het MRI-beeld van de meniscus na een jaar. De aanwezigheid van een meniscuslaesie op de initiële MRI was eveneens een significante voorspeller (OR 0.3, 95% CI 0.1-0.7), echter met een odds radio kleiner dan één, hetgeen een potentiële natuurlijke genezingstendens voor sommige meniscuslaesies suggereert. Verandering van het MRI-beeld van de meniscus was niet significant geassocieerd met de klinische uitkomst, hetgeen impliceert dat het niet nuttig is om een follow-up MRI-onderzoek van de menisci te verrichten ter verklaring van een klinische verslechtering.

In een andere studie, beschreven in **hoofdstuk 9**, onderzochten wij de prognostische factoren voor het ontstaan van nieuwe of verergering van bestaande degeneratieve afwijkingen (gonarthrose) tijdens de follow-up van een jaar. De aanwezigheid en ernst van femorotibiale arthrose op de follow-up MRI werd vergeleken met die op de initiële MRI met gebruik van de Kellgren en Lawrence schaal (18). Wij verrichtten univariabele en multivariabele logistische regressieanalyse om de prognostische waarde van dezelfde onafhankelijke variabelen als gebruikt in hoofdstuk 8 voor het ontstaan van nieuwe degeneratieve afwijkingen of progressie van bestaande arthrose te bepalen. Wij evalueerden tevens de associatie met klinische uitkomst, gemeten met de ervaren herstelscore. 117 patiënten werden geanalyseerd, inclusief de patiënten die tijdens de follow-up werden geopereerd. 33 knieën toonden op de initiële MRI-scan degeneratieve afwijkingen. Op de follow-up MRI vonden wij bij 22 van 85 initieel normale knieën nieuw ontstane degeneratieve afwijkingen. Progressie van preëxistente arthrose was zichtbaar bij 5 knieën. In de multivaribele analyse waren een leeftijd boven 50 jaar en een body mass index hoger dan 25 kg/m2 significante voorspellers voor de novo of progressieve gonarthrose ($p<0.10$). Veruit de meest significante voorspeller was echter de aanwezigheid van beenmergoedeem op de initiële MRI. Dit was in de multivariabele analyse zelfs de enige statistisch significante voorspeller (OR 5.29, 95% CI 1.64-17.1). Omdat wij een significante associatie vonden tussen nieuwe of progressieve degeneratieve afwijkingen en klinische uitkomst, concludeerden wij dat de aanwezigheid van beenmergoedeem op MRI na acuut knieletsel een sterke voorspeller is voor nieuw ontstane of progressieve gonarthrose op follow-up MRI na een jaar en dat dit in de klinische uitkomst tot uiting komt.

Er waren meerdere beperkingen van deze MRI follow-up studie. 17 van de 134 patiënten (13%) konden niet worden opgevolgd omdat zij niet meer traceerbaar waren of weigerden verder aan de studie deel te nemen. Dit percentage is echter laag vergeleken met andere studies (19,20). Om logistieke redenen was het niet mogelijk om de follow-up MRI-scans te laten beoordelen door dezelfde radiologen die ook de initiële MRI-onderzoeken hadden beoordeeld. Doordat de initiële en follow-up scans dus door verschillende beoordelaars werd gescoord zou er mogelijk een vertekening van de resultaten kunnen zijn ontstaan, maar waarschijnlijk is de kans hierop beperkt omdat door iedere beoordelaar scherp omschreven criteria werden gehanteerd bij het scoren van de meniscuslaesies en degeneratieve afwijkingen (18,21,22). Omdat het HONEUR kniecohort niet tot doel had om therapeutische mogelijkheden van traumatische knieletsels te evalueren, was de behandeling van onze patiënten niet exact gedocumenteerd. Hierdoor was het onbekend wat voor procedure er precies was verricht bij de 15 patiënten die een arthroscopie ondergingen tijdens de follow-up. Wij zijn van mening dat het ontbreken van deze informatie een betrouwbare interpretatie van het postoperatieve MRI-beeld van de meniscus onmogelijk maakt en om deze reden werden de geopereerde patiënten geëxcludeerd uit de analyse van het natuurlijke beloop van meniscuslaesies, maar werden deze wel opgenomen in een sensitiviteitsanalyse. In de analyse van nieuwe of progressieve degeneratieve afwijkingen werden de geopereerde patiënten wel geïncludeerd, maar verrichten wij een sensitiviteitsanalyse zonder deze patiënten. Beide sensitiviteitsanalyses veranderden de resultaten niet. Om de ernst van arthrose te graderen gebruikten wij de Kellgren en Lawrence schaal, welke werd ontwikkeld voor gebruik op röntgenfoto's. In recente studies werden de Whole Organ Magnetic Resonance Imaging Score (WORMS) (23) en de Knee Osteoarthritis Scoring System (KOSS) (24) geïntroduceerd als MRI-specifieke graderingssystemen, maar deze waren nog niet beschikbaar ten tijde van de initiële MRI in de periode 2002-2003. Omwille van vergelijkbaarheid en de prospectieve studieopzet, besloten wij om voor de beoordeling van de initiële en follow-up MRI-scans dezelfde schaal te gebruiken.

De twee klinische studies die werden beschreven in dit proefschrift verschilden niet alleen met betrekking tot de studieopzet en huisarts- versus ziekenhuissetting. Wanneer de patiëntenpopulaties worden vergeleken, blijkt dat de gemiddelde leeftijd van de patiënten in onze RCT op de afdeling spoedeisende hulp lager was (33.4 jaar versus 40.8 jaar (25) bij onze studie in de huisartspraktijk). Bij onze RCT was er tevens sprake van een meerderheid aan mannen (123 mannen, 66 vrouwen), terwijl de geslachtsverhouding in de HONEUR subgroepstudie meer gebalanceerd was (74 mannen, 60 vrouwen). Wij vergeleken de frequentie van traumatische knieletsels in beide studies en vonden in onze RCT op de eerste hulp 16 mediale meniscusscheuren (17%), 10 laterale meniscusscheuren (11%), 17 totale voorste kruisbandrupturen (18%) en geen volledige achterste kruisbandrupturen (0%) onder de 93 patiënten die waren gerandomiseerd in de diagnostische strategie met MRI. Onder de 134 patiënten uit het HONEUR kniecohort bij wie een initiële MRI was verricht vonden wij 35 mediale meniscusscheuren (26%), 26 laterale meniscusscheuren (19%), 14 totale voorste kruisbandrupturen (10%) en 2 complete achterste kruisbandrupturen (1%). De hogere frequentie van meniscusscheuren in de studie onder huisartspatiënten kan worden verklaard door de hogere gemiddelde leeftijd van patiënten en het feit dat het grootste deel van de meniscusscheuren een horizontaal verloop toonde. Horizontale meniscusscheuren worden bij de meeste patiënten beschouwd als een manifestatie van degeneratie en niet als een afwijking van traumatische origine. Het relatief grotere aantal complete voorste kruisbandrupturen in onze RCT op de spoedeisende hulp suggereert dat patiënten met het gevoel van een instabiele knie eerder geneigd zijn de eerste hulp van het ziekenhuis te bezoeken dan hun huisarts. De verschillende tijdsduur tussen het trauma en moment van MRI in beide studies (binnen een week versus 3 tot 6 weken na trauma) lijkt naar onze mening geen verklaring voor het verschil in frequentie van laesies.

Toekomstig onderzoek

Hoewel MRI zich reeds heeft bewezen als een betrouwbare techniek in de diagnostische work-up van knieklachten, blijft deze techniek zich ontwikkelen en zal deze in de toekomst ongetwijfeld nog verder verbeteren. In de komende jaren zal het onderzoek zich vooral richten op MRI van de knie met een hoge magnetische veldsterkte van 3.0 Tesla, in het bijzonder met betrekking tot het kraakbeen en moleculaire beeldvorming. 3.0 Tesla MRI van de knie biedt een substantiële verbetering van de signaal-ruis-verhouding, maar is daarentegen gevoeliger voor artefacten (26,27). Nieuwe MRI pulssequenties blijven zich aandienen, ook voor systemen met een meer reguliere magnetische veldsterkte (28). Om deze reden is het nodig een update van de systematische review te verrichten, waarbij ook artikelen worden geanalyseerd die zijn gepubliceerd na het jaar 2000. Studies verricht op een 3.0 Tesla MRI-scanner dienen te worden geïncludeerd teneinde het effect van magnetische veldsterkte op de diagnostische accuratesse beter in kaart te brengen. Omdat de beeldvorming van het kniekraakbeen met MRI in de afgelopen jaren een verbetering heeft doorgemaakt (29), kan bij een update van de systematische review mogelijk ook gekeken worden naar kraakbeenletsels. De toegenomen belangstelling voor beeldvorming van kraakbeen, zowel in het kader van traumatische chondraalletsels als degeneratieve arthrotische afwijkingen, werd aangewakkerd door nieuwe therapeutische opties voor kraakbeenlaesies, zoals autologe chondrocytentransplantatie. Om dergelijke behandelingen te kunnen plannen en evalueren is gedetailleerde beeldvorming van het kraakbeen noodzakelijk (30). Al deze recentelijk ontwikkelde technieken dienen nog te worden geëvalueerd in prospectieve studies om hun waarde in de dagelijkse praktijk vast te stellen.

De follow-up periode van één jaar in onze subgroep studie van het HONEUR kniecohort was relatief kort. Om het natuurlijke beloop van traumatische knieletsels, met name meniscuslaesies, op de langere termijn in kaart te brengen, ligt het in de bedoeling om een tweede follow-up MRI-scan bij onze patiënten na circa 6 jaar te verrichten.
In dit proefschrift is uitvoerig stilgestaan bij de vraag of het zinvol is om een nieuwe kosteneffectiviteitstudie te verrichten naar MRI in het acute stadium na trauma: dit is slechts gerechtvaardigd vanuit het perspectief van de Europese Unie. Het Europese perspectief is in de huidige tijd echter niet langer een

theoretische invalshoek, wanneer we bedenken dat steeds meer processen worden gereguleerd vanuit de Europese Unie. In de toekomst zou dit tot op zekere hoogte ook kunnen gelden voor de gezondheidszorg en zorgfinanciering. Het is zeker niet ondenkbaar dat er in de komende jaren kosteneffectiviteitstudies zullen worden geïnitieerd vanuit het perspectief van de Europese Unie en gefinancierd door een Europese instantie.

REFERENTIES

1. Cardol M, van Dijk L, de Jong JD, et al. Tweede Nationale Studie naar ziekten en verrichtingen in de huisartspraktijk. Huisartsenzorg: wat doet de poortwachter ? Utrecht, Bilthoven: NIVEL/RIVM, 2004.
2. Elvenes J, Jerome CP, Reikeras O, Johansen O. Magnetic resonance imaging as a screening procedure to avoid arthroscopy for meniscal tears. Arch Orthop Trauma Surg 2000; 120:14-16.
3. Weinstabl R, Muellner T, Vecsei V, Kainberger F, Kramer M. Economic considerations for the diagnosis and therapy of meniscal lesions: can magnetic resonance imaging help reduce the expense? World J Surg 1997; 21:363-368.
4. Vincken PW, ter Braak BP, van Erkel AR, et al. Effectiveness of MR imaging in selection of patients for arthroscopy of the knee. Radiology 2002; 223:739-746.
5. Carrino JA, Schweitzer ME. Imaging of sports-related knee injuries. Radiol Clin North Am 2002; 40:181-202.
6. Stiell IG, Greenberg GH, Wells GA, et al. Derivation of a decision rule for the use of radiography in acute knee injuries. Ann Emerg Med 1995; 26:405-413.
7. Hardaker WT, Jr., Garrett WE, Jr., Bassett FH, 3rd. Evaluation of acute traumatic hemarthrosis of the knee joint. South Med J 1990; 83:640-644.
8. Mitsou A, Vallianatos P. Clinical diagnosis of ruptures of the anterior cruciate ligament: a comparison between the Lachman test and the anterior drawer sign. Injury 1988; 19:427-428.
9. Nikken JJ. MRI for the initial evaluation of acute wrist, knee, and ankle trauma. Erasmus MC, Rotterdam, 2003 (Thesis).
10. Oostenbrink JB, Koopmanschap MA, Rutten FFH. Handleiding voor kostenonderzoek, methoden en richtlijnprijzen voor economische evaluaties in de gezondheidszorg. Amstelveen: College voor zorgverzekeringen, 2000.
11. Hunink MGM, Glasziou PP. Decision making in health and medicine - integrating evidence and values. Cambrige: Cambridge University Press, 2001.
12. Ades AE, Lu G, Claxton K. Expected value of sample information calculations in medical decision modeling. Med Decis Making 2004; 24:207-227.

13. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. J Health Econ 1999; 18:341-364.
14. Groot Koerkamp B, Hunink MGM, Stijnen T, Weinstein MC. Identifying key parameters in cost-effectiveness analysis using value of information: a comparison of methods. Health Econ 2006; 15:383-392.
15. Heintjes EM, Berger MY, Koes BW, Bierma-Zeinstra SM. Knee disorders in primary care: design and patient selection of the HONEUR knee cohort. BMC Musculoskelet Disord 2005; 6:45.
16. Boks SS, Vroegindeweij D, Koes BW, Hunink MG, Bierma-Zeinstra SM. Follow-up of posttraumatic ligamentous and meniscal knee lesions detected at MR imaging: systematic review. Radiology 2006; 238:863-871.
17. Briggs KK, Kocher MS, Rodkey WG, Steadman JR. Reliability, validity, and responsiveness of the Lysholm knee score and Tegner activity scale for patients with meniscal injury of the knee. J Bone Joint Surg Am 2006; 88:698-705.
18. Petersson IF, Boegard T, Saxne T, Silman AJ, Svensson B. Radiographic osteoarthritis of the knee classified by the Ahlback and Kellgren & Lawrence systems for the tibiofemoral joint in people aged 35-54 years with chronic knee pain. Ann Rheum Dis 1997; 56:493-496.
19. Ihara H, Miwa M, Deya K, Torisu K. MRI of anterior cruciate ligament healing. J Comput Assist Tomogr 1996; 20:317-321.
20. Zugaro L, Catalucci A, Barile A, Di Cesare E, Masciocchi C. Anterior cruciate ligament tears in athletes: assessment and clinico-diagnostic control with a dedicated system [Italian]. Radiol Med (Torino) 1998; 96:198-203.
21. Reicher MA, Hartzman S, Duckwiler GR, Bassett LW, Anderson LJ, Gold RH. Meniscal injuries: detection using MR imaging. Radiology 1986; 159:753-757.
22. Crues JV, 3rd, Mink J, Levy TL, Lotysch M, Stoller DW. Meniscal tears of the knee: accuracy of MR imaging. Radiology 1987; 164:445-448.
23. Peterfy CG, Guermazi A, Zaim S, et al. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage 2004; 12:177-190.
24. Kornaat PR, Ceulemans RY, Kroon HM, et al. MRI assessment of knee osteoarthritis: Knee Osteoarthritis Scoring System (KOSS)--inter-observer and intra-observer reproducibility of a compartment-based scoring system. Skeletal Radiol 2005; 34:95-102.
25. Boks SS, Vroegindeweij D, Koes BW, Hunink MGM, Bierma-Zeinstra SM. Magnetic resonance imaging abnormalities in symptomatic and contralateral knees: prevalence and associations with traumatic history in general practice. Am J Sports Med 2006; 34:1984-1991.
26. Craig JG, Go L, Blechinger J, et al. Three-tesla imaging of the knee: initial experience. Skeletal Radiol 2005; 34:453-461.

27. Sampson MJ, Jackson MP, Moran CJ, Moran R, Eustace SJ, Shine S. Three Tesla MRI for the diagnosis of meniscal and anterior cruciate ligament pathology: a comparison to arthroscopic findings. Clin Radiol 2008; 63:1106-1111.
28. Gold GE, Reeder SB, Yu H, et al. Articular cartilage of the knee: rapid three-dimensional MR imaging at 3.0 T with IDEAL balanced steady-state free precession--initial experience. Radiology 2006; 240:546-551.
29. Pai A, Li X, Majumdar S. A comparative study at 3 T of sequence dependence of T(2) quantitation in the knee. Magn Reson Imaging 2008.
30. James SL, Connell DA, Saifuddin A, Skinner JA, Briggs TW. MR imaging of autologous chondrocyte implantation of the knee. Eur Radiol 2006; 16:1022-1030.

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List of Publications

LIST OF PUBLICATIONS

Manuscripts based on studies described in this thesis

MR Imaging of the menisci and cruciate ligaments: a systematic review.
Oei EHG, Nikken JJ, Verstijnen ACM, Ginai AZ, Hunink MGM
Radiology 2003;226(3):837-48

Acute knee trauma: value of a short dedicated extremity MR imaging examination for prediction of subsequent treatment.
Oei EHG, Nikken JJ, Ginai AZ, Krestin GP, Verhaar JAN, van Vugt AB, Hunink MGM.
Radiology 2005; 234(1):125-133

Acute peripheral joint injury: cost and effectiveness of low-field-strength MR imaging - results of randomized controlled trial.
Nikken JJ, **Oei EHG**, Ginai AZ, Krestin GP, Verhaar JAN, van Vugt AB, Hunink MGM
Radiology 2005; 236(3):958-967

MRI for traumatic knee injury: a review.
Oei EHG, Ginai AZ, Hunink MGM
Seminars in Ultrasound, CT and MRI 2007; 28: 141-157

Value of information analysis used to determine the necessity of additional research: MR imaging in acute knee trauma as an example.
Groot Koerkamp B, Nikken JJ, **Oei EHG**, Stijnen T, Ginai AZ, Hunink MGM
Radiology 2008;246(2): 420-425

Costs and effectiveness of a brief MRI examination of patients with acute knee injury.
Oei EHG, Nikken JJ, Ginai AZ, Krestin GP, Verhaar JAN, van Vugt AB, Hunink MGM
European Radiology 2008, Sep 16. [Epub ahead of print]

MRI follow-up of conservatively treated meniscal knee lesions in general practice.
Oei EHG, Koster IM, Hensen JJ, Boks SS, Wagemakers HPA, Koes BW, Bierma-Zeinstra SMA, Hunink MGM
Submitted

Predictive factors for new onset or progression of osteoarthritis in the knee joint one year after trauma; MRI follow-up in general practice.
Koster IM, **Oei EHG**, Hensen JJ, Boks SS, Wagemakers HPA, Koes BW, Hunink MGM, Bierma-Zeinstra SMA
Submitted

Manuscripts not appearing in this thesis

Acute wrist trauma: value of a short dedicated extremity MR imaging examination in prediction of need for treatment.
Nikken JJ, **Oei EHG**, Ginai AZ, Krestin GP, Verhaar JAN, van Vugt AB, Hunink MGM.
Radiology 2005; 234(1):116-124.

Acute ankle trauma: value of a short dedicated extremity MR imaging examination in prediction of need for treatment.
Nikken JJ, **Oei EHG**, Ginai AZ, Krestin GP, Verhaar JAN, van Vugt AB, Hunink MGM.
Radiology 2005; 234(1):134-142.

PhD Portfolio

PHD PORTFOLIO SUMMARY

Name PhD student: Edwin H.G. Oei
Erasmus MC Department: Radiology and Epidemiology
Research School: Netherlands Institute for Health Sciences (NIHES)
PhD period: 2002-2009
Promotor: Prof. dr. M.G.M. Hunink
Copromotor: Dr. A.Z. Ginai

1. PHD TRAINING

General academic skills

- Introduction to Medical Writing, NIHES, Rotterdam, 2000
- Introduction to Statistical Software, NIHES, Rotterdam, 2001

Research skills

- MSc in Clinical Epidemiology, NIHES, Rotterdam, 1999-2001 (total study workload of approximately 120 ECTS): various courses in research methodology, including: Principles of Research in Medicine and Epidemiology, Study Design, Clinical Decision Analysis, Advanced Medical Decision Analysis, Introduction to Data-analysis, Regression Analysis, Topics in Evidence-based Medicine, Meta-analysis, Advanced Course on Diagnostic Research.
- Princples of Epidemiology and Decision Analysis in Clinical Research, Summer Session of the Harvard School of Public Health, Boston, USA, 2001
- EMCR Seminars on the Design, Conduct and Analyses of Clinical Trials, Consultation Center for Clinical Research, Erasmus MC Rotterdam, 2001

In-depth courses

- European Society for Magnetic Resonance in Medicine and Biology, School of MRI, Basic Course, Rotterdam, NL, 2000
- European Society for Magnetic Resonance in Medicine and Biology, School of MRI Clinical Course on Advanced MRI of the Musculoskeletal System, Heraklion, Greece, 2006

Presentations

Abstracts presented at the following national and international conferences:

- Annual Meeting of the Radiological Society of the Netherlands, Ermelo, 2001 (oral presentation)

- Annual Meeting of the Radiological Society of the Netherlands, Noordwijkerhout, 2002 (oral presentation)
- Annual Meeting of the Society of Medical Decision Making, San Diego, USA, 2001 (poster presentation)
- Annual Meeting and Scientific Assembly of the Radiological Society of North America, Chicago, USA, 2001, 2002, and 2008 (poster presentations)

National and international conferences

Attended the Annual Meeting of the Radiological Society of the Netherlands (Noordwijkerhout, Netherlands) in 2001, 2002, 2004, 2005, 2006, 2007, and 2008, the Annual Meeting of the Society of Medical Decision Making (San Diego, USA) in 2001, the Annual Meeting of the Society for Health Services Research in Radiology (San Diego, USA) in 2001, and the Annual Meeting and Scientific Assembly of the Radiological Society of North America (Chicago, USA) in 2001, 2002, and 2008.

Awards

2nd prize, Lee B. Lusted Student Prize in recognition of outstanding original student research in medical decision making, Annual Meeting of the Society for Medical Decision Making. San Diego, USA, October 2001

The Netherlands Institute for Health Sciences (NIHES) Award for best article written under the guidance of a NIHES tutor, Rotterdam, June 2002

Travel grants

A.A. van Beek Fonds, 2001
Vereniging Trustfonds Erasmus Universiteit Rotterdam, 2001 and 2002
Gerrit Jan Mulder Stichting, 2001 and 2003
Van Walree Fonds, Koninklijke Nederlandse Academie van Wetenschappen, 2002

2. TEACHING ACTIVITIES

- Supervising radiology and anatomy practicals for 1st to 4th year medical students at Erasmus MC, Rotterdam, 2004-2008
- Teaching 5th and 6th year medical students during their radiology clinical rotation, Erasmus MC, 2004-2009

Dankwoord

DANKWOORD

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About The Author

ABOUT THE AUTHOR

Edwin Oei was born on June 19th, 1978 in Rotterdam, the Netherlands. He grew up in Lelystad, attended the Christelijk College Nassau-Veluwe in Harderwijk, and graduated in 1996. He subsequently started his medical studies at the University of Antwerp (RUCA), Belgium, and from 1998 onwards continued his studies at the Erasmus University Rotterdam, the Netherlands. In 1999, he enrolled in the Master of Science program in Clinical Epidemiology at the Netherlands Institute for Health Sciences (NIHES), and as part of this training, he joined the Program for the Assessment of Radiological Technology, a joint research group of the Department of Epidemiology and the Department of Radiology of Erasmus MC, University Medical Center Rotterdam. Here, he embarked on the first research projects described in this thesis under the supervision of Prof. dr. M.G.M. Hunink. In 2001, he followed summer courses in Clinical Epidemiology at the Harvard School of Public Health in Boston, USA, and subsequently received Master's degrees in Medicine and Clinical Epidemiology. He then worked for several months as a researcher at the Department of Radiology of Erasmus MC and presented his work at international conferences. In October 2001, he won the Second Prize of the Lee B. Lusted student award competition at the Annual Meeting of the Society for Medical Decision Making in San Diego, USA, and in 2002 he received the NIHES award for the best paper written under the guidance of a NIHES tutor. After spending the last five months of his medical training at the Radiology Department of the Royal Adelaide Hospital in Adelaide, Australia, he obtained his medical degree in March 2004. In April 2004, Edwin started his residency in radiology at Erasmus MC (head of department: Prof. dr. G.P. Krestin) and continued working on his research projects concurrently with his specialization. He is scheduled to complete his residency in April 2009 and will then continue to work as a radiologist in the Department of Radiology at Erasmus MC, Rotterdam.