Skeletal Radiol (2003) 32:1–12
DOI 10.1007/s00256-002-0595-8

REVIEW ARTICLE

**G. Schulte-Altedorneburg**
**M. Gebhard**
**W.A. Wohlgemuth**
**W. Fischer**
**J. Zentner**
**R. Wegener**
**T. Balzer**
**K. Bohndorf**

# MR arthrography: pharmacology, efficacy and safety in clinical trials

Received: 25 March 2002
Revised: 11 September 2002
Accepted: 20 September 2002
Published online: 5 December 2002


G. Schulte-Altedorneburg · M. Gebhard
W.A. Wohlgemuth · W. Fischer · J. Zentner
K. Bohndorf (✉)
Department of Radiology,
Klinikum Augsburg, Stenglinstrasse 2,
86156 Augsburg, Germany
e-mail: radiol-klin.augsburg@gmx.de
Tel.: +49-821-4002441
Fax: +49-821-4003312

R. Wegener · T. Balzer
Clinical Development Diagnostics
and Radiopharmaceuticals II,
Schering AG, Berlin, Germany

**Abstract** *Objective:* A meta-analysis was carried out of clinical trials published between 1987 and 2001 in respect of the clinical pharmacology and safety as well as the diagnostic efficacy of gadolinium-DTPA (Gd-DTPA) for direct intra-articular injection before MRI examination. *Design:* Scientific papers (clinical, postmortem and experimental studies) and information from the manufacturer regarding intra-articular injection of Gd-DTPA that addressed questions of mode of action, optimal concentration and dose, elimination and safety were reviewed. Clinical studies were classified according to their study design. The sensitivity, specificity and accuracy of MR arthrography (MRA) were compared with a "gold standard" (arthroscopy, arthrotomy) and other radiological evidence for different joints. *Results:* Fifty-two clinical studies of the overall 112 studies addressed aspects of diagnostic efficacy of MRA in patients or in healthy volunteers. The shoulder was the most assessed joint (29 of 52 studies). Good (>80%) or even excellent (90–100%) sensitivity, specificity and accuracy were found for MRA in most indications, especially for the shoulder and knee joints and induced extension of rotator cuff lesions, labrum abnormalities and postoperative meniscal tears. Two millimoles per liter has proven to be the best concentration for intra-articular administration of Gd-DTPA. After passive complete diffusion from the joint within 6–24 h, complete and rapid renal elimination takes place after intra-articular injection. Local safety proved to be excellent after intra-articular administration of Gd-DTPA. Regarding systemic tolerance almost no side effects have been reported, but the same safety considerations apply for intra-articular administration of Gd-DTPA as for intravenous injection. *Conclusions:* The diagnostic efficacy of intra-articular MRA in most clinical conditions affecting major joints is greater than that of plain MRI. In some diagnostic problems MRA achieves almost the same sensitivity and specificity as the surgical gold standard. Given a sterile application, the intra-articular administration of Gd-DTPA in a concentration of 2 mmol/l prior to MRI is a safe procedure.

**Keywords** Magnetic resonance imaging · Arthrography · Effectiveness · Safety · Pharmacology

## Introduction

Clinical experience with the intra-articular administration of contrast-enhancing solutions for use in MR arthrography (MRA) now extends for over 10 years [1]. Apart from the rarely used application of NaCl solutions [2, 3, 4, 5], this experience is based almost exclusively on the application of gadolinium DTPA (Gd-DTPA). To date, Gd-DTPA is widely approved by the responsible state agency in a concentration of 500 mmol/l as an MR contrast agent for intravenous (i.v.) injection in some countries of the European Union and in the United States. Numerous studies and case reports have shown the diagnostic benefit of intra-articular administration of Gd-DTPA before MRI examination (direct MR arthrography).

In the present overview, we aimed to analyze the clinical pharmacology and safety of the intra-articular administration of Gd-DTPA as well as the diagnostic efficacy for the different joints based on the available literature from 1987 to 2001.

## Methods

### Clinical pharmacology

Clinical and experimental studies and monographs on pharmacodynamic and pharmacokinetic characteristics following intra-articular administration of Gd-DTPA were considered (key words: gadolinium-DTPA, Magnevist, side effects, dose, signal-noise ratio, MRI, intra-articular). Since specific studies on total body dose and local tissue exposure in man are lacking, experimental studies in animals as well as theoretical calculations based on experiences after i.v. administration of Gd-DTPA were taken into account. Recommendations for optimum concentration and dose in different joints and imaging windows are provided according to the literature and our own experience.

### Clinical trials – literature basis

Published papers on MRA were reviewed after a literature database Medline search (Knowledgefinder, Version 4.16, Aries Systems Corporation, and PubMed – National Library of Medicine; key words: MR arthrography, arthrography, direct arthrography, MRI, CT arthrography, shoulder, elbow, knee, ankle, hip wrist, finger) for the 15 year period 1987–2001. For the purposes of the present overview all publications reviewed fulfilled the (strict) quality criteria (see below) relating to the experimental design, valid methodology, size of the patient population examined or the quality of the journal (e.g., peer review) ($n$=112).

The type of study was determined as follows:

- "experimental study": studies in vitro or using defined phantoms ($n$ = 19);
- "clinical study": studies on patients or healthy volunteers ($n$ = 54);
- "postmortem study": studies on postmortem joints ($n$ = 39).

For the present review, all clinical studies ($n$=54) have been included in which direct MRA with gadolinium-containing solutions has been used for definite indications on the wrist, knee, shoulder, ankle, finger or hip joint. The focus of scientific interest in this regard has been studies of the shoulder joint. Only original papers from journals listed in Index Medicus are mentioned; abstracts or summaries from congress contributions have not been included. The clinical studies have been categorized as follows by their design:

- *"Controlled"*: prospective study related to a reference method such as arthroscopy or open surgery as the gold standard. The study has defined inclusion and exclusion criteria as well as a defined study protocol, in which information is provided about the diagnostic efficacy based at least on descriptive statistics. Nineteen studies are included, of which nine concern the shoulder [1, 6, 7, 8, 9, 10, 11, 12, 13], four the knee [14, 15, 16, 17], three the wrist [18, 19, 20], two the ankle [21, 22] and one the hip [23]. These studies comprise a total of 640 patients.
- *"Partially controlled"*: only some of the above-mentioned requirements of a controlled study are fulfilled or are fulfilled in only some of the population examined. Twenty-three studies were identified, of which 14 concern the shoulder [24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37], four the knee [38, 39, 40, 41], two the wrist [42, 43], two the hip [44, 45] and one the finger joints [46]. In these studies, a total of 2,011 patients were examined with MRA and 772 of them were studied under controlled conditions.
- *"Uncontrolled"*: the requirements of a controlled and partly controlled study are not fulfilled. Ten studies were included in this category, of which six concern the shoulder joint [2, 47, 48, 49, 50, 51] and one each the ankle [52] and the wrist [53]. In addition, various joints were examined in two large multicenter studies [54, 55] which were of great importance regarding safety aspects. A further 2,515 patients were exposed to intra-articular Gd-DTPA.

Thus, a total of 1,412 patients were studied under controlled conditions (arthroscopy/surgery) in 42 studies while a total of 5,166 patients were exposed to intra-articular Gd-DTPA in a total of 52 studies. Furthermore, two recent studies on patients' perception and discomfort during MRA of different joints in a total of 315 patients were included in the clinical study population [56, 57].

Sensitivity and specificity were calculated in 31 of the controlled and partly controlled studies, and the accuracy (in addition) in 18 studies. Other statistical statements connected with the determination of the agreement between MRA and arthroscopy/arthrotomy or conventional imaging are based on the use of kappa values [7, 12, 13, 14, 32], the chi-square test [12, 20, 32], Fisher's exact test [22, 24] and the Wilcoxon signed rank test [24] as well as the McNemar test [9, 12, 17, 21].

Side effects and complications of intra-articular administration of Gd-DTPA mentioned in the studies quoted are reported. In particular, two major open trials which focused on the adverse events classified as tolerance indicators and other adverse events of MRA are considered [54, 55]. Although neither study has been published in a scientific journal or included in Medline, they are considered because of the large number of patients examined and the unique approach concerning the examination of adverse events.

Scientific papers, monographs (clinical, postmortem and experimental studies and reports) and information from the manufacturer that addressed questions of mode of the action, optimum concentration and dose, elimination and safety as well as the influence of magnetic field strength and iodinated contrast agent on the image quality were reviewed.

## Results

### Clinical pharmacology

#### *Basic pharmacological characterization and mode of action*

Gd-DTPA for intra-articular injection is usually used in a concentration of 2 mmol/l. The active ingredient is gadopentetate dimeglumine, which is the *N*-methylglucamine salt of a stable gadolinium complex based on diethylenetriamine penta-acetic (DTPA). The gadolinium ion has seven unpaired electrons resulting in strong paramagnetic properties and, hence, a very strong hydrogen-proton spin lattice (T1) relaxation effect. The stable chelated ion maintains strong paramagnetic properties while providing excellent safety for the otherwise toxic gadolinium. If the joint is filled with gadolinium-containing fluid, the signal in the cavity increases with the use of T1-weighted sequences, and all intra-articular structures, even those with a weak or intermediate signal (including hyaline and fibrous cartilage, ligaments, tendons, joint capsule), are clearly contrasted. In order to study the relationship between field strength and signal emission, the relaxivities of Gd-DTPA were determined at field strengths of 0.0002–4.7 T [58, 59]. A decrease in T1 relaxivity was found in the low field range below 0.4 T but did not change significantly on transition to the medium and high field range up to 2 T.

#### *Optimum concentration and dose*

Depending on the pulse sequence chosen, the maximum signal intensity measured in in vitro experiments is found at Gd concentrations between 0.5 [60] and 2.5 mmol/l [50, 61]. For a T1-weighted sequence with TE/TR = 500/18 ms as is normally used in joint studies, the highest signal intensity and, hence, also the highest contrast, can be expected from a 1 mmol/l Gd-DTPA solution. However, dilution of the applied contrast medium by existing inflammation- or trauma-related effusion can occur in vivo. A dilution effect of the injected Gd-DTPA commonly occurs not only when there is an increased collection of intra-articular fluid (effusion) but must also be considered under physiological conditions. Thus, at a concentration of 2 mmol/l, an adequate contrast medium effect is still available even in the case of a 1:1 dilution.

Bearing in mind individual circumstances, for example postinflammatory or post-traumatic states such as adhesive capsulitis, recommendations regarding the volume to be administered per joint are given in Table 1.

**Table 1** Recommended volume of Gd-DTPA to be administered per joint

| Joint | Volume required (ml) | Reference |
|---|---|---|
| Shoulder | | |
| Instability | 15–20 | [29] |
| Rotator cuff lesion | 10–12 | [13] |
| Wrist | 4 | [19] |
| Finger joint | 1–2 | |
| Hip | 10–20 | [23, 44, 54, 55] |
| Knee joint | 25–50 | [15, 54, 55] |
| Ankle | 12–20 | [21] |

#### *Total body dose and local tissue exposure after intra-articular and i.v. administration*

In some countries, Gd-DTPA is licensed for intravenous administration as a paramagnetic contrast medium in MRI up to a total body dose of 0.3 mmol/kg body weight in adults (0.2 mmol/kg in children), but the standard dosage administered is 0.1 mmol/kg body weight. Although no figures for the total body dose exist in the case of intra-articular administration, it can be roughly estimated from a simple calculation taking the individual body weight into account:

Given a concentration of 2 mmol/l and a patient weight of 70 kg, a theoretical total body dose of 50 ml × 2 μmol/ml (= 2 mmol/l) divided by 70 kg = 1.4 μmol/kg results from a maximum administered volume of 50 ml. Depending on the size of the joint, a volume between 10 and 40 ml is usually injected. This theoretically calculated maximum whole body dose after intra-articular administration is, therefore, about 200 times lower than the maximum permissible and approved intravenous dose.

Gd-DTPA, as a hydrophilic agent, diffuses throughout the entire extracellular space after intravenous injection. It has a distribution volume of about 0.21–0.23 l/kg body weight [62]; in theory, therefore, the maximum interstitial concentration after an intravenous dose of 0.3 mmol/kg or 0.21–0.23 l/kg is 1.3–1.4 mmol/l.

The intra-articular gadolinium concentrations measured after intravenous administration of 0.1 mmol/kg body weight Gd-DTPA or Gd-DOTA are between 0.029 and 0.44 mmol/l [63, 64, 65]. These values are lower than would be expected for uniform distribution in the extracellular space (see above). The discrepancy between the mean measured and the calculated values can be explained by the fact that a large proportion of the surface of the joint cavity shows limited diffusion by bradytrophic and non-perfused cartilage, so that free diffusion is slowed down correspondingly. Since only the synovial membrane of the joint capsule can be regarded as a diffusing tissue, equalization of the concentration

with the rest of the extracellular space can be achieved only after a prolonged period of time – during which, however, the total amount of gadolinium in the body has already fallen again markedly because of renal excretion. It must also be recognized that the physiologically or pathologically available joint fluid further dilutes the contrast agent administered into the joint. It can be assumed that local intolerance reactions in the joint due to the concentration after intra-articular injection are unlikely to be any more frequent than after systemic contrast medium administration. This assumption is confirmed by the safety reports (see below).

*Elimination from joints and body*

Apart from the experimental results in animals [66], only a few clinical studies exist which permit at least an estimate of the timeframe in which gadolinium-DTPA leaves the joint [47, 67, 68], and no studies in man exist which have specifically addressed the elimination of gadopentetate dimeglumine after intra-articular injection by repeated sampling of synovial fluid or urinary kinetics. However, according to calculations, plasma and urine concentrations will drop rapidly below the detection limit. According to a study which examined the imaging window after intra-articular injection of the clinically used 2 mmol/l Gd-DTPA solution into the shoulder joint the highest signal intensity was achieved immediately after the injection, and the intensity fell within the first 120 min [68]. The level of usable contrast was shown to be nondiagnostic in the joint after 6 and 24 h [47, 68].

It is clear that, just as after intravenous administration, complete and rapid renal elimination takes place after intra-articular injection as well as passive diffusion out of the joint, since no significant amounts of gadolinium have been demonstrated in surgical preparations either in animal experiments or in pathological studies [66, 69].

Results acquired in animal experiments and in vitro regarding the pharmacodynamics and pharmacokinetics of gadolinium after local administration show that, although free gadolinium is taken up completely by hyaline cartilage (i.e. by all three layers) within 24 h, complex-bound Gd-DTPA diffuses much more slowly and in much smaller amounts than free gadolinium into the cartilage tissue [66]. These results were confirmed in 10 patients in whom an endoprosthesis was implanted because of pronounced arthrosis of the knee. Gd-DTPA was injected into the pertinent knee in a concentration of 1–5 mmol/l at 17–137 h preoperatively. The surgically removed sections of cartilage were examined by mass spectroscopy for their gadolinium content at specified sites. All values were found to be close to the lowest limit of detection (= 0.05 mg/kg) [66, 70].

*Interaction between Gd-DTPA and iodinated contrast media*

The joints are usually punctured either without any technical aids (e.g., knee) or under X-ray fluoroscopic control (e.g., shoulder), when a small amount of iodinated contrast medium is usually injected to ensure that the needle is in the joint cavity. Occasionally, iodinated contrast medium is also used in order to obtain both conventional or CT-assisted arthrograms and magnetic resonance images after a single joint puncture [8, 47]. Both the intrinsic signal behavior of the X-ray contrast medium and the influence of the contrast medium on the relaxation behavior of Gd-DTPA must then be considered.

An in vitro and clinical MRA study of different ionic and non-ionic iodinated contrast media (all with a 300 mg/ml content of iodine) showed a much higher signal intensity than with physiological saline for T1-weighted sequences. This effect, which is not fully understood, was more pronounced with the ionic contrast medium ioxithalamate (Telebrix, Guerbet, Paris, France) than with the non-ionic monomeric compound iopromide (Ultravist, Schering, Berlin, Germany) or the dimeric preparation iotrolan (Isovist, Schering, Berlin, Germany) [50]. Despite this, no additive effect causing a further increase in signal intensity occurs after the admixture of X-ray contrast medium to gadolinium solutions, but rather a distinct loss of signal. A 25% decrease in the signal intensity can be expected in vitro even with a 15% volume X-ray contrast medium compared with a pure sodium chloride/Gd-DTPA solution [50].

Besides this, in a recent in vitro study three iodinated contrast agents were mixed and incubated with Gd-DTPA at a concentration approximating that used during MRA (1:20) in order to determine whether free toxic gadolinium ion dissociates from the gadopentetate dimeglumine complex. It was found that no gadolinium ion dissociated from the gadopentetate dimeglumine complex even after adding saline, lidocaine or epinephrine. These results have shown that the mixture of Gd-based and iodinated contrast material is safe and also can be mixed with epinephrine and/or lidocaine for clinical use [71].

## Clinical study population

Patients were recruited to the studies who had had joint pain over a long period of time with or without preceding trauma and who were to be diagnosed and, if necessary, treated with the help of arthroscopy or another surgical measure. MRA was performed with the agreement of the patient prior to the stated gold standard methods. The main exclusion criteria were known contraindications to an MR examination, including metallic implants,

a cardiac pacemaker and claustrophobia. The patient population was only described in detail with regard to sex and age distribution in some studies. In these studies there were 2,436 men (64.9%) and 1,317 women (35.1%) who underwent MRA.

## Diagnostic accuracy in clinical trials

All 42 controlled or partly controlled studies, in which the value of intra-articular MRA was tested against the current gold standards of arthroscopy or arthrotomy, were included in the analysis. Additionally, MRA was inconsistently compared with plain MRI, conventional arthrography or CT arthrography (CTA). When comparing MRA with the previously described gold standards, it should be remembered that even the gold standards themselves are limited (not all joint compartments can be directly visualized by arthroscopy because of the rigidity of the instruments) [72].

### *Shoulder joint*

Nine controlled and 14 partially controlled studies were evaluated. A total of 1,833 patients were included in these 23 studies. The above-mentioned requirements of a controlled study were fulfilled in 839 patients.

Compared with the gold standard, sensitivities and specificities of more than 80% were consistently found for labral lesions regardless of the location (superior, inferior, posterior sections of the labrum) and severity (partial or complete tears) of the lesion. In three of these studies, the sensitivity and/or specificity was as high as 100% [1, 8, 27]. These results regarding diagnostic efficacy were confirmed in further controlled [6, 9] and partially controlled studies [24, 25, 26, 27] of labral lesions in which MRA consistently displayed sensitivities around and above 90%. A comparison with CTA was made in two controlled [8, 9] and two uncontrolled studies [31, 33], and with plain MRI likewise in two controlled [1, 9] and two uncontrolled studies [29, 37]. In all studies, MRA proved to be superior to the other two modalities as regards the demonstrability of labral lesions (Figs. 1, 2). Only in respect of the demonstration of enthesophytes in the postero-inferior section of the glenoid was CTA found to be superior in one of the study series [33].

The detection of rotator cuff lesions was evaluated in eight studies, all of which showed the particular value of MRA in the diagnosis of incomplete ruptures of the rotator cuff as well as their differentiation from full-thickness tears. The sensitivities and specificities were consistently reported as being 80–100% [1, 8, 10, 11, 29, 30, 31, 32]. Agreement regarding the diagnosis of complete ruptures of the supraspinatus and infraspinatus tendon

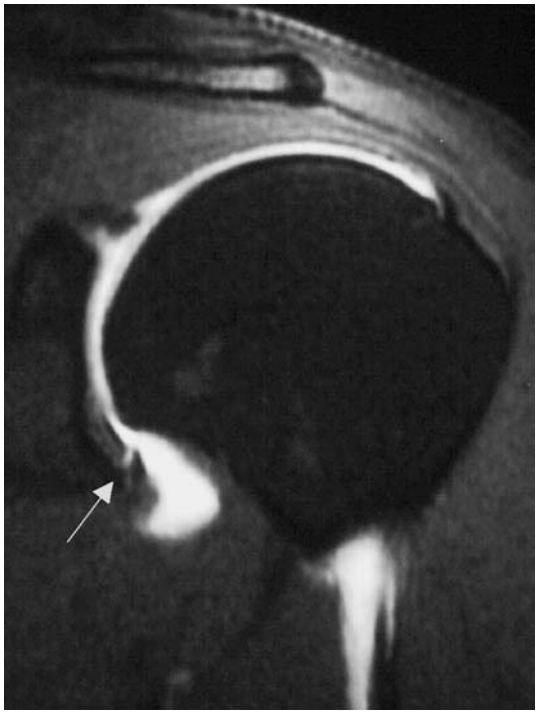

**Fig. 1** Shoulder MR arthrography (2 mmol/l Gd-DTPA, intra-articular) showing a tear of the inferior glenoid labrum. The site of the tear is demonstrated by a small linear extension of contrast medium (*arrow*) into the inferior labrum in this coronal, fat-saturated T1-weighted spin-echo (TR 568, TE 8) image of the shoulder

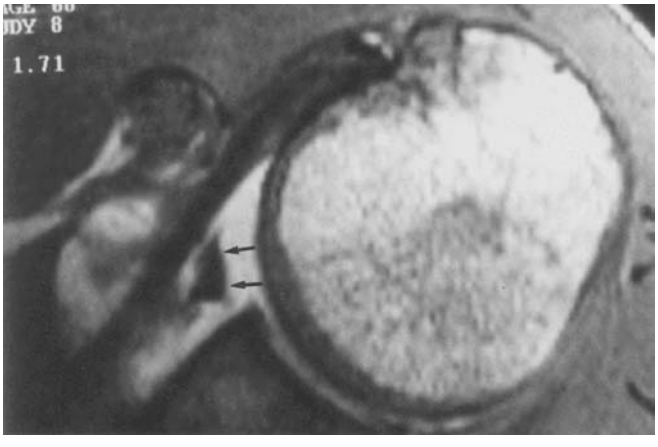


**Fig. 2** Shoulder MR arthrography (2 mmol/l Gd-DTPA, intra-articular) showing an anterior avulsion of the glenoid labrum. Axial T1-weighted spin-echo (TR 668, TE 8) image shows displacement of the anterior labrum (*arrows*) between subscapular tendon and glenoid; contrast medium is interposed between the labrum and the glenoid

and of tendinitis is high, as shown clearly by kappa values of between 0.65 and 0.93 [32]. The value of MRA was compared with CTA in the demonstration of partial or complete ruptures of the rotator cuff and statistically evaluated in one controlled study [8]. Regardless of the type or extent of the rupture, the sensitivity was 73% for CTA and 100% for MRA, while the specificity was 100% for both techniques. In comparison to plain MRI, MRA improves the detection rate of complete ruptures from 77% to 99% [1]. In a retrospective controlled analysis of 50 patients with the clinical diagnosis of rotator cuff tear, shoulder impingement syndrome, instability or chronic shoulder pain MRA showed a high sensitivity (91–100%) and good accuracy (72–90%) as well as a substantial interobserver agreement (kappa value 0.67) for the detection and grading of lesions in the subscapularis tendon [13]. Furthermore, the study revealed a superiority of parasagittal images compared with transverse images for this diagnosis [13].

In two studies on superior labral anterior posterior (SLAP) lesions, which are an important cause of shoulder disability, the sensitivity and specificity for detecting a SLAP-lesion were 84–92% and 69–91%, respectively [12, 26]. The interobserver reliability was moderate to substantial (0.44–0.77) [12]. A correct grading of different SLAP lesion types was available in 13 of 17 patients [26]. In addition, a more recent study has shown that the image interpretation with a fat-suppressed coronal oblique T1-weighted sequence provided the highest sensitivity (91%) for the detection of SLAP tears [12].

Two controlled studies [1, 9] with small numbers of cases have been published concerning the demonstration of free joint bodies by MRA. The results allow the conclusion that small loose bodies can be reliably delineated by MRA.

*Knee joint*

Several studies [14, 15, 16, 17, 39] (a total of 214 controlled cases) evaluating the accuracy of MRA in the demonstration of articular cartilage damage of the knee have shown that clinically relevant stages of surface irregularities of varying severity can be reliably detected. Although the sensitivity of MRA for the demonstration of the earliest stage with circumscribed softening and swelling of the cartilage is only 0–29%, this rises to 80–100% (specificity and accuracy: 91–100%) for the clinically relevant stages [14, 16, 17, 40]. Particularly for the later stages, MRA provides results which are in complete agreement with those of arthroscopy/arthrotomy. The detection of osteochondrosis dissecans is almost as good with MRA (success rate 93–100%) as arthroscopy, while plain MRI showed a success rate of 39–57% [40]. A comparison with CTA in the detection of cartilage lesions is provided in one series [17], which shows that both CTA and MRA are comparable with a sensitivity and specificity of 80–100%. In a comparative study of MRA and MRI in the detection and staging of naturally occurring cartilage lesions MRA has been shown to be superior to plain MRI: the sensitivity for detecting chondral lesions increased from 62% to 85% after intra-articular injection of Gd-DTPA; also the correct staging of the chondral lesion increased from 51% to 98% using surgery as the gold standard [14].

The excellent agreement between the MRA and the arthroscopy/arthrotomy findings with regard to degenerative changes of the meniscus is demonstrated by a sensitivity, specificity and accuracy of 100% for MRA in an analysis of 89 postoperative knees [38]. This is not surprising because MRI had already shown excellent results – a sensitivity of 92%, a specificity of 95% and an accuracy of 93% for T1-weighted (plain) MRI – in that study [38]. In contrast, the demarcation of recurrent tears following surgery is a difficult question. Excellent studies [15, 41] have shown that even here MRA allows a reliable diagnosis with a high detection rate (85–92%). In the detection of recurrent meniscal tears after surgery the sensitivity (69%), specificity (60%) and accuracy (66%) of conventional MRI increased to 89%, 86% and 88% respectively, after MRA [15]. Similar results were achieved in a smaller study where conventional arthrography, conventional MRI, MRA using iodinated contrast material and MRA using gadolinium were compared for the same indication. The accuracy of the different imaging techniques was 58%, 77%, 75% and 92%, respectively, confirming that MRA may be the best technique for the detection of postoperative meniscal tears [41].

*Ankle joint*

A comparison of MRA with the gold standards of arthroscopy and arthrotomy was performed involving 17 patients with chronic instability of the ankle and related to the demonstration of rupture of two ligaments (the anterior talofibular ligament and the calcaneofibular ligament) and the pertinent concomitant diseases [21]. A sensitivity, specificity and accuracy of 100% was found for the detection of a rupture of the anterior talofibular ligament and slightly lower values (sensitivity 90%, specificity 83% and accuracy 82%) for detection of a rupture of the calcaneofibular ligament.

Additionally, the previously mentioned study with arthroscopic/arthrotomic control [21] contains a comparison of MRA with MRI and conventional radiographs. While MRA showed a sensitivity, specificity and accuracy of 100% for the detection of a rupture of the calcaneofibular ligament, plain MRI achieved a sensitivity of only 50%, a specificity of 100% and an accuracy of 59%; the corresponding figures for the conventional radiographs were 57%, 100% and 65% for the detection of

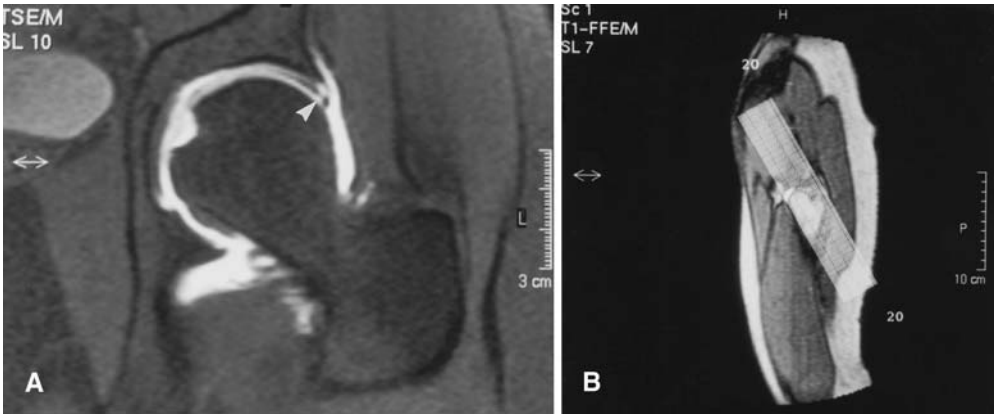


**Fig. 3A, B** Hip MR arthrography (2 mmol/l Gd-DTPA, intra-articular) showing a tear of the anterior superior part of the labrum acetabulare. Oblique-coronal T1-weighted fat-saturated (TR 545, TE 11) images with anterior angulation show extension of the contrast medium (*arrow*) into the hypointense labrum, indicative of a labral tear

a rupture of one of the two ligaments. MRA was likewise found to be superior to plain MRI in the demonstration of a rupture of the calcaneofibular ligament: sensitivity 90% versus 50%, specificity 83% versus 83% and accuracy 82% versus 63%.

Loose bodies were not detected by either MRI or conventional radiography in the two patients in whom they had been identified during surgery, but were demonstrated in one by MRA [21]. Cartilaginous lesions of the trochlea tali were demonstrated in two of three cases by MRI and radiography, while all three lesions were detected by MRA [21].

A recent arthroscopically controlled retrospective study assessing the diagnostic accuracy of MRA in anterolateral ankle impingement in 32 patients revealed a sensitivity, specificity, accuracy, positive and negative predictive value between 90% and 100% for the assessment of the anterolateral soft tissues [22].

Overall, MRA can be regarded as being more sensitive and specific than plain MRI and than conventional radiography in the detection of ruptures of the lateral ligaments of the ankle and detection of cartilaginous lesions.

*Hip joint*

A comparison of MRA with the gold standard with regard to the detection and assessment of the severity of a labral lesion was performed in 72 cases [23, 44, 45]. MRA after intra-articular injection of Gd-DTPA was shown to have a sensitivity and accuracy of more than 87%. The extent of the labral rupture was either not fully demonstrated or underestimated at MRA in three patients. In two of these patients, the hip could not be adequately filled with contrast medium because of shrinkage of the capsule [44]. One study [44] dealt with the demonstration of labral lesions and the classification of the severity of these lesions. A surgically controlled comparison of MRA versus plain MRI was performed in these cases ($n$=22). While plain MRI showed a sensitivity of only 30% and an accuracy of only 36%, MRA displayed almost complete agreement with the surgical results with a sensitivity of 90% and an accuracy of 91% (Fig. 3). Plain MRI underestimated – in some cases considerably – the extent of the labral lesion in 14 of 22 cases [44].

It can be concluded that direct MRA with a 2 mmol/l Gd-DTPA solution can reliably detect intra-articular pathology and is superior to plain MRI.

*Wrist joint*

In the series studied [18, 19, 42, 43] on the demonstration of a lesion of the triangular fibrocartilaginous complex (TFCC), a very high sensitivity and specificity of between 90% and 100% was shown for MRA in two studies [18, 42]; another study resulted in a sensitivity of 100% and a specificity of 80% [19]. A comparison of MRA with other diagnostic methods and the gold standard has so far been completed in only two studies with a total of 40 patients [19, 42]. In an earlier study, MRA proved to be as good as plain MRI and inferior to conventional arthrography in the detection of a TFCC lesion [19], whereas in the most recent study, using up-to-date technology, MRA proved to be clearly superior to plain MRI in sensitivity, specificity and accuracy [42] (Fig. 4).

Good (sensitivity and specificity 80%) and excellent results (sensitivity 100%, specificity 100% and accuracy 90%) were found for MRA in two smaller patient populations as regards the detection of a defect of the lunotriquetral ligament (LT) [18]. In contrast to this, MRA produced seven false-positive results for LT lesions in a report on 15 patients [19]. These results from 1992 were, however, obtained only with simple T1-weighted SE sequences without fat suppression and would nowadays be considered technically inadequate.

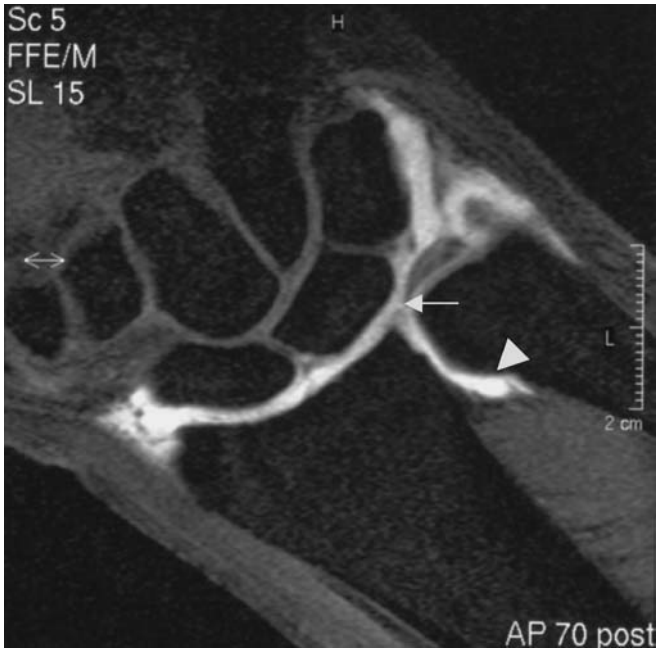


**Fig. 4** Wrist MR arthrography (2 mmol/l Gd-DTPA, intra-articular) demonstrating a complete tear of the triangular fibrocartilaginous complex (TFCC). Coronal, fat-saturated T1-weighted image (TR 31, TE 4.9, flip angle 20°) of the right wrist shows a small disruption (*arrow*) of the radial fixation of the TFCC with transition of the contrast medium into the distal radioulnar joint (*arrowhead*)

The diagnostic efficacy of MRA in ruptures of the scapholunate ligament (SL) was also examined in the above-mentioned studies. The results were comparable: While two of the three studies showed good (sensitivity 82% and specificity 86%) and complete (sensitivity, specificity and accuracy all 100%) agreement of MRA with the gold standard, an accuracy of only 67% was found for MRA in the previously described smaller study [19]. MRA of the LT and SL ligament has so far been compared with plain MRI in 35 patients and with conventional arthrography in 15 patients [19, 42]. In one study of 20 patients, MRA was clearly superior to plain MRI as regards lesions of both ligaments [42]. In another report on 15 patients, MRA was found to be the most accurate modality for the demonstration of a SL lesion in comparison with conventional arthrography and plain MRI, but still achieved an accuracy of only 66.7% compared with the gold standard [19]. For the detection of an LT lesion in the same population, the highest accuracy (80%) among the three modalities was found for plain MRI [19]. Unlike another study, compared with conventional arthrograms MRA showed a good sensitivity, specificity and accuracy of 85–100% for TFCC lesions in 30 patients but a moderate or even poor sensitivity, specificity and accuracy for SL (52–81%) and LT lesions (21–94%) was found [43]. In contrast, a comparison of MRA, MRI, three-compartment arthrography and arthroscopy in the assessment of the different parts of the scapholunate interosseous ligament (SLIL) revealed MRA to be significantly superior to MRI concerning the accurate delineation of the SLIL (95% versus 28%), the confidence level (90% versus 42%) and the true positive rates for SLIL defects (90% versus 52%) in 41 patients [20].

In conclusion, the number of all wrist cases to date is still too small for a definitive assessment of the efficacy in this indication; however, the trend is towards a diagnostic gain with MRA compared with plain MRI. State-of-the-art MR technology seems to improve the results of MRA and plain MRI of the wrist.

### *Finger joints*

The detection of a rupture of the collateral ulnar ligament at the carpometacarpal joint of the thumb was evaluated in a small study with eight patients. This indicated that both plain MRI and MRA are more reliable than stress radiography in the diagnosis of this condition [46]. An evaluation on a larger group of patients is still outstanding.

## Safety in clinical trials

A total of 5,166 patients have been exposed to intra-articular injection of Gd-DTPA in the quoted 52 studies (controlled, partly controlled and uncontrolled: see above). No adverse events were reported which could be attributed to the contrast agent. The side effects that are described consistently correspond to the intra-articular injection procedure itself and the volume injected, which leads to distension of the joint capsule and thus some distension discomfort.

Two major open trials have focused on recording adverse events classified as tolerance indicators and other adverse events following MRA with Gd-DTPA 2 mmol/l in a total of more than 2,300 patients [54, 55]. The majority of all other clinical studies quoted did not address safety aspects of intra-articular application of Gd-DTPA. Some studies briefly document the fact that the intra-articular injection was free from complications in a total of 922 patients [1, 19, 22, 23, 24, 27, 29, 32, 44].

The puncture of any joint always leads to slight pain. Therefore, the procedure is usually performed under local anesthesia of the skin and subcutaneous soft tissue down to the joint capsule. Similarly, the injection of fluid (and/or gas) into the joint always results in distension of the joint capsule and, consequently, distension pain.

A detailed examination of the local and general tolerance of Gd-DTPA 2 mmol/l has been made in a large,

open-label prospective study [54]. "Patient cards" completed by the patients themselves over 3 days were used to assess the tolerance of the examination. The evaluation based on 1,083 patient cards revealed that a "feeling of pressure in the joint" was experienced by 67% of the patients on the day of the examination, by 29.5% on the second day and by 15% on the third day. "Pain on moving" was reported by 61.6% of the patients on the day of the examination, by 49% on the 2nd day and by 38% on the third day.

A greater percentage of patients with hip examinations reported a feeling of pressure compared with those who had knee or shoulder examinations (79% versus 70% and 66%, respectively), probably due to the fact that the joint capsule of the hip is much tighter. More patients with hip and shoulder joint examinations reported pain on moving (68% and 63%) than those with a knee joint examination (45%), as a higher volume of effusion is tolerated in the knee. In addition, 990 patients in this study assessed the painfulness of the examination using a scale from 1 (not painful) to 7 (very painful): The pain was greatest in the case of the wrists, knees and hip joints (mean 2.3) and slightly less in the shoulder (mean 2.1).

A multi-center trial which included 470 patients showed essentially similar results [55]: Local tolerance was reported by the treating physician to be "good" in 98% of the examinations and "satisfactory" in 2%. General tolerance was reported to be "excellent" in 99% of the patients. "Patient cards" completed by the patients over 3 days were also used in this study. They revealed a continuous, highly significant decrease in patients' complaints (e.g., feeling of pressure in the joint and pain on moving) during the first 2 days after MRA. Using the same pain assessment scale the mean value of the pain of the examination was 2.8.

Two more recent studies on patients' perception and discomfort during MRA revealed that the pain and discomfort were worse than expected in only 6% and 1% of the patients, respectively, in a total of 315 patients [56, 57]. In one of these studies, which included 202 patients undergoing MRA of the shoulder, the arthrography-related discomfort was rated as less uncomfortable than MRI-related discomfort in 40% of the patients while 34% rated the discomfort of the two imaging methods to be equal [57].

Contamination of the joint with pathogens during the procedure is the major complication of joint puncture; this complication is, however, a risk of MRA compared with plain MRI and is independent of the type of substance being injected into the joint. For comparison, the infection rate for arthrography is reported to be 0.003% [73]. Infection rates of arthroscopy have been reported to range from 0 to 3.4% [74, 75].

No reports exist on "serious adverse events", such as anaphylactic shock or other events requiring treatment in an intensive care unit or hospitalization.

For systemic safety, and thus the possible influence on laboratory parameters, the total amount of Gd-DTPA applied is more important than the local concentration in one joint. Because of the much lower whole body dose of intra-articularly applied Gd-DTPA it is fair to say that laboratory changes are extremely unlikely, since no systematic changes have been described even for the usual intravenous dose (more than 20 million i.v. applications) [76].

The main risk factor for contrast-medium-induced renal failure is pre-existing impairment of renal function, the severity of which can be assessed from the serum creatinine values. Neither a prospective study in patients with various degrees of renal impairment nor a meta-analysis of phase III studies with Gd-DTPA [76] indicate any effect on kidney function after intravenous injection of Gd-DTPA in a concentration of 0.1 mmol/kg body weight. According to information from the manufacturers, there are sporadic reports regarding acute renal failure after i.v. injection of Gd-DTPA. Since the maximum whole body dose after intra-articular administration is much lower than the maximum permissible and approved intravenous dose, as described above, acute renal failure after intra-articular administration of Gd-DTPA is very unlikely.

According to the literature, no specific examination of the tolerance of Gd-DTPA in patients with impaired liver function exists, probably because the proportion of extrarenal elimination is very small [69].

No detailed report exists of experience regarding the tolerance of an intra-articular Gd-DTPA injection during pregnancy and in lactating women.

One study has investigated the excretion of Gd-DTPA into the breast milk after intravenous application of a dose of 0.1 mmol/kg body weight in 20 lactating women [77]. The cumulative amount of gadolinium excreted in breast milk during 24 h was measured. Administration of Gd-DTPA was well tolerated without any adverse events in all cases. The excreted dose was less than 0.04% (i.e., 0.003 mmol) of the applied intravenous Gd-DTPA dose. This is more than 100 times less than the permitted intravenous dose of 0.2 mmol/kg body weight for neonatal imaging. Suspension of breast feeding after intra-articular administration of 2 mmol/l Gd-DTPA is therefore not necessary.

## Conclusions

Detailed analysis of 52 original papers on MRA in all clinically relevant joints, observation of discussions of the diagnostic efficacy of MRA at all the major scientific conferences of the last few years, and our own observations over the last 6 years allow the following conclusions:

Two millimoles per liter has proved to be the best concentration for intra-articular administration of Gd-

DTPA and is used by the vast majority of investigators. The total quantity to be injected depends on the size of the joint. The detection rate of several pathological processes, conspicuity and visualization of lesions with MR arthrography using Gd-DTPA 2 mmol/l are better than with plain MRI in different joints. Intra-articular MRA with Gd-DTPA 2 mmol/l is superior to i.v. MRA because the distension of the joint capsule allows more precise diagnosis of tears (labrum, meniscus) and ruptures (e.g., supraspinatus tendon). MRA with Gd-DTPA 2 mmol/l has proved to be the diagnostic imaging gold standard for the majority of joints and for numerous problems. This is particularly true for the shoulder (labral lesions, rotator cuff rupture), the hip (labral lesions) and the knee (chondral and meniscal lesions). In the ankle, wrist, and finger joints it is reserved for special problems. Its use is not firmly established in the latter two joints because of less common indications and the resulting lower examination rate.

Furthermore, in order to assess the safety or the influence of intra-articular administration of Gd-DTPA 2 mmol/l on the safety parameters, it is permissible to resort to the existing, extensive data over more than 10 years with the i.v. administration of Gd-DTPA, since the pharmacodynamics and pharmacokinetics of Gd-DTPA apply after diffusion from the joint.

The side effects of intra-articular Gd-DTPA administration in a concentration of 2 mmol/l are predominantly related to the puncture of the joint and its filling with fluid, and consequently considered to be the general tolerance symptoms of any type of arthrography.

No extensive studies exist regarding the effect of the intra-articular administration of Gd-DTPA on the clinico-chemical parameters, particularly in patients with impaired kidney or liver function. Because of the identical (renal) elimination of Gd-DTPA after intravenous and intra-articular application, the extensive experience with i.v. application is valid. There is no contraindication to the intra-articular administration of Gd-DTPA 2 mmol/l in acute or chronic renal failure. This also applies to patients with reduced liver function. There is no scientific evidence that the intra-articular administration of Gd-DTPA 2 mmol/l has to be contraindicated in the presence of known allergic reaction to i.v. Gd-DTPA. However, we recommend restraint and surveillance of the patient during the examination.

## References


1. Flannigan B, Kursunoglu-Brahme S, Snyder S, et al. MR arthrography of the shoulder: comparison with conventional MR imaging. AJR Am J Roentgenol 1990; 155:829–832.
2. Zanetti M, Hodler J. Contrast media in MR arthrography of the glenohumeral joint: intra-articular gadopentetate vs saline: preliminary results. Eur Radiol 1997; 7:498–502.
3. Tirman PF, Stauffer AE, Crues JV III, et al. Saline magnetic resonance arthrography in the evaluation of glenohumeral instability. Arthroscopy 1993; 9:550–559.
4. Willemsen UF, Wiedemann E, Brunner U, et al. Prospective evaluation of MR arthrography performed with high-volume intraarticular saline enhancement in patients with recurrent anterior dislocations of the shoulder. AJR Am J Roentgenol 1998; 170:79–84.
5. Binkert CA, Zanetti M, Gerber C, Hodler J. MR arthrography of the glenohumeral joint: two concentrations of gadoteridol versus Ringer solution as the intraarticular contrast material. Radiology 2001; 220:219–224.
6. Chandnani VP, Gagliardi JA, Murane TG, et al. Glenohumeral ligaments and shoulder capsular mechanisms: evaluation with MR arthrography. Radiology 1995; 196:27–32.
7. Zanetti M, Weishaupt D, Gerber C, et al. Tendinopathy and rupture of the tendon of the long head of the biceps brachii muscle: evaluation with MR arthrography. AJR Am J Roentgenol 1998; 170:1557–1561.
8. Bachmann G, Bauer T, Jürgensen I, et al. The diagnostic accuracy and therapeutic relevance of CT arthrography and MRI arthrography of the shoulder (in German). RoFo Fortschr Geb Roentgenstr Bildgeb Verf 1998; 108:149–56.
9. Chandnani VP, Yeager TD, DeBerardino T, et al. Glenoid labral tears: prospective evaluation with MR imaging, MR arthrography and CT arthrography. AJR Am J Roentgenol 1993; 161:1229–1235.
10. Tirman PFJ, Bost FW, Steinbach LS, et al. MR arthrographic depiction of tears of the rotator cuff: benefit of abduction and external rotation of the arm. Radiology 1994; 192:851–856.
11. Bradley YC, Chandnani VP, Gagliardi JA, et al. Partial thickness supraspinatus tears: diagnosis by magnetic resonance arthrography. Australas Radiol 1995; 39:124–127.
12. Jee WH, McCauley TR, Katz LD, et al. Superior labral anterior posterior (SLAP) lesions of the glenoid labrum: reliability and accuracy of MR arthrography for diagnosis. Radiology 2001; 218:127–132.
13. Pfirrman CWA, Zanetti M, Weishaupt D, Gerber C, Hodler J. Subscapularis tendon tears: detection and grading at MR arthrography. Radiology 1999;213:709–714.
14. Kramer J, Recht MP, Imhof H, et al. Post-contrast MR arthrography in assessment of cartilage lesions. J Comput Assist Tomogr 1994; 18:218–223.
15. Applegate GR, Flannigan BD, Tolin BS, et al. MR diagnosis of recurrent tears in the knee: value of intra-articular contrast material. AJR Am J Roentgenol 1993; 161:821–825.
16. Giovagnoni A, Valeri G, Ercolani P, et al. Magnetic resonance arthrography in chondral knee conditions. Radiol Med 1995; 90:219–225.
17. Gagliardi JA, Chung EM, Chandnani VP. Detection and staging of chondromalacia patellae: relative efficacies of conventional MR imaging, MR arthrography and CT arthrography. AJR Am J Roentgenol 1994; 163:629–636.
18. Kovanlikaya I, Camil D, Cakmakci H, et al. Diagnostic value of MR arthrography in detection of intrinsic carpal ligament lesions: use of cine-MR arthrography as a new approach. Eur Radiol 1997; 7:1441–1445.

19. Schweitzer ME, Brahme SK, Hodler J, et al. Chronic wrist pain: SE and Short Tau IR MRI and conventional and MR arthrography Radiology 1992; 182:205–211.
20. Scheck RJ, Kubitzek C, Hierner R, et al. The scapholunate interosseous ligament in MR arthrography of the wrist: correlation with non-enhanced MRI and wrist arthroscopy. Skeletal Radiol 1997; 26:263–271.
21. Chandnani VP, Harper MT, Ficke JR, et al. Chronic ankle instability: evaluation with MR arthrography, MR imaging, and stress radiography. Radiology 1994; 192:189–194.
22. Robinson P, White LM, Salonen DC, Daniels TR, Ogilvie-Harris D. Anterolateral ankle impingement: MR arthrographic assessment of the anterolateral recess. Radiology 2001; 221:186–190.
23. Czerny C, Kramer J, Neuhold A, et al. Magnetresonanztomographie und Magnetresonanzarthrographie des Labrum acetabulare: Vergleich mit operativen Ergebnissen. RoFo Fortschr Geb Roentgenstr Bildgeb Verf 2001; 173:702–707
24. Palmer WE, Caslowitz PL. Anterior shoulder instability: diagnostic criteria determined from prospective analysis of 121 MR arthrograms. Radiology 1995; 197:819–825.
25. Cvitanic O, Tirman PFJ, Feller JF, et al. Using abduction and external rotation of the shoulder to increase the sensitivity of MR arthrography in revealing tears of the anterior glenoid labrum. AJR Am J Roentgenol 1997; 169:837–844.
26. Bencardino JT, Beltran J, Rosenberg ZS, et al. Superior labrum anterior-posterior lesions: diagnosis with MR arthrography of the shoulder. Radiology 2000; 214:267–271.
27. Palmer WE, Brown JH, Rosenthal DI. Labral-ligamentous complex of the shoulder: evaluation with MR arthrography. Radiology 1994; 190:645–651.
28. Sanders TG, Tirman PF, Linares R, et al. The glenolabral articular disruption lesion: MR arthrography with arthroscopic correlation. AJR Am J Roentgenol 1999; 172:171–175.
29. Hodler J, Kursunoglu-Brahme S, Snyder SJ, et al. Rotator cuff disease: assessment with MR arthrography versus standard MR imaging in 36 patients with arthroscopic confirmation. Radiology 1992; 182:431–436.
30. Palmer WE, Brown JH, Rosenthal DI. Rotator cuff: evaluation with fat suppressed MR arthrography. Radiology 1993; 188:683–687.
31. Lill H, Lange K, Reinbold WD, et al. MRT arthrography. Improved diagnostic procedure in shoulder instability (in German). Unfallchirurgie 1997;100:186–190.
32. Löw R, Kreitner KF, Runkel M, et al. Low-field MR arthrography of the shoulder: early results using an open 0.2 T MR system (in German). RoFo Fortschr Geb Roentgenstr Bildgeb Verf 1998; 168:316–322.
33. Roger B, Skaf A, Hooper AW, Lektrakul N, Yeh L, Resnick D. Imaging findings in the dominant shoulder of throwing athletes: comparison of radiography, arthrography, CT arthrography, and MR arthrography with arthroscopic correlation. AJR Am J Roentgenol 1999;172:1371–1380.
34. Kreitner KF, Gerbe P, Kersjes W, et al. MR arthrography of the shoulder: possible indications for clinical use (in German). RoFo Fortschr Geb Roentgenstr Bildgeb Verf 1994; 160:137–142.
35. Hodler J, Kursunoglu-Brahme S, Flannigan B, et al. Injuries of the superior portion of the glenoid labrum involving the insertion of the biceps tendon: MR findings in 9 cases. AJR Am J Roentgenol 1992; 159:565–568.
36. Tirman PFJ, Bost FW, Garvin GJ, et al. Posteriosuperior glenoid impingement of the shoulder: findings at MR imaging and MR arthrography with arthroscopic correlation. Radiology 1994; 193:431–436.
37. Hottya GA, Tirman PF, Bost FW, et al. Tear of the posterior shoulder stabilizers after posterior dislocation: MR imaging and MR arthrographic findings with arthroscopic correlation. AJR Am J Roentgenol 1998; 171:763–768.
38. Engel A, Kramer J, Nehrer S. Proton spin tomography in meniscus diagnosis (in German). Orthopaede 1994; 23:112–116.
39. Engel A, Kramer J, Stiglbauer R, et al. Articular cartilage defect detectability in human knees with MR-arthrography. Eur Radiol 1993; 3:161–165.
40. Kramer J, Stiglbauer R, Engel A, et al. MR Contrast arthrography (MRA) in osteochondritis dissecans. J Comput Assist Tomogr 1992; 16:254–260.
41. Sciulli RL, Boutin RD, Brown RR, et al. Evaluation of the postoperative meniscus of the knee: a study comparing conventional arthrography, conventional MR imaging, MR arthrography with iodinated contrast material and MR arthrography with gadolinium-based contrast material. Skeletal Radiol 1999; 28:508–514.
42. Scheck RJ, Romagnolo A, Hierner R, et al. The carpal ligaments in MR arthrography of the wrist: correlation with standard MRI and wrist arthroscopy. J Magn Reson Imaging 1999; 9:468–474.
43. Zanetti M, Bräm J, Hodler J. Triangular fibrocartilage and intercarpal ligaments of the wrist: does MR arthrography improve standard MRI? J Magn Reson Imaging 1997; 7:590–594.
44. Czerny C, Hofmann S, Neuhold A, et al. Lesions of the acetabular labrum: accuracy of MR imaging and MR arthrography in detection and staging. Radiology 1996; 200:225–230.
45. Petersilge CA, Haque MA, Petersilge WJ, et al. Acetabular labral tears: evaluation with MR arthrography. Radiology 1996; 200:231–235.
46. Harper MT, Chandnani VP, Spaeth J, et al. Gamekeeper's thumb: diagnosis of ulnar collateral ligament injury using magnetic resonance imaging, magnetic resonance arthrography and stress radiography. J Magn Reson Imaging 1996; 6:322–328.
47. Kopka L, Funke M, Fischer U, et al. MR arthrography of the shoulder with gadopentetate dimeglumine: influence of concentration, iodinated contrast material and time on signal intensity. AJR Am J Roentgenol 1994; 163:621–623.
48. Petersilge CA, Lewin JS, Duerk JL, Hatem SF. MR arthrography of the shoulder: rethinking traditional imaging procedures to meet the technical requirements of MR imaging guidance. AJR Am J Roentgenol 1997; 169:1453–1457.
49. Funke M, Kopka L, Vosshenrich J, et al. MR arthrography in the diagnosis of rotator cuff tears. Acta Radiol 1996; 37:627–632.
50. Kopka L, Funke M, Fischer U, et al. Signal characteristics of x-ray contrast media and their interaction with Gd-DTPA in MRT (in German). RoFo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr 1994; 160:349–352.
51. Rand T, Trattnig S, Breitenseher M, et al. Postoperative MR arthrography of the shoulder joint (in German). Radiologe 1996; 36:966–970.
52. Mayer DP, Schoenhaus H, Jay RM, et al. Magnetic resonance arthrography of the ankle. J Foot Surg 1992; 31:584–607.
53. Beaulieu CF, Ladd AL. MR arthrography of the wrist: scanning-room injection of the radiocarpal joint based on clinical landmarks. AJR Am J Roentgenol 1998; 170:606–608.

54. Dr Robert Heinz & Partner GmbH. Studie Magnevist 02. Klinische Prüfung der Phase III von Magnevist (Gadolinium-DTPA) zur Darstellung von kontrastierten Gelenken in der Kernspintomographie. 1995.
55. Dr Robert Heinz & Partner GmbH. Studie Magnevist 02. Ergebnisse einer offenen, unkontrollierten, multizentrischen klinischen Prüfung der Phase III mit Magnevist 2 mmol/l (Gadolinium-DTPA) zur Darstellung von kontrastierten Gelenken in der Kernspintomographie. 1996.
56. Robbins MI, Anzilotti Jr KF, Katz LD, Lange RC. Patient perception of magnetic resonance arthrography. Skeletal Radiol 2000;29: 265–269.
57. Binkert CA, Zanetti M, Hodler J. Patient's assessment of discomfort during MR arthrography of the shoulder. Radiology 2001; 221:775–778.
58. Rinck PA, Muller RN. Field strength and dose dependence of contrast enhancement by gadolinium-based MR contrast agents. Eur Radiol 1999; 9:998–1004.
59. Rinck PA, Fischer HW, van der Elst L, et al. Field-cycling relaxometry: medical applications. Radiology 1988; 168:843–849.
60. Hajek PC, Sartoris DJ, Neumann CH, et al. Potential contrast agents for MR arthrography: in vitro evaluation and practical observations. AJR Am J Roentgenol 1987; 149:97–104.
61. Speck U. Special characteristics of the contrast media for magnetic resonance imaging. In: Speck U. Contrast media. Berlin Heidelberg New York: Springer, 1999:84–87.
62. Turnheim K. Wasser und Elektrolyte. Therapie von Störungen des Wasser- und Elektrolythaushaltes sowie des Säure-Basen-Gleichgewichtes. In: Forth W, Henschler D, Rummel W, Starke K, eds. Allgemeine und spezielle Pharmakologie, 6th edn. Mannheim: BI Wissenschaftsverlag, 1992:410–415.
63. Drape JL, Thelen P, Gay-Dapassier P, et al. Intra-articular diffusion of Gd-DOTA after i.v. injection in the knee: MRI evaluation. Radiology 1993; 188:227–234.
64. Yamoto M, Tamai K, Yamaguchi T, et al. MRI of the knee in rheumatoid arthritis: Gd-DTPA perfusion dynamics. J Comput Assist Tomogr 1993; 17:781–785.
65. Kursunoglu-Brahme S, Riccio T, Weisman HM, et al. Rheumatoid knee: role of gadopentetate-enhanced MR-imaging. Radiology 1990; 176:831–835.
66. Engel A, Hajek P, Kramet J, et al. Magnetic resonance knee arthrography: enhanced contrast by gadolinium complex in the rabbit and in humans. Acta Orthop Scand Suppl 1990; 240:1–57.
67. Reiser M, Peters PE, Bongartz G, et al. MR-Arthrographie des Kniegelenkes nach intraartikulärer Gd-DTPA-Injektion. In: Lissner J, Doppman JL, eds. MR '89: 3. Int. Kernspintomographie Symposium Garmisch-Partenkirchen, January 1989. Cologne: Deutscher Ärzte-Verlag, 1990:16–21.
68. Jevtic V, Beravs K, Praprotnik T. Magnetic resonance arthrography (MR arthrography) of the shoulder joint: signal intensity changes of 2 mmol/1Gd-DTPA solution after 2, 6 and 24 hours. Sixth Scientific Meeting of the European Society of Musculoskeletal Radiology, Edinburgh, 6–9 October 1999, Abstract book, p 8.
69. Weinmann HJ. Eigenschaften von Gd-DTPA-Dimeglumin. In: Felix R, Heshiki A, Hosten N, Hricak H, eds. Monographie Magnevist. Berlin: Blackwell Wissenschaft, 1999:15.
70. Engel A, Hamilton G, Hajek P, Fleischmann D. In vitro uptake of 153-gadolinium and gadolinium complexes by hyaline articular cartilage. Eur J Radiol 1990; 11:104–106.
71. Brown RR, Clarke DW, Daffner RH. Is a mixture of gadolinium and iodinated contrast material safe during MR arthrography? AJR Am J Roentgenol 2000; 175:1087–1090.
72. Rössler H, Rüther W. In: Rössler H, Rüther W. Orthopädie. Munich: Urban & Schwarzenberg, 1997:28–29.
73. Newberg AH, Munn CS, Robbins AH. Complications of arthrography. Radiology 1985; 155:605–606.
74. Dick W, Glinz W, Henche HR, Ruckstuhl J, Wruhs O, Zollinger H. Complications of arthroscopy. A review of 3,714 cases. Arch Orthop Trauma Surg 1978; 92:69–73.
75. Bigliani LU, Flatow EL, Deliz ED. Complications of shoulder arthroscopy. Orthop Rev 1991; 20:743–751.
76. Niendorf HP, Alhassan A, Balzer T, Clauss W, Geens V. Sicherheit und Risiken von Gd-DTPA: klinische Erfahrungen nach über 20,000,000 Anwendungen. In: Felix R, et al. eds. Magnevist. Eine Monographie. Berlin: Blackwell Wissenschaft, 1999.
77. Kubik-Huch RA, Gottstein-Aalame NM, Frenzel T, et al. Gadopentetate dimeglumine excretion into human breast milk during lactation. Radiology 2000; 216:555–558.