Everyday Practice

MRI contrast media: What clinicians need to know

CHANDAN J. DAS, SOWMYA MAHALINGAM, JYOTINDU DEBNATH, SANJAY DHAWAN

ABSTRACT

Magnetic resonance imaging (MRI) is an imaging modality that uses the differential spinning of protons (hydrogen) in the body when exposed to an external magnetic field, to produce cross-sectional images of the body. The advent of MRI is a boon to mankind as it does not involve ionizing radiation and provides superior soft tissue contrast even without administration of contrast media. The contrast media used in MRI were developed many years after MRI was already in use, the first being gadopentetate dimeglumine—a non-specific extracellular gadolinium chelate. Extracellular agents are the most widely used, although tissue-specific agents have been developed and are used as problem-solving tools in specific conditions. Tolerance to gadolinium-based contrast agents is excellent. The tissue-specific agents do have some adverse effects, though none of them are life-threatening. However, identification of a condition called nephrogenic systemic fibrosis has forced a rethink about the liberal usage of MRI contrast agents.

Natl Med J Inda 2010;23:292–6

INTRODUCTION

Magnetic resonance imaging (MRI) has been known for its exquisite intrinsic soft tissue contrast resolution since it has been put in clinical use. The soft tissue contrast in the image depends to a great extent on the type of pulse sequence and acquisition parameters used in obtaining the images. It is on the basis of the different relaxation properties of tissues that MRI allows differentiation of normal from pathological tissues. However, if differences in relaxation times between contiguous healthy and pathological tissues are minimal, then differentiation by MRI becomes difficult. In these situations, the use of MRI contrast media helps to create a difference in the relaxation properties of various tissues and accentuates the contrast between normal and abnormal tissues, thus helping to characterize various abnormalities. MRI contrast media are either paramagnetic or superparamagnetic metal ions which alter the MR signal from the surrounding tissues depending on the concentration of the agent and the pulse sequence. These agents are also used to study perfusion and flow-related abnormalities and obtain functional information.

All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India
CHANDAN J. DAS, SOWMYA MAHALINGAM Department of Radiology

167 Military Hospital, Pathankot, Punjab, India
JYOTINDU DEBNATH

DCA Imaging Centre, New Delhi 110001, India
SANJAY DHAWAN

Correspondence to CHANDAN J. DAS; *docchandan17@gmail.com*

Before we discuss the MRI contrast media, we briefly review the magnetic properties of matter. There are 3 types of magnetic properties of matter: paramagnetism, diamagnetism and ferromagnetism. A *paramagnetic* substance has its own magnetic field and the local magnetic field of a paramagnetic molecule shortens the relaxation times of surrounding hydrogen nuclei. In clinical MRI, this relaxation enhancement effect of the paramagnetic agent (e.g. gadolinium) is utilized to enhance the MRI signal (on T_1-weighted images) from the concerned tissues. A *diamagnetic* substance creates a magnetic field opposite to an externally applied magnetic field causing a repulsive effect. *Ferromagnetic* substances include certain materials such as iron, cobalt, nickel, etc. which exhibit strong interactions with magnets and can be easily magnetized.

An ideal MRI contrast medium would have certain characteristics: (i) MRI signal directly proportional to the concentration of the contrast medium, (ii) strongly paramagnetic, (iii) chemically stable and non-reactive *in vivo*, (iv) should be quickly eliminated from the body.[1]

EVOLUTION OF MRI CONTRAST MEDIA

During the initial stages of development of MRI contrast media, various paramagnetic contrast agents were used. These included nitric oxide and paramagnetic ions such as elemental iron, manganese, cobalt, nickel, copper, etc. which had unpaired electrons in the inner orbits of the atom.[1] Subsequently, gadolinium was considered a potential MRI contrast media.[2] Gadolinium, a rare earth element of the lanthanide series, has 7 unpaired electrons and has the maximum paramagnetic effect. However, free gadolinium was found to be highly toxic and hence gadolinium had to be chelated with ethylenediaminetetraacetic acid (EDTA) or diethylenetriaminepentaacetic acid (DTPA) which formed stable complexes *in vivo* free from toxicity. In the early 1980s, various authors reported their initial experience of successfully using gadolinium chelates as an MRI contrast medium.[3–5] Soon, gadolinium-based contrast agents (GBCAs) became an important component of MRI of various regions of the body. Subsequently, many more gadolinium chelates with slightly differing physico-chemical properties, and non-gadolinium compounds were developed.

CLASSIFICATION

There are 2 main categories of MRI contrast agents, namely paramagnetic and superparamagnetic.

Paramagnetic contrast agents

Paramagnetic agents reduce the T_1 and T_2 relaxation times and increase tissue signal on T_1-weighted images (positive enhancers). Paramagnetic agents have been the most widely used intravascular

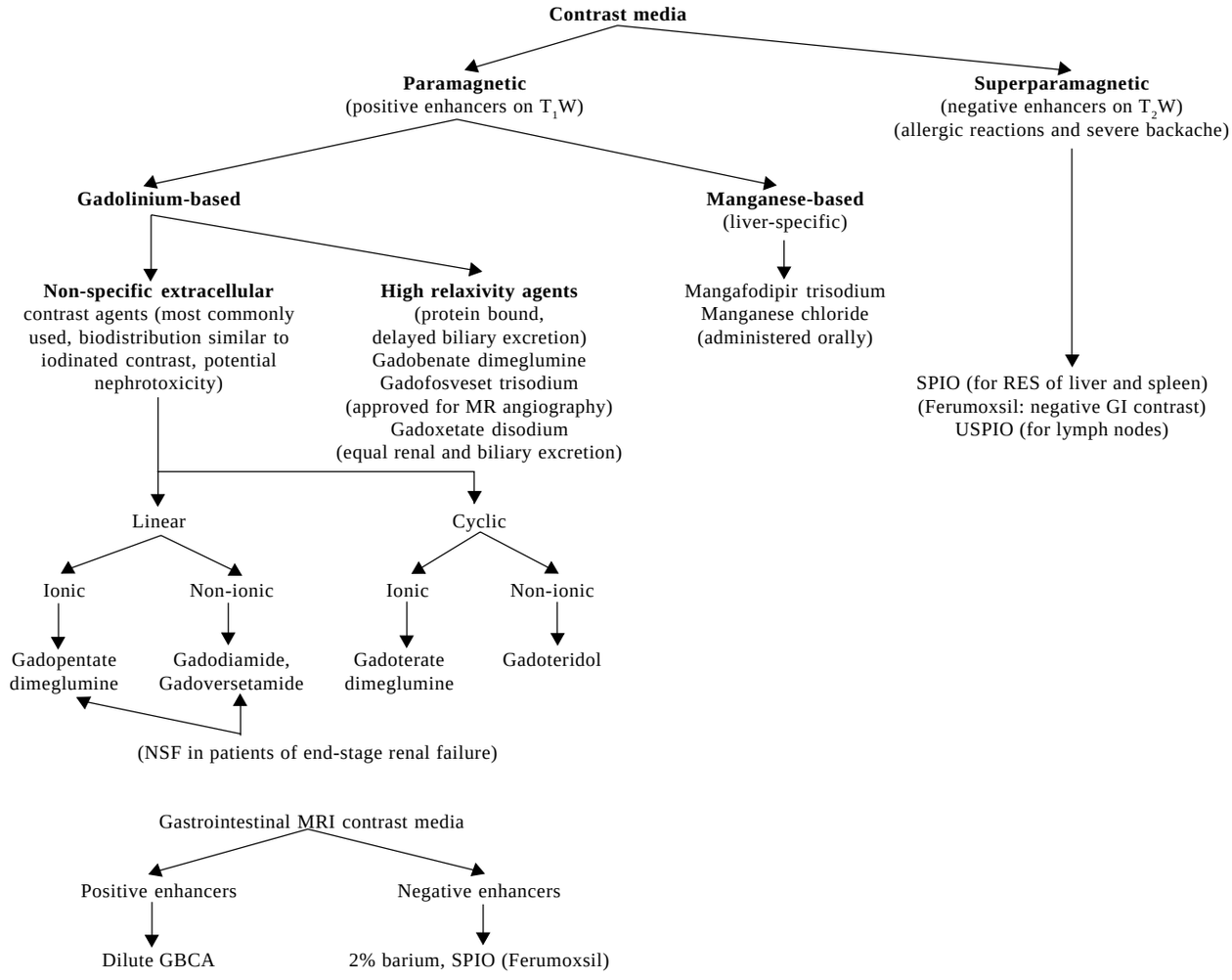

FIG 1. Contrast media used for magnetic resonance imaging
RES reticuloendothelial system NSF nephrogenic systemic fibrosis SPIO superparamagnetic iron oxide GI gastrointestinal
USPIO ultra-small superparamagnetic iron oxide GBCA gadolinium-based contrast agents

MRI contrast media. Most paramagnetic contrast agents have gadolinium as the active constituent. Manganese, which has relaxation properties similar to gadolinium, has also been used. As mentioned earlier, all paramagnetic contrast agents are chelated with an appropriate ligand to minimize *in vivo* toxicity of free gadolinium or manganese.

Gadolinium-based contrast agents (GBCAs). These are of 2 types: (i) non-specific extracellular gadolinium chelates (most commonly used); and (ii) high relaxivity agents. The non-specific extracellular gadolinium compounds do not bind to any protein; their biodistribution and pharmacokinetics are essentially similar to iodinated radiographic contrast agents. The high relaxivity agents bind to proteins and behave like non-specific extracellular gadolinium chelates immediately after the bolus injection, but show delayed biliary excretion. Hence, high relaxivity agents can be used for hepatobiliary imaging as well. Four subtypes of extracellular gadolinium chelates are now available: (i) linear ionic, e.g. gadopentate dimeglumine (Magnevist), (ii) linear non-ionic, e.g. gadodiamide (Omniscan), gadoversetamide (OptiMARK) (iii) cyclic ionic, e.g. gadoterate dimeglumine, (iv) cyclic non-ionic, e.g. gadoteridol (ProHance). Examples of high relaxivity agents include gadobenate dimeglumine (MultiHance), gadofosveset trisodium (Vasovist) and gadoxetate disodium (EOVIST, Primovist). Among the high relaxivity agents, gadoxetate disodium has the maximum biliary excretion (almost equal biliary and renal excretion) and has a convenient delayed imaging time of 10–20 minutes. Gadofosveset trisodium (Vasovist) remains in the blood pool for a long time. The prolonged circulation time allows for steady-state imaging as well as first-pass imaging. It has recently been approved for MR angiography in the USA.[6–10]

Manganese-based contrast agents. These are also known as liver-specific contrast agents, having manganese as the active constituent instead of gadolinium. Manganese is a powerful T_1 relaxation agent. Compared with gadolinium, manganese has higher intracellular uptake and T_1 relaxivity in liver tissue. At present, there are 2 manganese-based compounds, namely mangafodipir trisodium (Teslascan) and manganese chloride (LumenHance). Orally administered liposomal encapsulated manganese chloride reaches the liver via the portal circulation and results in reduction of T_1 relaxation in the liver tissues.

Superparamagnetic contrast agents

A superparamagnetic substance behaves in a manner similar to a paramagnetic substance. In clinical MRI practice, small or ultra-small particles of superparamagnetic iron oxide are used as contrast agents. There are 2 types of contrast agents based on superparamagnetic iron oxides: (i) superparamagnetic iron oxide (SPIO) used for the reticuloendothelial system (RES) of the liver and spleen; (ii) ultra-small superparamagnetic iron oxide (USPIO) used for imaging of lymph nodes. These iron oxide particles are coated with dextrans (e.g. ferumoxide) or carboxydextrans (e.g. ferucarbotran) to prevent uncontrolled aggregation of the magnetic crystals. Subsequent to intravenous injection, SPIO particles accumulate in the RES of the liver (Kupffer cells) and spleen. The SPIO particles in the RES of the liver and spleen reduce T_2 relaxation time and act as negative enhancers. With administration of SPIO, the normal liver appears dark on T_2-weighted images while lesions which are devoid of phagocytic cells stand out as bright. It is usually given as a slow infusion and imaging is done half an hour after the completion of infusion. Lymph node imaging is done 24–36 hours after the slow infusion of USPIO. Normal lymph nodes take up USPIO particles and appear dark in a T_2- or T_2*-weighted sequence, while diseased lymph nodes, e.g. metastatic lymph nodes do not show any change in signal intensity. Metastatic lymph nodes do not lose their signal intensity and appear uniformly or focally bright. When the hyperintense focus accounts for more than 30% of the nodal area, the node is considered metastatic. Sinerem and Combidex are two commercially available USPIO agents used to detect metastatic disease in the lymph nodes. Ferumoxsil (GastroMARK, Lumirem) is used as a negative oral contrast agent and improves visualization of adjacent abdominal tissues such as the pancreas and is particularly useful during magnetic resonance cholangiopancreatography (MRCP).[6,7,11,12]

Gastrointestinal contrast agents

A number of gastrointestinal MRI contrast media are available, but are used infrequently. They can be classified as positive or negative enhancers based on whether they increase or decrease the signal from the gastrointestinal (GI) lumen. They are also classified on the basis of their magnetic properties as paramagnetic, diamagnetic and superparamagnetic agents such as the intravascular contrast media.[13] Among various GI contrast media, dilute gadolinium-based solutions and dilute barium (which is diamagnetic) are commonly used due to their easy availability, low cost and tolerability. Gadolinium-based solutions act as positive enhancers while dilute barium (2%) acts as a negative contrast on T_1-weighted sequence. Superparamagnetic particles are another class of negative enteral contrast media particularly useful during MRCP examinations. With positive agents, native T_1 sequences without intravenous contrast provide the best quality images while with negative agents, intravenous contrast is advisable as the darkened lumen stands out against the bright wall, enabling detection of luminal wall thickening.[14] The usage of enteral contrast is specifically indicated in patients with inflammatory bowel disease and pancreatic imaging, where delineation of the duodenum helps in accurate diagnosis.[15] An ideal enteral contrast medium should have the following criteria: (i) uniform marking of the gastrointestinal tract, (ii) little or no absorption by the stomach or intestines, (iii) complete excretion, (iv) no motion or susceptibility artifacts and (v) easy availability/affordability.

SELECTING AN MRI CONTRAST MEDIUM

The availability of a wide variety of MRI contrast media necessitates an understanding of the properties as well as side-effects, to select a single contrast agent. Extracellular gadolinium-based contrast agents are by far the cheapest, most commonly available, most tolerable and most versatile. They allow lesion detection as well as characterization in a majority of cases. However, in a subgroup of patients, e.g. in a case of hepatocellular carcinoma (HCC), especially in a cirrhotic liver, small lesions are likely to be missed as the surrounding liver has heterogeneous enhancement. In this setting, SPIO plays an important role, as small lesions stand out as bright foci. In a grossly cirrhotic liver, due to poor phagocytic function, signal suppression is neither strong nor uniform enough to provide good contrast-to-noise ratio.[16] Fibrosis can cause false-positive as well as false-negative results as fibrosis with a round configuration can be mistaken for nodules and fibrotic areas can mask underlying nodules. To increase the detection of small HCCs, double contrast MRI is used.[17–20] This protocol consists of a bolus of gadolinium injected after an infusion of SPIO. These two agents are complementary to each other. While gadolinium detects lesions based on vascularity and hepatocyte uptake, SPIO detects lesions based on the lack of Kupffer cell activity. However, the exact role of double contrast imaging is yet to be established. Also, the procedure is more complex, expensive and is associated with the risk of exposing the patient to two contrast agents. At present, the consensus is that if a single contrast agent can be used, it should be a GBCA, preferably a hepatocyte-specific agent.

SAFETY OF MRI CONTRAST MEDIA

Adverse reactions following intravenous gadolinium contrast media are less common than with iodinated agents. Less than 1% of patients develop allergy-like or anaphylactoid reactions and most of these are mild, transient and self-limiting.[7] Risk factors for acute reactions include a history of allergy, bronchial asthma or previous reaction to MRI contrast media. Like any other drug, MRI contrast media can cause mild allergic reactions, nausea, flushing, headache, rash, etc. The superparamagnetic contrast agents, namely SPIO and USPIO, have allergic reactions, nausea, headache and flushing as their usual mild adverse reactions. An adverse effect unique to RES agents is severe backache, which may lead to discontinuation of the infusion in about 3% of patients. Also, the tolerability is less than that for gadolinium chelates. Manganese-based contrast agents have been associated with nausea, headache and pruritus. A potential long term neurological risk exists with mangafodipir trisodium, as free manganese is known to accumulate in certain parts of the brain.

Nephrotoxicity

GBCAs have long been considered as a safe alternative to iodine-based contrast media for various radiographic investigations including contrast-enhanced CT scan in patients with compromised renal functions. There are reports of the use of high doses (about 50–60 ml) of GBCA for pulmonary angiography in patients with compromised renal functions. [21,22] However, such reports drew substantial criticisms as well.[23,24] The issue of renal safety of gadolinium-based MR contrast agents remains controversial and has gained importance in the recent past as there are conflicting reports in the literature about the renal safety of GBCAs.[25–27] Most MR contrast agents have osmolalities that are approximately equal to or greater than those of commonly used low-osmolality iodinated contrast agents. Hence, one could expect GBCAs to be equally, if not more, potentially nephrotoxic when compared with equally efficacious volumes of low osmolality iodinated contrast agents. In practice, this situation usually does not arise because of

the low total volume of GBCAs used. Contrast-induced nephropathy (CIN) is rare with doses <0.3 mmol/kg body weight.[28,29] The European Society of Radiology does not recommend the use of high dose GBCA in patients with compromised renal functions.

Nephrogenic systemic fibrosis

Nephrogenic systemic fibrosis (NSF) has predominant cutaneous manifestations and is one of the most serious complications of GBCAs. It is a rare debilitating as well as lethal disease first reported and described in 2000, occurring in patients with end-stage renal failure who were on dialysis and who had been exposed to GBCAs in normal/high doses either once or on multiple occasions.[30] The pathophysiology of NSF is incompletely understood.

Of the 5 US FDA-approved GBCAs, gadodiamide (Omniscan), gadoversetamide (optiMARK) and gadopentetate (Magnevist) have been shown to be associated with NSF. These agents are thermodynamically unstable, gadodiamide being the most unstable. These ions get deposited in the skin and cause antigenic triggering in susceptible patients who have a combination of predisposing factors such as renal failure, acidosis and pro-inflammatory conditions.

The cutaneous manifestations are the first to develop, spread in a symmetrical caudo-cranial and distal-to-proximal manner involving the limbs. Erythema, oedema, papules, plaques and induration progress to fibrosis and contractures causing severe restriction of movement. There is fibrosis of the visceral organs and death occurs due to cardiac/pulmonary causes or worsening of renal failure.[31,32] At present, there is no complete cure for NSF. Few cases have shown disease remission after rapid reversal of renal failure.[33] The only partially effective treatment is improvement of renal function, although plasmapheresis and photopheresis have been tried.

The US FDA recommends avoidance of all gadolinium contrast media in patients with renal insufficiency grades 4 and 5 (glomerular filtration rate [GFR] <30 ml/minute per 1.73 m^2) or any grade of acute renal failure in liver transplantation patients or candidates. Some of the FDA and ACR guidelines[34] to prevent the occurrence of NSF are:

1. All patients referred for MRI should be pre-screened with a question enquiring about a history of renal disease and dialysis. Gadolinium-enhanced contrast MR should be replaced with an unenhanced study, if possible. If a contrast study is necessary and unavoidable, non-ionic and linear compounds should be replaced by an ionic and cyclic chelate such as gadobenate dimeglumine.
2. Gadodiamide (Omniscan) should be avoided in patients with any level of renal dysfunction.
3. In patients with GFR <60 ml/minute per 1.73 m^2 and those with acute renal injury, avoidance of GBCAs should be considered unless the benefit of a contrast-enhanced MR examination clearly outweighs the potential risks. If GBCAs are to be used in such patients, the lowest efficacious dose should be considered and the MR examination should be monitored.
4. If patients on haemodialysis receive GBCAs, immediate dialysis should be instituted preferably within 2 hours of the MR examination with a repeat dialysis at 24 hours. Although haemodialysis as well as peritoneal dialysis can remove the chelates, haemodialysis is more effective. If the patient is on peritoneal dialysis, there should be no period of 'dry' abdomen in the immediate post-study period.[6,7,35]

CONCLUSION

At present, gadolinium chelates (non-specific extracellular contrast agents) are the most widely used. They are easily available, have good tolerability and provide for excellent lesion detection and characterization. The main concern with GBCAs is NSF, which occurs only in end-stage renal failure. For specific indications, tissue-specific agents such as hepatobiliary, lymph node-specific and blood-pool agents are available. Most of these tissue-specific agents have been introduced recently, are expensive and their long term effects are not known. In India, only gadolinium chelates are available.

REFERENCES

1 Brasch RC. Work in progress: Methods of contrast enhancement for NMR imaging and potential applications. A subject review. *Radiology* 1983;**147:**781–8.
2 Weinmann HJ, Brasch RC, Press WR, Wesbey GE. Characteristics of gadolinium–DTPA complex: A potential NMR contrast agent. *AJR Am J Roentgenol* 1984;**142:**619–24.
3 Laniado M, Weinmann HJ, Schörner W, Felix R, Speck U. First use of GdDTPA/dimeglumine in man. *Physiol Chem Phys Med NMR* 1984;**16:**157–65.
4 Carr DH, Brown J, Bydder GM, Steiner RE, Weinmann HJ, Speck U, *et al*. Gadolinium–DTPA as a contrast agent in MRI: Initial clinical experience in 20 patients. *AJR Am J Roentgenol* 1984;**143:**215–24.
5 Felix R, Schörner W, Laniado M, Niendorf HP, Claussen C, Fiegler W, *et al*. Brain tumors: MR imaging with gadolinium–DTPA. *Radiology* 1985;**156:**681–8.
6 Lin SP, Brown JJ. MR contrast agents: Physical and pharmacologic basics. *J Magn Reson Imaging* 2007;**25**:884–99.
7 Thomson HS, Webb JAW. Contrast media: Safety issues and EUSR guidelines. In: Baert AL, Knauth M (eds). *Medical radiology: Diagnostic imaging*. 2nd revised ed. Berlin:Springer; 2009:153–205.
8 Hamm B, Staks T, Mühler A, Bollow M, Taupitz M, Frenzel T, *et al*. Phase I clinical evaluation of Gd-EOB-DTPA as a hepatobiliary MR contrast agent: Safety, pharmacokinetics, and MR imaging. *Radiology* 1995;**195:**785–92.
9 Vogl TJ, Pegios W, McMahon C, Balzer J, Waitzinger J, Pirovano G, *et al*. Gadobenate dimeglumine—a new contrast agent for MR imaging: Preliminary evaluation in healthy volunteers. *AJR Am J Roentgenol* 1992;**158:**887–92.
10 Rofsky NM, Earls JP. Mangafodipir trisodium injection (Mn-DPDP). A contrast agent for abdominal MR imaging. *Magn Reson Imaging Clin N Am* 1996;**4:**73–85.
11 Stark DD, Weissleder R, Elizondo G, Hahn PF, Saini S, Todd LE, *et al*. Superparamagnetic iron oxide: Clinical application as a contrast agent for MR imaging of the liver. *Radiology* 1988;**168:**297–301.
12 Winter TC 3rd, Freeny PC, Nghiem HV, Mack LA, Patten RM, Thomas CR Jr, *et al*. MR imaging with i.v. superparamagnetic iron oxide: Efficacy in the detection of focal hepatic lesions. *AJR Am J Roentgenol* 1993;**161:**1191–8.
13 Hahn PF. Advances in contrast-enhanced MR imaging. Gastrointestinal contrast agents. *AJR Am J Roentgenol* 1991;**156:**252–4.
14 Rieber A, Aschoff A, Nüssle K, Wruk D, Tomczak R, Reinshagen M, *et al*. MRI in the diagnosis of small bowel disease: Use of positive and negative oral contrast media in combination with enteroclysis. *Eur Radiol* 2000;**10:**1377–82.
15 Low RN, Francis IR. MR imaging of the gastrointestinal tract with i.v., gadolinium and diluted barium oral contrast media compared with unenhanced MR imaging and CT. *AJR Am J Roentgenol* 1997;**169:**1051–9.
16 Elizondo G, Weissleder R, Stark DD, Guerra J, Garza J, Fretz CJ, *et al*. Hepatic cirrhosis and hepatitis: MR imaging enhanced with superparamagnetic iron oxide. *Radiology* 1990;**174:**797–801.
17 Hanna RF, Kased N, Kwan SW, Gamst AC, Santosa AC, Hassanein T, *et al*. Double-contrast MRI for accurate staging of hepatocellular carcinoma in patients with cirrhosis. *AJR Am J Roentgenol* 2008;**190:**47–57.
18 Bhartia B, Ward J, Guthrie JA, Robinson PJ. Hepatocellular carcinoma in cirrhotic livers: Double-contrast thin-section MR imaging with pathologic correlation of explanted tissue. *AJR Am J Roentgenol*. 2003;**180:**577–84.
19 Qayyum A, Thoeni RF, Coakley FV, Lu Y, Guay JP, Ferrell LD. Detection of hepatocellular carcinoma by ferumoxides-enhanced MR imaging in cirrhosis: Incremental value of dynamic gadolinium-enhancement. *J Magn Reson Imaging* 2006;**23:**17–22.
20 Ward J, Guthrie JA, Scott DJ, Atchley J, Wilson D, Davies MH, *et al*. Hepatocellular carcinoma in the cirrhotic liver: Double-contrast MR imaging for diagnosis. *Radiology* 2000;**216:**154–62.
21 Remy-Jardin M, Dequiedt P, Ertzbischoff O, Tillie-Leblond I, Bruzzi J, Duhamel A, *et al*. Safety and effectiveness of gadolinium-enhanced multi-detector row spiral CT angiography of the chest: Preliminary results in 37 patients with contraindications to iodinated contrast agents. *Radiology* 2005;**235:**819–26.
22 Remy-Jardin M, Bahepar J, Lafitte JJ, Dequiedt P, Ertzbischoff O, Bruzzi J, *et al*. Multi-detector row CT angiography of pulmonary circulation with gadolinium-based contrast agents: Prospective evaluation in 60 patients. *Radiology* 2006;**238:**1022–35.

23 Morcos SK, Remy-Jardin M. Gadolinium-based contrast media for multi-detector row spiral CT pulmonary angiography in patients with renal insufficiency. *Radiology* 2006;**238:**1077; author reply 1077–8.
24 Nyman U, Elmståhl B, Leander P. Suggesting gadolinium-based contrast media for CT in azotemic patients is not based on historical, clinical, and experimental data. *Radiology* 2007;**244:**622–3.
25 Boyden TF, Gurm HS. Does gadolinium-based angiography protect against contrast-induced nephropathy?: A systematic review of the literature. *Catheter Cardiovasc Interv* 2008;**71:**687–93.
26 Perazella MA. Current status of gadolinium toxicity in patients with kidney disease. *Clin J Am Soc Nephrol* 2009;**4:**461–9. Review. Erratum in: *Clin J Am Soc Nephrol* 2009;**4:**866.
27 Ledneva E, Karie S, Launay-Vacher V, Janus N, Deray G. Renal safety of gadolinium-based contrast media in patients with chronic renal insufficiency. *Radiology* 2009;**250:**618–28.
28 Ergün I, Keven K, Uruç I, Ekmekçi Y, Canbakan B, Erden I, *et al*. The safety of gadolinium in patients with stage 3 and 4 renal failure. *Nephrol Dial Transplant* 2006;**21:**697–700.
29 Thomsen HS. Gadolinium-based contrast media may be nephrotoxic even at approved doses. *Eur Radiol* 2004;**14:**1654–6.
30 Cowper SE, Robin HS, Steinberg SM, Su LD, Gupta S, LeBoit PE. Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. *Lancet* 2000;**356:**1000–1.
31 Mendoza FA, Artlett CM, Sandorfi N, Latinis K, Piera-Velazquez S, Jimenez SA. Description of 12 cases of nephrogenic fibrosing dermopathy and review of the literature. *Semin Arthritis Rheum* 2006;**35:**238–49.
32 Shabana WM, Cohan RH, Ellis JH, Hussain HK, Francis IR, Su LD, *et al*. Nephrogenic systemic fibrosis: A report of 29 cases. *AJR Am J Roentgenol* 2008;**190:**736–41.
33 Cowper SE. Nephrogenic systemic fibrosis: The nosological and conceptual evolution of nephrogenic fibrosing dermopathy. *Am J Kidney Dis* 2005;**46:**763–5.
34 Kanal E, Barkovich AJ, Bell C, Borgstede JP, Bradley WG Jr, Froelich JW, *et al*. ACR Blue Ribbon Panel on MR Safety. ACR guidance document for safe MR practices: 2007. *AJR Am J Roentgenol* 2007;**188:**1447–74.
35 Joffe P, Thomsen HS, Meusel M. Pharmacokinetics of gadodiamide injection in patients with severe renal insufficiency and patients undergoing hemodialysis or continuous ambulatory peritoneal dialysis. *Acad Radiol* 1998;**5:**491–502.