**Table C-17. Harms from MRI in included non-pancreatic-cancer studies**

| **Study** | **Study Design** | **N Patients** | **Diagnosis** | **Age, Years (Mean±SD)** | **% Male** | **N Harmed (%)** | **Adverse Events** | **Notes** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Semelka et al. 201396 | Proof-of-concept | 59 | Patients with orders for brain or abdominal MRI scans | 52 (range, 5–85) | 52.5 | 0 | Not applicable | Setting: Department of Radiology at a U.S. university hospitalTiming: NRCA: gadobutrol (Gadavist; Bayer) vs. gadobenate dimeglumine (MultiHance; Bracco) |
| Albiin et al. 201297 | Efficacy | 3131 patients received 0.8 g and 0.4 g, 30 patients received 0.2 g | Healthy | 24.3 (range, 18–48) | 56.2% | ≥1 AE25 (80.6%) at 0.8 g, 18 (58.1%) at 0.4 g, and 10 (33.3%) at 0.2 g≥1 ADR22 (71.0%) at 0.8 g, 13 (41.9%) at 0.4 g, and 7 (23.3%) at 0.2 g | Mild ADRs/AEs32 at 0.8 g, 14 at 0.4 g, 6 at 0.2gModerate ADRs/AEs6 at 0.8 g, 1 at 0.4 g, 1 at 0.2 gSevere ADRs/AEs1 at 0.8 g, 1 at 0.2 gMost common ADRs were diarrhea, nausea, headache and fatigue. | Setting: University hospital, SwedenTiming: Feb. to May 2010CA: manganese chloride tetrahydrate (CMC-001)“Liver MRI using 0.8 g CMC-001 has the highest efficacy and still acceptable ADRs and should therefore be preferred.” |

|  **Table C-17. Harms from MRI in included non-pancreatic-cancer studies (continued)** |
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| **Study** | **Study Design** | **N Patients** | **Diagnosis** | **Age, Years (Mean±SD)** | **% Male** | **N Harmed (%)** | **Adverse Events** | **Notes** |
| Bredart et al. 201298 | Prospective, non-randomized, multicenter | 365 | At risk for breast cancer | 59.1% <50 years, 26.9% 50–59 years, 14% ≥60 | 0 | NR  | Significant MRI discomfort was due to immobility (37.5%), lying in the tunnel (20.6%), noise of the machine (64.6%), or panic feelings during MRI (6.1%). | Setting: 21 cancer centers, teaching hospitals, or private clinics in FranceTiming: Nov. 2006 to June 2008 |
| Maurer et al. 201299 | Post-marketing surveillance | 84,62150% neurological exams, 12.2% internal organs, 32.1% musculo­skeletal system, 2.3% MR angio­graphies, 4.9% not specified | 19,354 (22.9%) were considered at risk11.4% history of allergies, 6.6% hypertension, 2.3% CHD, 1.9% CNS disorders, 1.3% bronchial asthma, 1.3% beta­blocker treatment, 1.2% cardiac insufficiency, 0.9% renal failure, 0.8% history of allergic reaction to contrast medium, 1.3% liver dysfunction, 1.3% other | 52.0±16.9 | 45.4 | 285 (0.34%)421 AEs | 65 different AEs were reported. 10 most common included nausea (0.2%), vomiting (0.1%) and less than 1% of patients had the following symptoms: pruritus, urticaria, dizziness, feeling of warmth, retching, sweating increased, paresthesia, and taste alteration. Serious AEs: 8 (<0.01%)3 of these patients had life-threatening AEs, 1 of the 3 had inpatient treatment. “A causal relationship with GD-DOTA was considered probable in 1 patient, possible in 4 patients, and doubtful in 3 patients.” | Setting: 129 German radiology centers Timing: Jan. 2004 to Jan. 2010CA: gadoteric acid (Gd‑DOTA, Dotarem®), manually injected in 74.5%, automated injection in 25.5%Classification: WHO Adverse Reaction Terminology (1998)Allergies and history of allergic reaction to contrast medium were significantly associated (at 0.001 level) with increased risk of adverse events. Renal failure, liver dysfunction or betablocker intake were not associated with increased risk of adverse events. |
| Voth et al. 2011100 | Integrated retrospective analysis (34 clinical studies) | 4,549Received gadobutrol (Gadovist/ Gadavist)1,844 received comparator contrast agents | Severe renal impairment:38 gadobutrol, 5 comparatorModerate renal impairment:328 gadobutrol, 132 comparatorMild renal impairment:846 gadobutrol, 416 comparatorImpaired liver function:214 gadobutrol, 82 comparatorCardiovascular disease:1,506 gadobutrol, 435 comparatorHistory of allergies:462 gadobutrolHistory of allergies to contrast agents:33 gadobutrol | 54.2±16.6 gadobutrol54.7±14.5 comparator | 58.5% gado­butrol52.7% compara­tor | 182 (4.0%) gadobutrol-related 74 of 1,844 (4.0%) related to comparators | Serious AEs: 2117 (0.4%) gadobutrol, 4 (0.2%) comparatorDrug-related serious AEs:1 (<0.1%) gadobutrol | Setting: 55.3% Europe, 7.2% U.S./Canada, 7.7% South/Central America, 29.6% Asia, 0.3% AustraliaTiming: Trials conducted between 1993 and 2009CA: gadobutrol (Gadovist/Gadavist); comparator contrast agents included gadopentetate dimeglumine (Magnevist, N= 912), gadoteridol(ProHance, N=555), gadoversetamide(OptiMark, N=227), orgadodiamide (Omniscan, N=150).Classification: MedDRA v. 12.1“Gadobutrol was well tolerated by patients with impaired liver or kidney function, and by patients with cardiovascular disease.” |
| Forsting and Palkowitsch 2010101 | Integrated retrospective analysis (6 clinical studies) | 14,29914.7% MRA  | NR | 53.7 | 46.6 | 78 (0.55%)82.4% occurred within 5 minutes of administration, 1 patient had an ADR 9 hours post-injection | Serious: 2 (0.01%) gadobutrol-related; 1 severe anaphylactoid reaction,1 itching/swelling of throatMost frequently reported: nausea (0.25%) | Setting: 300 radiology centers in Europe and CanadaTiming: 2000 to 2007CA: gadobutrol“Gadobutrol 1.0M is well tolerated and has a good safety profile. The occurrence of ADRs observed following the intravenous injection of gadobutrol is comparable with the published data of other Gd-based contrast agents.” |
| Ichikawa et al. 2010102 | Multicenter, open-label, prospective Phase III | 178 | Suspected focal hepatic lesions | 66 (range, 31–82) | 72.4 | 44 (24.7%) | Mild: 56Moderate: 6 | Setting: 15 radiology departments in JapanTiming: Aug. 2001 to July 2003CA: Combined unenhanced and gadoxetic acid disodium (Gd-EOB-DTPA) |
| Ishiguchi and Takahashi 2010103 | Post-marketing surveillance  | 3,444 | Liver disorder: 9.52%Kidney disorder: 2.85% | 1% <15 years, 58.51% 15 to <65 years, 40.30% ≥65 | 49.45 | 32 (0.93%) | Mild: 36 (0.49% gastrointestinal-related disorders most commonly reported)Moderate: 42 patients with nausea, 2 with abnormal liver function | Setting: Department of Radiology at a medical university in JapanTiming: March 2001 to March 2005CA: Gadoterate Meglumine (Gd-DOTA)“Statistically significant risk factors for experiencing adverse reactions were general condition, liver disorder, kidney disorder, complication, concomitant treatments, and Gd-DOTA dose.” |
| Leander et al. 2010104 | Crossover randomized | 18 | Healthy | 25.0 | 100 | 19 AEs | 19 mild gastrointestinal  | Setting: Swedish university hospitalTiming: NRCA: oral Manganese (McCl2) |
| Hammerstingl et al. 2009105 | Multicenter, Phase III, randomized, inter­individually controlled comparison | 572292 gadobutrol, 280 gadopentetate | Patients with known focal lesions of the liver or suspected liver lesions  | – | – | 24 (4.2%)10 (3.4%) gadobutrol, 21 (5.0%) gadopentetate | 4 AEs definitely related to agents, 14 AEs possibly/probably related to agentsNo serious or severe AEs were reported. | Setting: 25 centers in 8 European countriesTiming: NRCA: gadobutrol (Gadovist), gadopentetate (Magnevist) |
| Shah-Patel et al. 2009106 | Retro­spective chart review | 106,800 total49,731 MRI | NR | Range 18–86 | NR | 15 (0.03) | Mild: 4Itching or hivesModerate: 6Vomiting: 3, Lightheaded sensation: 1Fall: 1, Headache: 1Severe: 1Shortness of breath (before examination)Others: 4Infiltrations at IV site: 2Mild burns due to contact with magnetic resonance coil during the examination | Setting: Outpatient radiology in New York, NYTiming: over 4 yearsTotal harms: 59 (0.06%)CA: gadopentetate dimeglumine (Magnevist; Berlex)Patients requiring assistance from emergency medical services: 18 (31%) |

ADR=Adverse drug event; AE=adverse event; CA=contrast agent; CHD=coronary heart disease; CNS=central nervous system; Gd=gadolinium; Gd-DTPA=Gd-diethylenetriamine penta-acetic acid; MRA=magnetic resonance angiography; NR=not reported; NSF=nephrogenic systemic fibrosi