**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 hospital  Timing: NR  CA: gadobutrol (Gadavist; Bayer) vs. gadobenate dimeglumine (MultiHance; Bracco) |
| Albiin et al. 201297 | Efficacy | 31  31 patients received 0.8 g and 0.4 g, 30 patients received 0.2 g | Healthy | 24.3 (range,  18–48) | 56.2% | ≥1 AE 25 (80.6%) at 0.8 g, 18 (58.1%) at 0.4 g, and 10 (33.3%) at 0.2 g  ≥1 ADR 22 (71.0%) at 0.8 g, 13 (41.9%) at 0.4 g, and 7 (23.3%) at 0.2 g | Mild ADRs/AEs 32 at 0.8 g, 14 at 0.4 g, 6 at 0.2g  Moderate ADRs/AEs 6 at 0.8 g, 1 at 0.4 g, 1 at 0.2 g  Severe ADRs/AEs 1 at 0.8 g, 1 at 0.2 g  Most common ADRs were diarrhea, nausea, headache and fatigue. | Setting: University hospital, Sweden  Timing: Feb. to May 2010  CA: 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 France  Timing: Nov. 2006 to June 2008 |
| Maurer et al. 201299 | Post-marketing surveillance | 84,621  50% 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 risk  11.4% 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. 2010  CA: 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) | 4,549  Received gadobutrol (Gadovist/ Gadavist)  1,844 received comparator contrast agents | Severe renal impairment: 38 gadobutrol, 5 comparator  Moderate renal impairment: 328 gadobutrol, 132 comparator  Mild renal impairment: 846 gadobutrol, 416 comparator  Impaired liver function: 214 gadobutrol, 82 comparator  Cardiovascular disease: 1,506 gadobutrol, 435 comparator  History of allergies: 462 gadobutrol  History of allergies to contrast agents: 33 gadobutrol | 54.2±16.6 gadobutrol  54.7±14.5 comparator | 58.5% gado­butrol  52.7% compara­tor | 182 (4.0%) gadobutrol-related  74 of 1,844 (4.0%) related to comparators | Serious AEs: 21  17 (0.4%) gadobutrol, 4 (0.2%) comparator  Drug-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% Australia  Timing: Trials conducted between 1993 and 2009  CA: gadobutrol (Gadovist/Gadavist);  comparator contrast agents included gadopentetate dimeglumine (Magnevist, N= 912), gadoteridol  (ProHance, N=555), gadoversetamide  (OptiMark, N=227), or  gadodiamide (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) | 14,299  14.7% 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 throat  Most frequently reported: nausea (0.25%) | Setting: 300 radiology centers in Europe and Canada  Timing: 2000 to 2007  CA: 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: 56  Moderate: 6 | Setting: 15 radiology departments in Japan  Timing: Aug. 2001 to July 2003  CA: 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: 4  2 patients with nausea, 2 with abnormal liver function | Setting: Department of Radiology at a medical university in Japan  Timing: March 2001 to March 2005  CA: 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 hospital  Timing: NR  CA: oral Manganese (McCl2) |
| Hammerstingl et al. 2009105 | Multicenter, Phase III, randomized, inter­individually controlled comparison | 572  292 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 agents  No serious or severe AEs were reported. | Setting: 25 centers in 8 European countries  Timing: NR  CA: gadobutrol (Gadovist), gadopentetate (Magnevist) |
| Shah-Patel et al. 2009106 | Retro­spective chart review | 106,800 total  49,731 MRI | NR | Range 18–86 | NR | 15 (0.03) | Mild: 4  Itching or hives  Moderate: 6  Vomiting: 3, Lightheaded sensation: 1 Fall: 1, Headache: 1  Severe: 1  Shortness of breath (before examination)  Others: 4  Infiltrations at IV site: 2  Mild burns due to contact with magnetic resonance coil during the examination | Setting: Outpatient radiology in New York, NY  Timing: over 4 years  Total 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