Orally Administered Mangoral (Manganese Chloride Tetrahydrate) And Intravenously Administered Gadobenate Dimeglumine For MRI Of Colorectal Liver Metastases - An Intraindividual Comparison

K. Shamsi[1], T. B. Brismar[2], N. Kartalis[2], G. T. Sica[3], P. Ramchandani[4], A. G. Gilet[5], N. Gupta[6], C. Bjartmar[7]

[1]Conshohocken, PA, [2]Stockholm, SWEDEN, [3]New York, NY, [4]Narberth, PA, [5]Chappaqua, NY, [6]Bryn Mawr, PA, [7]Malmo, SWEDEN.

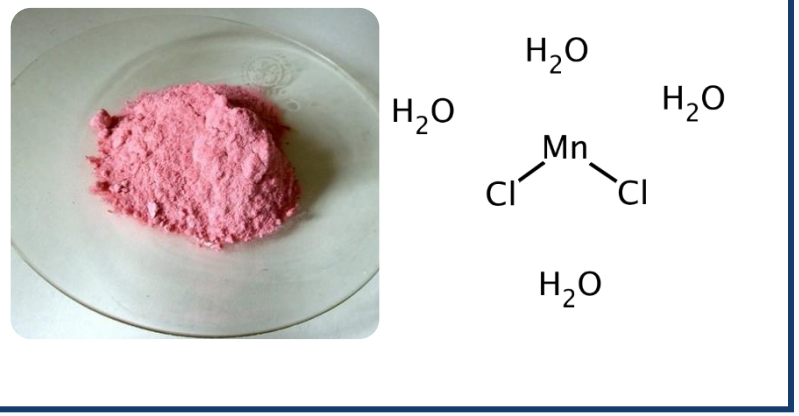
Disclosures

Kohkan Shamsi works as Consultant for Ascelia Pharma
Carl Bjartmar is an employee of Ascelia pharma

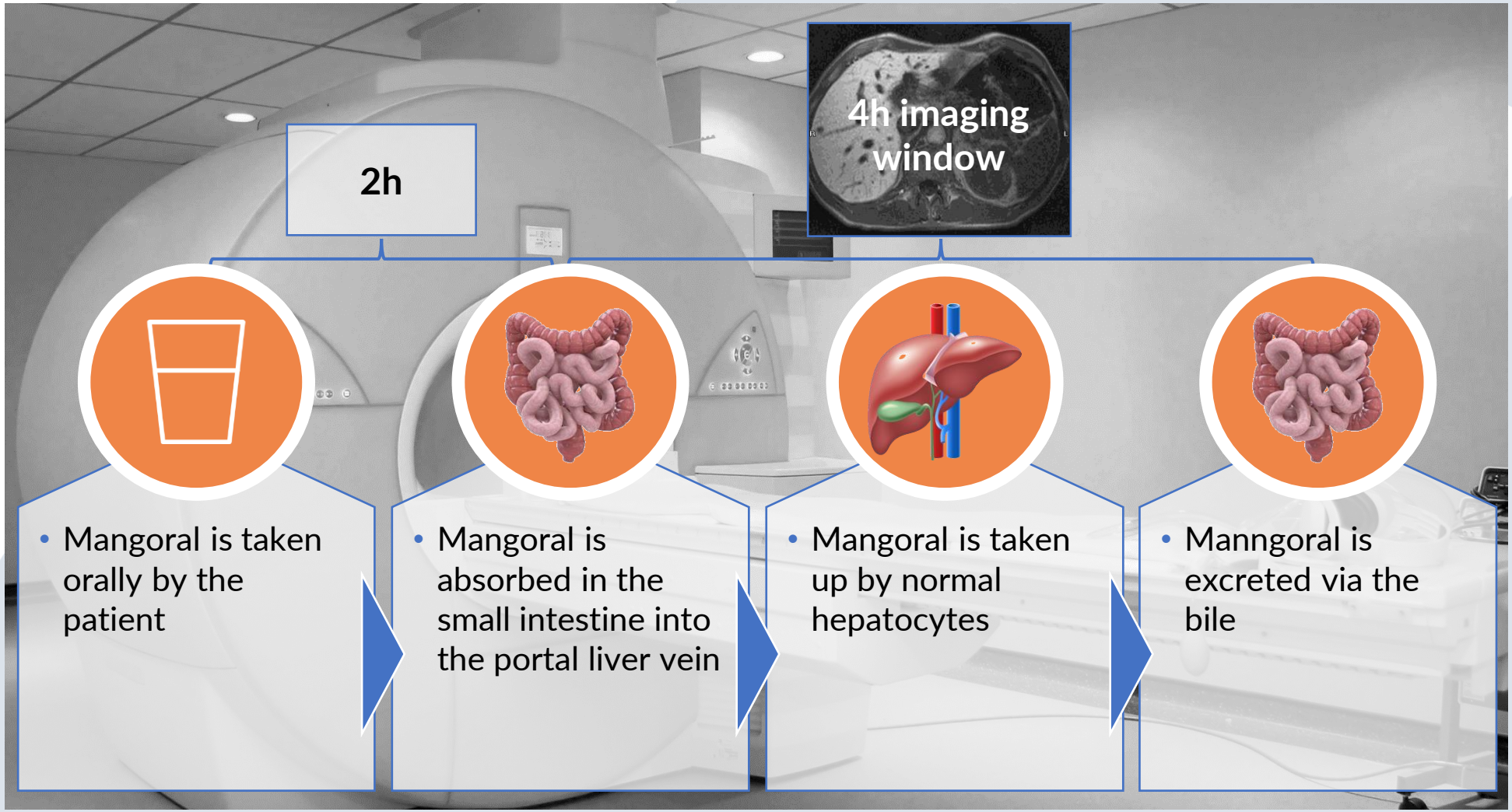
Mangoral – manganese-based oral liver specific MRI contrast agent

- Manganese (II) chloride tetrahydrate – a natural trace element
  - Also contains two absorption promoters, L-Alanine and Vitamin D3
  - Powder is mixed with 200 mL of water and is taken orally
- Phase II data has shown improved efficacy of Mangoral compared to unenhanced MRI and good safety profile
- It is being developed as liver contrast agent in patients with impaired renal function – phase III study is ongoing

Manganese (II) chloride tetrahydrate



Mangoral – Mode of action



Background of the study

- A single center open label randomized cross-over phase III study was performed to evaluate the diagnostic quality of Mangoral-enhanced MRI (MMRI) in patients with liver metastases in comparison to Gadobenate dimeglumine-enhanced MRI (GMRI)*
- The study was performed in Karolinska Institute, Sweden in 2007
- Twenty patients with known liver metastasis received both Mangoral and Gadolinium BOPTA.
    - Mangoral dose: 1600 mg; Gadolinium BOPTA dose: 0.1 mmol/kg of body weight
- MR imaging was performed with 1.5T machine within 1 wk of each MRI
- Diagnosis of metastasis was confirmed by histopathology, other imaging modalities or by clinical consensus
- Intra-individual efficacy assessments were performed at the study site by consensus read by two readers

Purpose of current study

- To confirm and compare diagnostic efficacy of MMRI and GMRI assessed by 3 independent readers

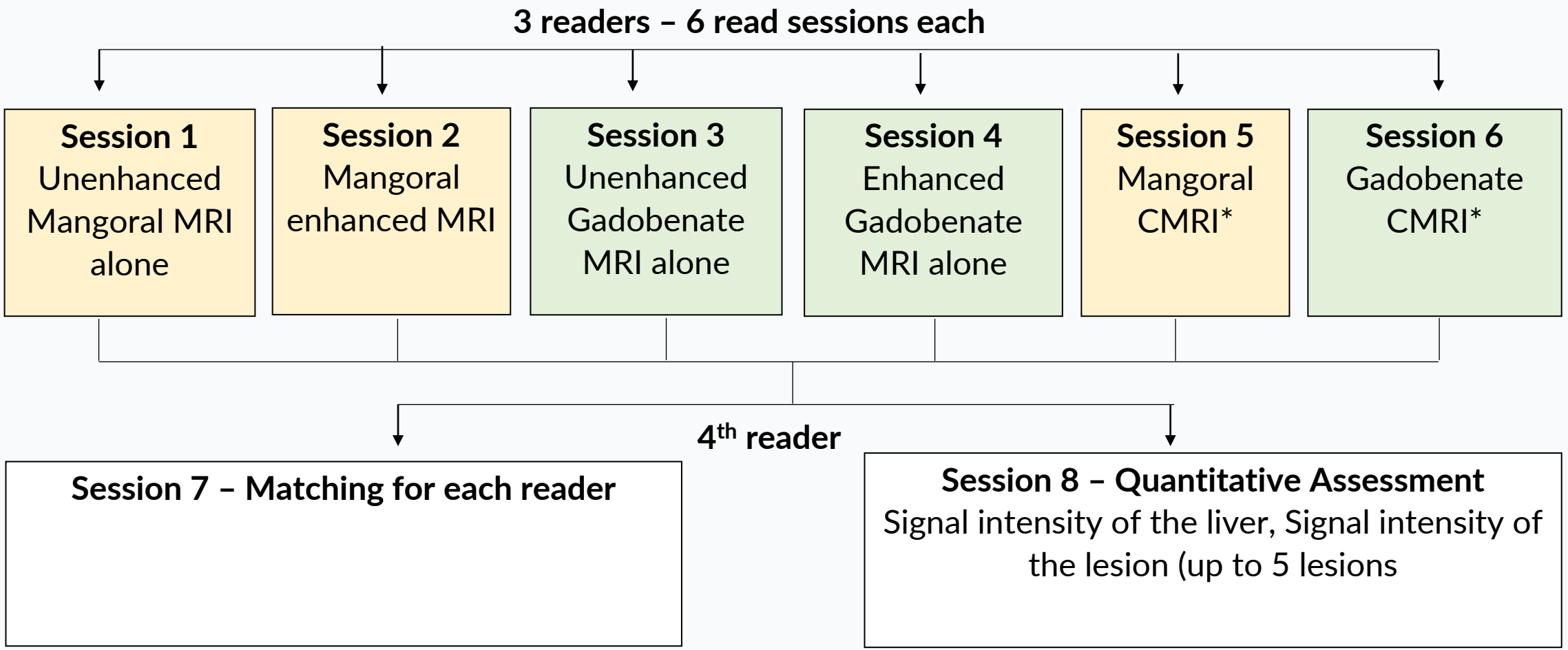
*https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3269572/pdf/330_2011_Article_2288.pdf

Methods and materials of the re-read

- Three independent radiologists with > 5 years of liver MRI experience evaluated unenhanced and enhanced T1 and T2-weighted images
- Efficacy parameters
    - number and size of the detected lesions
    - lesion border delineation using 4-point scale (poor, moderate, good excellent)
    - lesion contrast compared to liver using a 4-point scale. (poor, moderate, good excellent)
    - Quantitative assessments
- A fourth radiologist tracked and matched the lesions identified by each of the three readers and performed additional quantitative assessments
- Comparative efficacy analyses were performed between
    - Unenhanced MRI and enhanced MMRI and GMRI
    - MMRI and GMRI

Descriptive statistics and CI were used to assess the differences.

Read methodology



*CMRI: combined MRI (unenhanced + enhanced MRI)

Results: number of lesions

Higher number of lesions were detected by Mangoral enhanced MRI compared to unenhanced MRI for all 3 readers

Number of lesions detected by MMRI and unenhanced MRI			
Reader	Statistic	Unenhanced	Mangoral CMRI
1	n	20	20
	Mean (SD)	1.85 (1.226)	2.55 (1.538)
	Median	1.50	2.00
	Min, Max	0.00, 5.00	1.00, 6.00
	95% CI	1.28, 2.42	1.83, 3.27
2	n	20	20
	Mean (SD)	1.85 (0.988)	2.15 (1.424)
	Median	1.50	2.00
	Min, Max	1.00, 4.00	0.00, 6.00
	95% CI	1.39, 2.31	1.48, 2.82
3	n	20	20
	Mean (SD)	1.90 (1.165)	3.15 (1.954)
	Median	1.50	3.00
	Min, Max	0.00, 4.00	0.00, 8.00
	95% CI	1.35, 2.45	2.24, 4.06

Results: number of lesions

A higher number of liver lesions were detected by MMRI compared to GMRI by all 3 readers with overlapping 95%-confidence intervals

Number of lesions detected by MMRI and GMRI			
Reader	Statistic	MMRI	GMRI
1	n	20	20
	Mean (SD)	2.55 (1.538)	2.40 (1.847)
	Median	2.00	2.00
	Min, Max	1.00, 6.00	0.00, 8.00
	95% CI	1.83, 3.27	1.54, 3.26
2	n	20	20
	Mean (SD)	2.15 (1.424)	1.60 (1.231)
	Median	2.00	1.00
	Min, Max	0.00, 6.00	0.00, 4.00
	95% CI	1.48, 2.82	1.02, 2.18
3	n	20	20
	Mean (SD)	3.15 (1.954)	2.65 (1.694)
	Median	3.00	2.00
	Min, Max	0.00, 8.00	0.00, 6.00

Results: size of smallest lesions

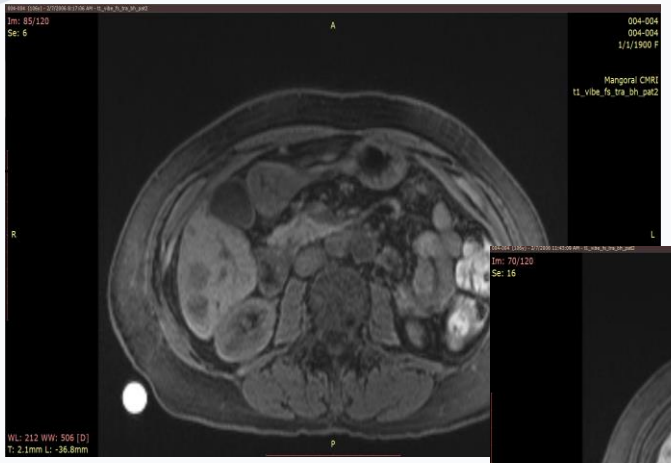
Mean size of smallest lesion detected by MMRI was smaller for 3 readers compared to GMRI with overlapping 95%-confidence intervals

Size of smallest lesion			
Reader	Statistic	MMRI	GMRI
1	n	20	20
	Mean (SD)	14.00 (9.096)	14.45 (8.841)
	Median	11.50	11.50
	Min, Max	4.00, 40.00	5.00, 40.00
	95% CI	9.74, 18.26	10.31, 18.59
2	n	20	17
	Mean (SD)	18.35 (9.184)	19.35 (9.027)
	Median	16.50	15.00
	Min, Max	9.00, 42.00	9.00, 38.00
	95% CI	14.05, 22.65	14.71, 23.99
3	n*	19	18
	Mean (SD)	12.21 (10.250)	14.78 (11.128)
	Median	12.00	11.50
	Min, Max	1.00, 42.00	4.00, 39.00
	95% CI	7.27, 17.15	9.24, 20.31

Results: lesion border delineation

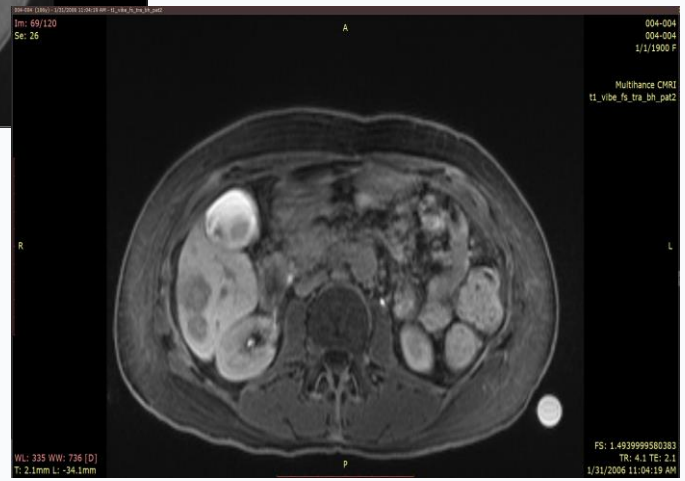
Two out of 3 readers showed higher scores for lesion delineation for MMRI compared to GMRI with overlapping CIs

MMRI vs. GMRI of Lesion Border Delineation			
Reader	Statistic	MMRI	GMRI
1	n	20	19
	Mean (SD)	6.40 (3.926)	7.00 (6.164)
	Median	5.00	5.00
	Min, Max	1.00, 14.00	1.00, 26.00
	95% CI	4.56, 8.24	4.03, 9.97
2	n*	19	17
	Mean (SD)	5.95 (4.327)	4.41 (3.144)
	Median	4.00	3.00
	Min, Max	1.00, 15.00	1.00, 12.00
	95% CI	3.86, 8.03	2.80, 6.03
3	n*	19	19
	Mean (SD)	9.37 (6.265)	7.79 (5.192)
	Median	8.00	6.00
	Min, Max	2.00, 28.00	1.00, 18.00
	95% CI	6.35, 12.39	5.29, 10.29



Unenhanced liver MRI
T1-weighted image

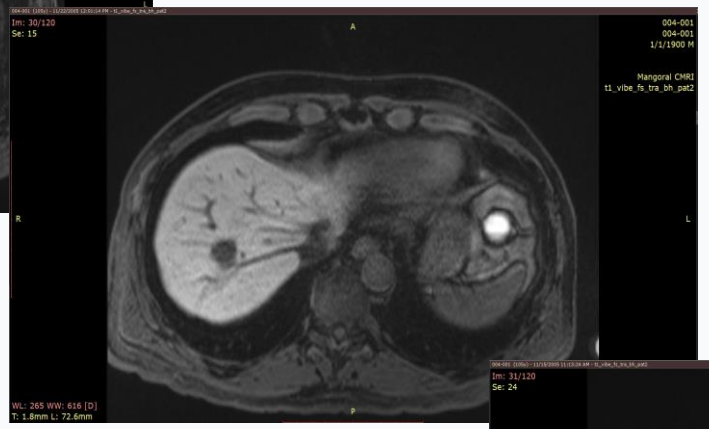
Mangoral enhanced liver MRI
T1-weighted image



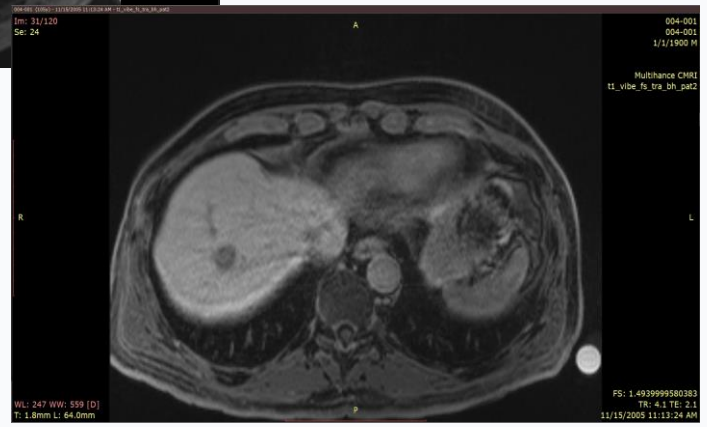
Gadobenate enhanced liver MRI
T1-weighted image – hepatocyte phase

Signal-to-noise ratio, Lesion-to-liver contrast was similar for MMRI and GMRI

Unenhanced liver MRI
T1-weighted image



Mangoral enhanced liver MRI
T1-weighted image



Gadobenate enhanced liver MRI
T1-weighted image – hepatocyte phase

Conclusions and clinical relevance

- Orally administered mangoral enhanced MRI showed similar efficacy in terms of lesion detection, lesion visualization, and lesion delineation of liver metastases as compared to intravenous gadobenate enhanced MRI

- Manganese based contrast agent could be a valuable alternative for MRI of the liver in patients in whom use of gadolinium agents is restricted or contra-indicated

Thank you.