RESEARCH ARTICLE

Comparison of Gadobenate Dimeglumine and Gadopentetate Dimeglumine for Breast MRI Screening: a Meta-analysis

Xiao-Ping Yang[1], Yue-Dong Han[1], Jian-Jun Ye[1], Gang Chen[1], Ying Luo[1], Hong-Xia Ma[2], Xue-Wen Yu[2], Juan-Qin Niu[1], Fang-Yuan Ren[1], You-Ming Guo[2]*

Abstract

Background: As a common and essential contrast medium at present, gadobenate dimeglumine has shown better performance than some other agents when applied to Breast Magnetic Resonance Imaging Screening (Breast MRI Screening). Nevertheless, reports on the diagnostic performance of these two mediums (gadobenate dimeglumine and gadopentetate dimeglumine) are not completely consistent. Objective: To assess the diagnostic value of gadobenate dimeglumine and gadopentetate dimeglumine for Breast MRI Screening in patients suffering from breast cancer and to provide more convinced evidence to guide clinical practice in terms of appropriate contrast agents. Data Sources and Review Methods: Original articles in English and Chinese published before January 2013 were selected from available databases (The Cochrane Library, PUBMED, EMBASE, Chinese Biomedical Literature Database, Chinese Scientific Journals Full-text Database, Chinese Journal Full-text). The criteria for inclusion and exclusion were based on the standard for diagnosis tests. Meta-Disc software (Version 1.4) was used for data analysis. Then, the area under curve (AUC) of SROC and the spearman rank correlation of sensitivity against (1-specificity) were calculated. Results: Total of 17 researches involving 1934 patients were included. The pooled sensitivity of gadobenate dimeglumine and gadopentetate dimeglumine were 0.99 (0.97, 1.00) and 0.93 (0.88, 1.00) respectively. The pooled specificity for these two contrast agents were 0.924 (0.902, 0.943) and 0.838 (0.817, 0.858) respectively, and the AUC of SROC curve were 0.9781 and 0.9215 respectively. Conclusions: Gadobenate dimeglumine can be regarded as a more effective and feasible contrast medium for Breast MRI Screening. At least 5% differences in diagnostic performance are usually considered as clinically relevant.

Keywords: Gadobenate dimeglumine - gadopentetate dimeglumine - breast MRI screening - meta-analysis

Asian Pac J Cancer Prev, **15 (12)**, 5089-5095

Introduction

Regarded as one of the most common cancer distributed worldwide in female patients, breast cancer holds the ratio of 23% among all the malignant tumors. What's worse, in recent years, its incidence has risen rapidly with more than 1 million new cases emerging each year (Siegel et al., 2012). While, it has been approved that, breast cancer is one kind of malignancy that can be reduced mortality distinctly by image examinations. Correspondingly, a great many screening examinations arise and thrive, such as Breast MRI Screening, ultrasound, computed tomography and so on. However, for high risk women, really only Breast MRI Screening is used widely for screening clinically. Nevertheless, differentiation between benign and malignant breast lesions remains a difficult diagnosis problem, especially in dense fibroglandular breasts (Kuhl 2007). As we all know, misdiagnose may lead to severe delays, and unnecessary medical treatments may not be needed actually. Thus, more efficacious surveillances which can inspect breast lesions more exactly and earlier, also confirmed by more convinced evidence, have been in demand urgently.

Breast MRI Screening, which is breast MR imaging, has been reported as a promising adjunctive screening tool in specific high-risk populations, including women with a strong family history of breast/ovarian cancer or treated as Hodgkin's disease. It is well ascertained that patients with a genetic predisposition toward breast cancer benefit from MR imaging screening (Kriege et al., 2004), and MRI is already recommended by the American Cancer Society as a screening procedure for high-risk women only (Lehman et al., 2005). On account of its relatively outstanding spatial resolution of lesions and superior contrast techniques of soft tissue, Breast MRI Screening offered an overall sensitivity of 90% and specificity of 72% in detecting breast lesions in a published meta-analysis (Saslow et al., 2007). Comparatively speaking,

*[1]Department of Radiology, the First Hospital of Medical College of Xi'an Jiaotong University, Xi'an, [2]Department of Radiology, General Hospital of Lanzhou Command PLA, Lanzhou, Ganshu, China [&]Equal contributors *For correspondence: yangxiaoppinglz@163.com*

of the techniques available for breast cancer detection and staging, Breast MRI Screening plays a relatively sensitive role to some extent. While, there exists another challenges regarding how to strengthen the function of MRI more efficiently to enhance surveillance further for patients with breast cancer. That is, any approach to improve the diagnostic performance of MRI further could greatly affect the initial one to patient work-up, the subsequent treatment and outcome of patients with diagnosed disease, and also may have a profound effect on screening guidelines.

It is acknowledged that, contrast-enhanced MRI with contrast agents is capable of making better effects. Currently, contrast agents used commonly are as follows: Magnevist, Multihance, OptiMark, Omniscan and so on (Boetes et al., 2004). Despite all of these agents doing a good job in the detection of breast cancer, there are plenty of disparities among them individually. Take dose for example, some agents may reach equivalent or much more significant effects with half dose or even less, and some may possess fewer adverse reactions compared with other agents. As one kind of gadolinium complexes series with relatively much more common application than some existing ones nowadays, gadopentetate dimeglumine (brand name: Magnevist) plays a greatly considerable role in contrast-enhanced MRI. Meanwhile, in recent years, there appears a new contrast agent gadobenate dimeglumine whose trade name is Multihance, showing better performances plausibly in contrast-enhanced MRI through numerous cases. Recently, quite a lot of studies demonstrated better diagnostic performance with a higher relaxivity MR contrast agent named gadobenate dimeglumine than the standard relaxivity agent gadopentetate dimeglumine (most commonly used at present) when administered at equivalent doses or even less. Gadopentetate dimeglumine (molecular weight: 938; molecular formula: $C_{14}H_{20}GdN_3O_{10}\cdot 2C_7H_{17}NO_5$) and other similar contrast agents possess roughly twofold higher R1 relaxivity in vivo owing to weak, transient interaction with serum albumin, compared with gadobenate dimeglumine (molecular weight: 1058.16; molecular formula: $C_{22}H_{28}GdN_3O_{11}\cdot 2C_7H_{17}NO_5$). However, these comparision studies were all single-center or small-scale trials. In this paper, our study aims to perform a comprehensive meta-analysis which eliminated limitations associated with to overcome the shortcomings of these studies and to obtain the overall diagnostic performance of the two kinds of contrast agents, gadobenate dimeglumine and gadopentetate dimeglumine, which, to our knowledge, had not previously been investigated.

Materials and Methods

Literature search

We made use of the combined medical subject headings (MeSH) of magnetic resonance, mammography, gadobenate dimeglumine, gadopentetate dimeglumine, Magnevist, Multihance, with the exploded terms breast cancer and breast neoplasms. PUBMED (1966.1-2013.1), EMBASE (1974.1-2013.1), the Cochrane Library (2013 issue 1), Chinese Biomedical Literature Database (1978.1-2013.1), Chinese Journal Full-text Database (1979.1-2013.1), Chinese science and technology periodicals database (1989.1-2012.1) were searched independently by two investigators for all publications in English and Chinese language. In addition, the published reference lists of these articles were systematically searched. If any disagreement arose, it was figured out through discussions with the third one.

Included trials

Types of studies. We included studies whose topics were the diagnostic performance of gadobenate dimeglumine or gadopentetate dimeglumine when applied to breast MRI screening compared with the golden standard including pathological examination and following-up. Studies were excluded if the absolute numbers of true positive (TP), false positive (FP), true negative (TN), and false negative (FN) were not reported, or could not be derived. Any disagreements on eligibility were resolved by discussions andconsensuses between the two independent investigators.

Types of participants. These identified patients were all adults (age>18 years) with very suspicious breast lesions, and scheduled to receive pathological examination, that is pre-surgical evaluation, or be followed-up. Ethnicity and nationality were not limited. Patients were excluded from the study if they had received any other contrast agents during 48 hours before the appointed agent administration, or had any other medical treatment that would significantly decrease the chances of obtaining reliable data. Patients with a history of hypersensitivity to gadolinium mediums or contraindicating with MRI were also excluded from the study. Approvals for these studies included were obtained from the local ethics committee and all patients enrolled were provided written informed consent for protocols of these studies and the subsequent elaboration of data.

Document screening and data extraction

The review was undertaken by two independent reviewers. The search strategy described above was developed and performed to identify eligible studies. The results, combined with all titles, abstracts, or the full text when necessary, were screened independently by two authors. In case of disagreement between the two authors, the full articles were obtained and inspected independently by the third author. Data extraction was carried out independently by the same reviewers using standard data extraction forms. It has been developed to record design details of these studies, including publication year, country, tesal of the magnetic field, the dosage of contrast medium, the details among participants (total number of patients and number of cases "lost to follow-up", mean age, total lesions, benign lesions, malignant lesions), the interval between MRI and pathological examination, characteristics and outcomes which contained the absolute numbers of true positive (TP), false positive (FP), true negative (TN), and false negative (FN).

Quality evaluation

The study quality conformed to the QUADAS (quality

assessment of diagnostic accuracy studies) which was formulated by Whiting (Whiting et al., 2006) and has been received consistent acknowledgement worldwide, also included in Systematic Reviews guidelines. The quality items assessed were as follows: Item 1: was the spectrum of patients representative of the patients who will receive the test in practice?; Item 2: were selection criteria clearly described?; Item 3: was the reference standard likely to classify correctly the target condition?; Item 4: was the time period between reference standard and index test short enough to make sure that the target condition did not change between these two tests?; Item 5: did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?; Item 6: did patients receive the same reference standard regardless of the index test results?; Item 7: was the reference standard independent of the index test (i.e. the index test did not generate part of the reference standard); Item 8: was the execution of the index test described in sufficient detail to permit replication of the test; Item 9: was the execution of the reference standard described in sufficient detail to permit its replication?; Item 10: were the index test results interpreted without knowledge of the results of the reference standard?; Item 11: were the reference standard results interpreted without knowledge of the results of the index test?; Item 12: were the same clinical data available when test results were interpreted or would be available when the test is used in practice?; Item 13: were uninterpretable / intermediate test results reported?; Item 14: were withdrawals from the study explained. Two of us tested every criterion step by step, and checked outcomes together. When faced with disagreement, discussion with a third one.

Statistical analysis

Statistical analysis was performed by Meta-Disc 1.4 software (Zamora et al., 2006). Statistical heterogeneity among studies was assessed by means of chi square. Then, SROC (the Summary Receiver Operating Characteristic) curves were drawn and the summary areas under the SROC (AUC) were calculated. The more close to 1 AUC, the more veracity diagnostic examination is, that is, the more diagnostic value of the examination is. Spearman correlation coefficients were calculated to indicate whether there existed factors other than differences in cutoff points for accuracy estimates across individual studies.

Results

Literature search

According to the search strategy and methods of data collection, 729 studies were identified preliminarily (PUBMED: 562 articles, EMBASE: 154 articles, the Cochrane Library: 13 articles, Chinese Biomedical Literature Database: no article, Chinese Journal Full-text Database: no article, Chinese science and technology periodicals database: no article) (Table 1). 80 duplicates were removed firstly. And then 581 articles were identified to be irrelevant through screening of their abstracts, whose topics were not the diagnostic values on gadobenate dimeglumine or gadopentetate dimeglumine for contrast-enhanced breast MRI screening. Thus, 68 articles were

Table 1. The Characteristics of 17 Included Studies

Authors	Country	Tesal	Dose (A) (mmol/kg)	Interval**	Mean age (SD)	Patients (n)	Excluded (n)	Total lesions (n)	Benign lesions (n)	malignant lesions (n)
Pediconi 2007	Italy	1.5	0.1	1-31d	52 (--)	118	0	169	---	---
Luciani 2011	Italy	1.5	0.1	unclear	50.7 (11.5)	58	12	55	31	24
Authors	**Country**	**Tesal**	**Dose (B) (mmol/kg)**	**Interval****	**Mean age (SD)**	**Patients (n)**	**Excluded (n)**	**Total lesions (n)**	**Benign lesions (n)**	**malignant lesions (n)**
Alamo 2001	Germany	1.5	0.1	1-15d	48 (--)	149	109	152	23	17
Fenlon 1997	America	1.5	0.1	1-7d	51 (--)	47	3	44	23	21
Fischer 1999	Germany	1.5	0.1	unclear	54.3 (--)	522	59	548	143	405
Fobben 1995	America	1.5	0.1	1-28d	--	89	0	91	70	21
Goerres 2003	Switzerland	1.5	0.1	unclear	57.2 (10.2)	49	17	--	--	--
Helbich 1997	Austria	1.5/0.5**[1]	0.1	1-31d	47 (--)	74	8	75	49	26
Kawashima 2001	Japan	1.5	0.1	6-20d	--	26	0	26	9	17
Kneeshaw 2006	UK	1.5	0.1	≥10d	57.4 (--)	88	0	88	68	20
Stomper 1995	America	1.5	0.1	1-14d	54 (--)	49	0	51	26	25
Woodhams 2010	Japan	1.5	0.1	11-40	--	398	0	403	87	316
Authors	**Country**	**Tesal**	**Dose (A/B)* (mmol/kg)**	**Interval****	**Mean age (SD)**	**Patients (n)**	**Excluded (n)**	**Total lesions (n)**	**Benign lesions (n)**	**malignant lesions (n)**
Knopp 2003	Germany	1.5/1.0/ 0.5*[1]	0.05, 0.10, 0.20/0.1	1d-1 month	54.5 (--)	189	3	400	297	103
Martincich 2011	Italy	1.5	0.1/0.1	2d-7d	52.8 (12.3)	162	12	216	72	144
Pediconi 2005	Italy	1.5	0.1/0.1	2d-7d	47.8 (10.0)	26	1	46	8	38
Pediconi 2008	Italy	1.5	0.1/0.1	2d-7d	50.8 (12.9)	47	0	78	28	50
Sardanelli 2005	Italy	1.5	0.05, 0.10, 0.20/0.1	2d-1 month	54.3 (12.0)	72	5	67	17	50

*Dose (A/B) means the dose of contrast agents, that is A on behalf of gadobenate dimeglumine and B on behalf of gadopentetate dimeglumine, respectively. **Interval means the interval between examinations of contrast agents **[1] means the tesal in Knopp ranged from 1.5 to 0.5, but 1.5T system applied to 155/189 patients, 1.0T 24/189 patients, 0.5T 10/189 patients, respectively. To achieve adequate spatial and temporal resolution, each imager was required to have a gradient of at least 15mT/m2. *[1] means studies in Thomas were performed on a 1.5-T unit in 63 patients and on a 0.5-T unit in three patients with commercially available bilateral breast coils and standard software.

Table 2. The diagnostic test parameters of 17 included studies

Study							Gadopentetate Dimeglumine						
	FP/n	FN/n	TN/n	Sen/%	Spe%	Acc%	TP/n	FP/n	FN/n	TN/n	Sen/%	Spe%	Acc%
Alamo 2001	---	---	---	---	---	---	17	5	0	18	100	76.5	87.5
Fenlon 1997	---	---	---	---	---	---	19	2	2	21	90	91	90.9
Fischer 1999	---	---	---	---	---	---	375	50	30	93	93	65	85
	---	---	---	---	---	---	18	15	3	55	85.7	78.6	80.2
Fobben 1995	---	---	---	---	---	---	16	21	5	49	76.2	70	71.4
	---	---	---	---	---	---	18	8	3	62	85.7	88.6	87.9
Goerres 2003	---	---	---	---	---	---	11	1	3	17	79	94	88
Helbich 1997	---	---	---	---	---	---	25	9	1	40	96.2	81.6	86.7
Kawashima 2001	---	---	---	---	---	---	8	0	9	9	47	100	65
Kneeshaw 2006	---	---	---	---	---	---	15	7	5	61	75	89.7	86.4
Knopp 2003	1	11	19	66.7	95	77.4	23	0	25	13	47.9	100	59
	6	6	14	81.8	70	77.4	26	2	22	11	54.2	84.6	60.7
Luciani 2011	3	0	24	100	88.9	94.6	---	---	---	---	---	---	---
Martincich 2011	13	13	1291	91.1	99	98.2	121	29	28	1272	81.2	97.8	96.1
	24	8	1280	94.5	98.2	97.8	123	40	26	1261	82.6	96.9	95.4
	41	7	1263	95.2	96.9	96.7	126	81	23	1220	84.6	93.8	92.8
Pediconi 2005	1	1	7	94.7	100	95.6	36	0	10	8	76.3	100	80.4
Pediconi 2007	6	0	90	100	94	95	---	---	---	---	---	---	---
Pediconi 2008	8	1	20	98	71.4	88.5	38	12	12	16	76	57.1	69.2
Sardanelli 2005	3	6	14	88	82.4	86.6	---	---	---	---	---	---	---
Stomper 1995	---	---	---	---	---	---	25	10	0	16	100	61.5	80.4
Woodhams 2010	---	---	---	---	---	---	53	4	4	5	93	56	89

Table 3. Quality Assessment Of Methodology Of Included Studies

Study	Item2	Item3	Item4	Item5	Item6	Item7	Item8	Item9	Item10	Item11	Item12	Item13	Item14
Alamo 2001	yes	yes	yes	yes	yes	yes	yes	yes	yes	unclear	unclear	yes	yes
Fenlon 1997	yes	yes	yes	yes	yes	yes	yes	yes	yes	unclear	unclear	yes	yes
Fischer 1999	yes	yes	unclear	yes	yes	yes	yes	yes	yes	unclear	unclear	yes	yes
Fobben 1995	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	unclear	yes	unclear
Goerres 2003	yes	yes	unclear	yes	no	yes	yes	yes	yes	unclear	unclear	yes	yes
Helbich 1997	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	yes
Kawashima 2001	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	yes
Kneeshaw 2006	yes	yes	unclear	yes	no	yes	yes	yes	yes	yes	no	yes	yes
Knopp 2003	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	yes
Luciani 2011	yes	yes	unclear	yes	no	yes	yes	yes	yes	yes	yes	yes	yes
Martincich 2011	yes	yes	yes	yes	unclear	yes	yes	yes	yes	yes	no	yes	yes
Pediconi 2005	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	yes
Pediconi 2007	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	yes
Pediconi 2008	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	yes
Sardanelli 2005	yes	yes	yes	yes	yes	yes	yes	yes	yes	unclear	no	yes	yes
Stomper 1995	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	unclear
Woodhams 2010	yes	yes	yes	yes	no	yes	yes	yes	yes	unclear	unclear	yes	yes

included in depth with full texts. 49 studies were excluded because the absolute numbers of true positive (TP), false positive (FP), true negative (TN), and false negative (FN) could not be derived from their full texts. Because the dosage unit of contrast media can't be translated, that is to say, the absolute difference on dosage among these studies is unknown, 2 articles were rejected. 17 studies (Fobben et al., 1995; Stomper et al., 1995; Fenlon et al., 1997; Helbich et al., 1997; Fischer et al., 1999; Alamo et al., 2001; Kawashima et al., 2001; Goerres et al., 2003; Knopp et al., 2003; Pediconi et al., 2005; Sardanelli et al., 2005; Kneeshaw et al., 2006; Pediconi et al., 2007; Pediconi et al., 2008; Woodhams et al., 2010; Luciani et al., 2011; Martincich et al., 2011) with 1934 patients were included based on the inclusion criteria and the data integrity.

Description of Studies

17 trials which involved 1934 patients met the specified criteria, and the languages in full texts were all English. Meanwhile, all reports covered the absolute numbers of true positive (TP), false positive (FP), true negative (TN), and false negative (FN) or could be derived. All of these studies were prospective except for one reference (Sardanelli et al. 2005) which was a retrospective report. Four references (Knopp et al. 2003; Pediconi et al. 2005; Pediconi et al. 2008; Martincich et al. 2011) reported available data on these two agents. Three references (Sardanelli et al. 2005; Pediconi et al. 2007; Luciani et al. 2011) only reported relevant data on gadobenate dimeglumine, and ten studies (Fobben et al. 1995; Stomper et al. 1995; Fenlon et al. 1997; Helbich et al. 1997; Fischer et al. 1999; Alamo et al. 2001; Kawashima

Table 4. The Result of Comparison between Gadobenate Dimeglumine with the Golden Standard (95%Ci)

CIncluded studies	SPE	PLR	NLR	OR
Knopp 2003 (a)	0.950 (0.751, 0.999)	13.333 (1.944, 91.449)	0.351 (0.214, 0.574)	38.000 (4.484, 322.07)
Knopp 2003 (b)	0.700 (0.457, 0.881)	2.727 (1.370, 5.429)	0.260 (0.119, 0.566)	10.500 (2.854, 38.634)
Luciani 2011	0.889 (0.708, 0.976)	7.862 (2.947, 20.973)	0.020 (0.001, 0.309)	399.00 (19.628, 8110.8)
Martincich 2011 (a)	0.990 (0.983, 0.995)	91.376 (53.076, 157.31)	0.090 (0.054, 0.151)	1016.0 (461.47, 2236.9)
Martincich 2011 (b)	0.982 (0.973, 0.988)	51.356 (34.484, 76.484)	0.056 (0.028, 0.109)	920.0 (405.52, 2087.2)
Martincich 2011 (c)	0.969 (0.958, 0.977)	30.280 (22.355, 41.014)	0.050 (0.024, 0.102)	611.70 (269.29, 1389.5)
Pediconi 2005	0.875 (0.473, 0.997)	7.826 (1.251, 48.977)	0.025 (0.004, 0.176)	315.00 (17.613, 5633.7)
Pediconi 2007	0.714 (0.513, 0.868)	3.430 (1.907, 6.169)	0.028 (0.004, 0.198)	122.50 (14.371, 1044.2)
Pediconi 2008	0.938 (0.869, 0.977)	14.599 (6.930, 30.753)	0.023 (0.002, 0.362)	626.54 (34.020, 11538.9)
Sardanelli 2005	0.824 (0.566, 0.962)	4.987 (1.777, 13.996)	0.146 (0.067, 0.319)	34.222 (7.554, 155.03)
Pooled value	0.974 (0.969, 0.979)[b]	12.852 (5.777, 28.594)[c]	0.084 (0.041, 0.173)[d]	194.86 (61.617, 616.26)[e]

a pooled sensitivity=0.924 (0.902, 0.943), df=9, *P*=0.000, **b** pooled specificity=0.974 (0.969, 0.979), df=9, *P*=0.000, **c** pooled PLR=12.852 (5.777, 28.594), df=9, *P*=0.000, **d** pooled NLR=0.084 (0.041, 0.173), df=9, *P*=0.000, **e** pooled OR=194.86 (61.617, 616.26), df=9, *P*=0.000

Table 5. The result of comparison between gadopentetate dimeglumine with the golden standard (95%CI)

Included studies	SPE	PLR	NLR	OR
Alamo, 2001	0.783 (0.563, 0.925)	4.242 (2.028, 8.873)	0.036 (0.002, 0.559)	117.73 (6.052, 2290.0)
Fenlon, 1997	0.913 (0.720, 0.989)	10.405 (2.748, 39.401)	0.104 (0.028, 0.392)	99.750 (12.766, 779.41)
Fischer, 1999	0.650 (0.566, 0.728)	2.648 (2.114, 3.317)	0.114 (0.079, 0.164)	23.250 (14.012, 38.578)
Fobben, 1995 (a)	0.786 (0.671, 0.875)	4.000 (2.472, 6.473)	0.182 (0.063, 0.522)	22.000 (5.709, 84.780)
Fobben, 1995 (b)	0.700 (0.579, 0.804)	2.540 (1.651, 3.906)	0.340 (0.156, 0.742)	7.467 (2.420, 23.041)
Fobben, 1995 (c)	0.886 (0.787, 0.949)	7.500 (3.818, 14.732)	0.161 (0.056, 0.461)	46.500 (11.162, 193.71)
Goerres, 2003	0.944 (0.727, 0.999)	14.143 (2.065, 96.883)	0.227 (0.083, 0.623)	62.333 (5.729, 678.15)
Helbich, 1997	0.816 (0.680, 0.912)	5.235 (2.887, 9.494)	0.047 (0.007, 0.323)	111.11 (13.263, 930.84)
Kawashima, 2001	1.000 (0.664, 1.000)	9.444 (0.607, 147.06)	0.556 (0.351, 0.880)	17.000 (0.854, 338.26)
Kneeshaw, 2006	0.897 (0.799, 0.958)	7.286 (3.456, 15.360)	0.279 (0.130, 0.598)	26.143 (7.275, 93.944)
Knopp, 2003 (a)	1.000 (0.753, 1.000)	13.429 (0.869, 207.44)	0.540 (0.405, 0.719)	24.882 (1.400, 442.28)
Knopp, 2003 (b)	0.846 (0.546, 0.981)	3.521 (0.958, 12.934)	0.542 (0.369, 0.796)	6.500 (1.299, 32.521)
Martincich, 2011 (a)	0.978 (0.968, 0.985)	36.432 (25.213, 52.642)	0.192 (0.138, 0.268)	189.55 (109.17, 329.11)
Martincich, 2011 (b)	0.969 (0.958, 0.978)	26.849 (19.616, 36.750)	0.180 (0.127, 0.255)	149.14 (88.019, 252.70)
Martincich, 2011 (c)	0.938 (0.923, 0.950)	13.582 (10.881, 16.955)	0.165 (0.113, 0.240)	82.512 (50.142, 135.78)
Pediconi, 2005	1.000 (0.631, 1.000)	13.979 (0.941, 207.60)	0.237 (0.136, 0.412)	59.095 (3.144, 1110.7)
Pediconi, 2008	0.571 (0.372, 0.755)	1.773 (1.125, 2.796)	0.420 (0.233, 0.756)	4.222 (1.568, 11.371)
Stomper, 1995	0.615 (0.406, 0.798)	2.522 (1.567, 4.059)	0.031 (0.002, 0.498)	80.143 (4.393, 1462.1)
Woodhams, 2010	0.556 (0.212, 0.863)	2.092 (1.004, 4.358)	0.126 (0.042, 0.384)	16.563 (3.144, 87.2630
Pooled value	0.935 (0.927, 0.942)[b]	6.104 (3.589, 10.382)[c]	0.224 (0.156, 0.322)[d]	36.287 (19.334, 68.108)[e]

a pooled sensitivity=0.838 (0.817, 0.858), df=18, *P*=0.000, **b** pooled specificity=0.935 (0.927, 0.942), df=18, *P*=0.000, **c** pooled PLR=6.104 (3.589, 10.382), df=18, *P*=0.000, **d** pooled NLR=0.224 (0.156, 0.322), df=18, *P*=0.000, **e** pooled OR=36.287 (19.334, 68.108), df=18, *P*=0.000

et al. 2001; Goerres et al. 2003; Kneeshaw et al. 2006; Woodhams et al. 2010) on gadopentetate dimeglumine. Three trials (Knopp et al. 2003; Sardanelli et al. 2005; Martincich et al. 2011) were multicenter studies, and four trials claimed definitely that they were sponsored by certain organizations. But these studies were performed independently and separated from industry supports. All these studies had been approved by the Institutional Review Board and written informed consents were obtained in all cases. Unfortunately, no article mentioned economic evaluation besides one (Knopp et al. 2003) with full safety evaluation. The comprehensive characteristics of these studies included are shown in Table 1, and the diagnostic test parameters of 17 studies included are shown in Table 2.

Methodological Quality of Studies

No report on item4 was found in four studies (Fischer et al. 1999; Goerres et al. 2003; Kneeshaw et al. 2006; Luciani et al. 2011). Results of "no" on item 6 were shown in seven studies (Stomper et al. 1995; Helbich et al. 1997; Goerres et al. 2003; Kneeshaw et al. 2006; Pediconi et al. 2007; Woodhams et al. 2010; Luciani et al. 2011) and no report in one study (Martincich et al. 2011). No report on item 11 and item 14 was found in six studies (Fenlon et al. 1997; Fischer et al. 1999; Alamo et al. 2001; Goerres et al. 2003; Sardanelli et al. 2005; Woodhams et al. 2010) and two studies (Fobben et al. 1995; Stomper et al. 1995) respectively. No report on item 12 was found in six studies (Fobben et al. 1995; Fenlon et al. 1997; Fischer et al. 1999; Alamo et al. 2001; Goerres et al. 2003; Woodhams et al. 2010) and results of "no" in seven studies (Kawashima et al. 2001; Knopp et al. 2003; Pediconi et al. 2005; Sardanelli et al. 2005; Kneeshaw et al. 2006; Pediconi et al. 2008; Martincich et al. 2011). The methodological quality of the included trials is shown comprehensively in Table 3.

Meta-Analysis result

The result of comparison between gadobenate dimeglumine with the golden standard was as follows: the pooled sensitivity was 0.924 (95%CI: 0.902, 0.943), the pooled specificity was 0.974 (95%CI: 0.969, 0.979), the pooled PLR was 12.852 (95%CI: 5.777, 28.594), the pooled NLR was 0.084 (95%CI: 0.041, 0.173), the SROC (AUC) was 0.9781, and Q* was 0.9336 (Table 4

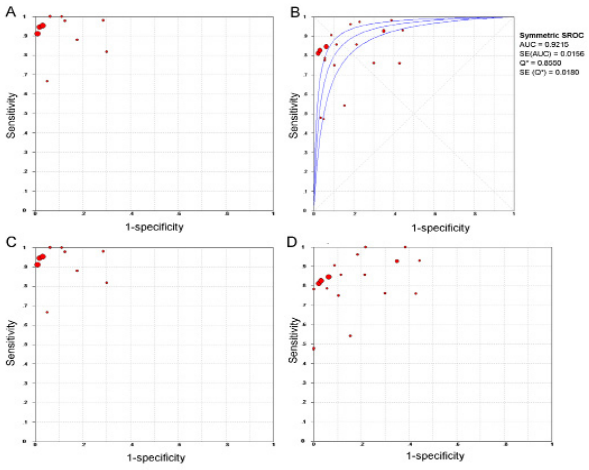

Figure 1. SROC curve of gadobenate dimeglumine (**A**), gadopentetate dimeglumine (**B**), and ROC plane of gadobenate dimeglumine (**C**) and gadopentetate dimeglumine (**D**)

and Figure 1A), the ROC plane could not performance a "shoulder-arm" shape (Figure 1C).

The result of comparison between gadopentetate dimeglumine with the golden standard was as follows: the pooled sensitivity was 0.838 (95%CI: 0.817, 0.858), the pooled specificity was 0.935 (95%CI: 0.927, 0.942), the pooled PLR was 6.104 (95%CI: 3.589, 10.382), the pooled NLR was 0.224 (95%CI: 0.156, 0.322), the SROC (AUC) was 0.9215, and Q* was 0.8550 (Table 5 and Figure 1B) , the ROC plane could not performance a "shoulder-arm" shape (Figure 1D).

Spearman correlation coefficients were as follows: the Spearman correlation coefficients were equal to 0.119 for gadobenate dimeglumine and 0.474 for gadopentetate dimeglumine.

Discussion

In this meta-analysis, we included 17 studies meeting all inclusion and exclusion criteria. After systematic quality assessment of methodology of the studies included through the Meta-Disc software, we obtained the overall sensitivity of gadobenate dimeglumine and gadopentetate dimeglumine, 0.924 (95%CI: 0.902, 0.943), 0.838 (95%CI: 0.817, 0.858) respectively, and specificity 0.974 (95%CI: 0.969, 0.979), 0.935 (95%CI: 0.927, 0.942) respectively. The rate of missed diagnosis on gadopentetate dimeglumine was 16.2% and gadobenate dimeglumine 7.6%. Their rate of misdiagnose showed 6.5% and 2.6% respectively. In addition, the area under the curve of SROC was 0.9781 for gadobenate dimeglumine, and 0.9215 for gadopentetate dimeglumine. The above data revealed that these both of the contrast media possessed outstanding diagnostic capability, while gadobenate dimeglumine did a much better job than gadopentetate dimeglumine .

Nevertheless, the noticeable heterogeneity among these individual studies existed. For this reason, it was requisite to investigate the source of heterogeneity, to determine the potential impact factors and to evaluate the appropriateness of statistical pooling of accuracy estimates from various studies.

Meta-disc was performed to assess threshold effect from representation of accuracy estimates from each study in a ROC plane, and Spearman correlation coefficients was calculated between the log (SEN) and log (1-SPE) (Zamora et al. 2006). All lack of "shoulder-arm" shape of the points in the ROC plane (Figure 1C and 1D), the Spearman correlation coefficients were equal to 0.119 for gadobenate dimeglumine and 0.474 for gadopentetate dimeglumine, which indicated that there should be factors other than differences in cutoff points for accuracy estimates across individual studies.

Furthermore, another limitation of our study was the mediocre quality of some certain studies included in the meta- analysis. As is known to all, the quality of meta-analysis depends on that of these studies included. We adopted the QUADAS tool, which was precisely developed for quality evaluation of diagnostic studies and had been applied to capture severe methodological defects (Whiting et al. 2006), to evaluate the methodological quality of studies in the meta-analysis. The quality of several studies in the meta-analysis was suboptimal, in terms of item 4 (was the time period between reference standard and index test short enough), item 6 (did patients receive the same reference standard regardless of the index test results), item 11 (were the reference standard results interpreted without knowledge of the results of the index test), item 12 (were the same clinical data available when test results were interpreted or would be available when the test is used in practice), and item 14 (were withdrawals from the study explained (Tab 3).

In addition, there were some other shortcomings concerning the article. Firstly, the effect of characteristics of the patients could not be examined due to lack of data. Secondly, the reference standard, which is the golden standard, ranged from pathological examination to following-up. Thirdly, most results revealed heterogeneity, which implied the needs for high-quality studies. Fourthly, only one study reported safety evaluation, and further cost-effectiveness analysis should be conducted. Nevertheless, gadolinium-based MR contrast agents had long been considered safe for routine diagnostic imaging (Semelka et al., 2012), and it is acknowledged that several sporadic individual adverse drug effects could not be avoided. Besides, according to our investigations, the difference of the costs between gadobenate dimeglumine and gadopentetate dimeglumine in the actual transactions might exist.

In conclusion, gadobenate dimeglumine appeared to be a more efficient contrast medium with more sensitive diagnostic performance compared with gadopentetate dimeglumine according to studies existed already up to the search time, in spite of many inherent defects which included studies had but could not be avoided. Thus, much more high-quality studies are in need urgently, and on account of methodological limitations, much more systematic investigations in depth are also necessary to confirm the diagnostic value on gadobenate dimeglumine profoundly.

Acknowledgements

Our team did not accept any fees, funding, or

honoraria directly or indirectly from other industry, and no employees from other companies involved in this study.

References

Alamo L, Fischer U (2001). Contrast-enhanced color doppler ultrasound characteristics in hypervascular breast tumors: comparison with MRI. *Eur Radiol*, **11**, 970-7.

Boetes C, Veltman J, van Die L, et al (2004). The role of MRI in invasive lobular carcinoma. *Breast Cancer Res Tr*, **86**, 31-7.

Fenlon HM, Phelan NC, O'Sullivan P, et al (1997). Benign versus malignant breast disease: comparison of contrast-enhanced MR imaging and Tc-99m tetrofosmin scintimammography. *Radiology*, **205**, 214-20.

Fischer U, Kopka L, Grabbe E (1999). Breast carcinoma: Effect of preoperative contrast-enhanced mr imaging on the therapeutic approach1. *Radiology*, **213**, 881-8.

Fobben ES, Rubin CZ, Kalisher L, et al (1995). Breast MR imaging with commercially available techniques: radiologic-pathologic correlation. *Radiology*, **196**, 143-52.

Goerres GW, Michel SC, Fehr MK, et al (2003). Follow-up of women with breast cancer: comparison between MRI and FDG PET. *Eur Radiol*, **13**, 1635-44.

Helbich TH, Becherer A, Trattnig S, et al (1997). Differentiation of benign and malignant breast lesions: MR imaging versus Tc-99m sestamibi scintimammography. *Radiology*, **202**, 421-9.

Kawashima H, Tawara M, Suzuki M, et al (2001). Effectiveness of dynamic MRI for diagnosing pericicatricial minimal residual breast cancer following excisional biopsy. *Eur J Radiol*, **40**, 2-9.

Kneeshaw *P*, Lowry M, Manton D, et al (2006). Differentiation of benign from malignant breast disease associated with screening detected microcalcifications using dynamic contrast enhanced magnetic resonance imaging. *The Breast*, **15**, 29-38.

Knopp MV, Bourne MW, Sardanelli F, et al (2003). Gadobenate dimeglumine-enhanced MRI of the breast: analysis of dose response and comparison with gadopentetate dimeglumine. *Am J Roentgenol*, **181**, 663-76.

Kriege M, Brekelmans CT, Boetes C, et al (2004). Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. *New Engl J Med*, **351**, 427-37.

Kuhl CK (2007). Current Status of Breast MR Imaging Part 2. Clinical Applications1. *Radiology*, **244**, 672-91.

Lehman CD, Blume JD, Weatherall P, et al (2005). Screening women at high risk for breast cancer with mammography and magnetic resonance imaging. *Cancer*, **103**, 1898-905.

Luciani M, Pediconi F, Telesca M, et al (2011). Incidental enhancing lesions found on preoperative breast MRI: management and role of second-look ultrasound. *La Radiologia Medica*, **116**, 886-904.

Martincich L, Faivre-Pierret M, Zechmann C M, et al (2011). Multicenter, double-blind, randomized, intraindividual crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine for breast MR imaging (DETECT Trial). *Radiology*, **258**, 396-408.

Pediconi F, Catalano C, Occhiato R, et al (2005). breast lesion detection and characterization at contrast-enhanced MR mammography: gadobenate dimeglumine versus gadopentetate dimeglumine1. *Radiology*, **237**, 45-56.

Pediconi F, Catalano C, Padula S, et al (2008). Contrast-enhanced MR mammography: improved lesion detection and differentiation with gadobenate dimeglumine. *Am J Roentgenol*, **191**, 1339-46.

Pediconi F, Catalano C, Roselli A, et al (2007). Contrast-enhanced MR Mammography for evaluation of the contralateral breast in patients with diagnosed unilateral breast cancer or high-risk lesions1. *Radiology*, **243**, 670-80.

Sardanelli F, Iozzelli A, Fausto A, et al (2005). Gadobenate dimeglumine–enhanced MR imaging breast vascular maps: association between invasive cancer and ipsilateral increased vascularity1. *Radiology*, **235**, 791-7.

Saslow D, Boetes C, Burke W, et al (2007). American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA: a cancer journal for clinicians*, **57**, 75-89.

Semelka RC, Hernandes MdA, Stallings CG, Castillo M (2012). Objective evaluation of acute adverse events and image quality of gadolinium-based contrast agents (gadobutrol and gadobenate dimeglumine) by blinded evaluation. Pilot study. *Magn Reson Imag*, **31**, 96-101.

Siegel R, Naishadham D, Jemal A (2012). Cancer statistics, 2012. *CA: a Cancer J Clin*, **62**, 10-29.

Stomper PC, Herman S, Klippenstein DL, et al (1995). Suspect Breast lesions: findings at dynamic gadolinium-enhanced MR imaging correlated. *Radiology*, **197**, 387-95.

Whiting PF, Weswood ME, Rutjes AW, et al (2006). Evaluation of QUADAS, a tool for the quality assessment of diagnostic accuracy studies. *BMC Med Res Methodol*, **6**, 9.

Woodhams R, Kakita S, Hata H, et al (2010). Identification of residual breast carcinoma following neoadjuvant chemotherapy: diffusion-weighted imaging-comparison with contrast-enhanced MR imaging and pathologic findings1. *Radiology*, **254**, 357-66.

Zamora J, Abraira V, Muriel A, et al (2006). Meta-DiSc: a software for meta-analysis of test accuracy data. *BMC Med Res Methodol*, **6**, 31.