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

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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

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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, misdiagnosis 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,
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系列 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: C14H20GdN3O10·2C7H17NO5) 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: C22H28GdN3O11·2C7H17NO5). However, these comparison 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 and consensuses 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., if 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 in practice?; Item 13: were the 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/B)* | Interval** | Mean age (SD) | Patients (n) | Excluded (n) | Total lesions (n) | Benign lesions (n) | Malignant lesions (n) |
|------------|---------|---------|-------------|------------|---------------|--------------|--------------|-------------------|----------------------|----------------------|
| Pedicioni  | Italy   | 1.5     | 0.1         | 1-31d      | 52 (--)       | 118          | 0            | 169               | --                   | --                   |
| Luciani    | Italy   | 1.5     | 0.1         | 1-31d      | 50.7 (11.5)   | 58           | 12           | 55                | 31                   | 24                   |
| Alamo      | Germany | 1.5     | 0.1         | 1-15d      | 48 (--)       | 149          | 109          | 152               | 23                   | 17                   |
| Fenlon     | America | 1.5     | 0.1         | 1-7d       | 51 (--)       | 47           | 3            | 44                | 23                   | 21                   |
| Fischer    | Germany | 1.5     | 0.1         | 1-31d      | 54.3 (--)     | 522          | 59           | 548               | 143                  | 405                  |
| Fobben     | Switzerland | 1.5 | 0.1         | 1-28d      | --           | 89           | 0            | 91                | 70                   | 21                   |
| Goerres    | Switzerland | 1.5 | 0.1         | 1-31d      | 57.2 (10.2)   | 49           | 17           | --                | --                   | --                   |
| Hellbich   | Austria | 1.5,0.5  | 0.1         | 1-31d      | 47 (--)       | 74           | 8            | 75                | 49                   | 26                   |
| Kawashima  | Japan   | 1.5     | 0.1         | 6-20d      | --            | 26           | 0            | 26                | 9                    | 17                   |
| Kneeshaw   | UK      | 1.5     | 0.1         | ≥10d       | 57.4 (--)     | 88           | 0            | 88                | 68                   | 20                   |
| Stomper    | America | 1.5     | 0.1         | 1-14d      | 54 (--)       | 49           | 0            | 51                | 26                   | 25                   |
| Woodhams   | Japan   | 1.5     | 0.1         | 11-40      | --            | 398          | 0            | 403               | 87                   | 316                  |

*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; ***means the tesal in Knopp ranged from 1.5 to 0.5, but 1.5 T system applied to 155/189 patients, 1.0 T 24/189 patients, 0.5 T 10/189 patients, respectively. To achieve adequate spatial and temporal resolution, each imager was required to have a gradient of at least 15 mT/m². ** means studies in Thomas were performed on a 1.5-T unit in 63 patients and on a 0.3-T unit in three patients with commercially available bilateral breast coils and standard software.

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### Table 2. The diagnostic test parameters of 17 included studies

| Study            | FP/n | FN/n | TN/n | Sen/% | Spe% | Acc% | 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   |
| Fobben 1995      | ---  | ---  | ---  | ---   | ---  | ---  | 18   | 15   | 3    | 55    | 85.7 | 78.6 | 80.2 |
| Goerres 2003     | ---  | ---  | ---  | ---   | ---  | ---  | 16   | 21   | 5    | 49    | 76.2 | 70   | 71.4 |
| Knop 2003        | ---  | ---  | ---  | ---   | ---  | ---  | 18   | 8    | 3    | 62    | 85.7 | 88.6 | 87.9 |
| Martincich 2011  | ---  | ---  | ---  | ---   | ---  | ---  | 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 |
| Knop 2003        | 1    | 11   | 19   | 66.7  | 95   | 77.4 | 23   | 0    | 25   | 13    | 79.7 | 100  | 59   |
| Luciani 2011     | 3    | 0    | 24   | 100   | 88.9 | 94.6 | ---  | ---  | ---  | ---   | ---  | ---  | ---  |
| Martinich 2011   | 13   | 13   | 1291 | 91.1  | 99   | 98.2 | 121  | 29   | 28   | 1272  | 81.2 | 97.8 | 96.1 |
| Stomper 1995     | 24   | 8    | 1280 | 94.5  | 98.2 | 97.8 | 123  | 40   | 26   | 1261  | 82.6 | 96.9 | 95.4 |
| Sardanelli 2005  | 41   | 7    | 1263 | 95.2  | 96.9 | 96.7 | 126  | 81   | 23   | 1220  | 84.6 | 93.8 | 92.8 |
| Pediconi 2005    | 6    | 6    | 14   | 81.8  | 70   | 77.4 | 26   | 2    | 11   | 54.2  | 84.6 | 60.7 |
| Pediconi 2007    | 6    | 0    | 90   | 100   | 94   | 95   | ---  | ---  | ---  | ---   | ---  | ---  | ---  |
| Pediconi 2008    | 8    | 1    | 20   | 98    | 71.4 | 88.5 | 38   | 12   | 12   | 16    | 75   | 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   | yes   | yes   | yes   | yes   | yes   | yes   | yes    | unclear | unclear | yes    | yes    |
| Fobben 1995      | yes   | yes   | yes   | yes   | yes   | yes   | yes   | yes   | yes    | yes    | yes    | yes    | yes    |
| Goerres 2003     | yes   | yes   | yes   | yes   | yes   | yes   | yes   | yes   | yes    | yes    | yes    | yes    | yes    |
| Knop 2003        | yes   | yes   | yes   | yes   | yes   | yes   | yes   | yes   | yes    | yes    | yes    | yes    | yes    |
| Luciani 2011     | yes   | yes   | yes   | yes   | yes   | yes   | yes   | yes   | yes    | no     | yes    | yes    | yes    |
| Martinich 2011   | yes   | yes   | yes   | yes   | yes   | yes   | yes   | yes   | yes    | yes    | no     | yes    | yes    |
| Kneeshaw 2006    | yes   | yes   | yes   | yes   | yes   | yes   | yes   | yes   | yes    | no     | yes    | yes    | yes    |
| Knop 2003        | yes   | yes   | yes   | yes   | yes   | yes   | yes   | yes   | yes    | yes    | no     | yes    | yes    |
| Martinich 2011   | yes   | yes   | yes   | yes   | yes   | 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   | yes   | yes   | yes   | yes   | yes    | yes    | no     | 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    | no     | yes    | yes    | yes    |
| Stomper 1995     | yes   | yes   | yes   | yes   | yes   | yes   | yes   | yes   | yes    | yes    | clear  | yes    | yes    |
| Woodhams 2010    | yes   | yes   | yes   | yes   | yes   | yes   | yes   | yes   | yes    | unclear | clear  | yes    | yes    |

**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 (Knop et al. 2003; Pediconi et al. 2005; Pediconi et al. 2008; Martinich 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 et al. 2001; Goerres et al. 2003; Knop 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) with 1934 patients were included based on the inclusion criteria and the data integrity.
Table 4. The Result of Comparison between Gadobenate Dimeglumine with the Golden Standard (95% CI)

| Included studies | SPE   | PLR   | NLR   | OR    |
|------------------|-------|-------|-------|-------|
| Knopp 2003 (a)   | 0.950 | 13.333 | 0.351 | 38.000 |
| Knopp 2003 (b)   | 0.700 | 2.727 | 0.260 | 10.500 |
| Luciani 2011     | 0.889 | 7.862 | 0.200 | 399.00 |
| Martincich 2011 (a) | 0.990 | 91.376 | 0.090 | 1016.0 |
| Martincich 2011 (b) | 0.982 | 51.356 | 0.056 | 920.00 |
| Martincich 2011 (c) | 0.969 | 30.280 | 0.050 | 611.70 |
| Pediconi 2005    | 0.875 | 7.826 | 0.025 | 315.00 |
| Pediconi 2007    | 0.714 | 3.430 | 0.028 | 122.50 |
| Pediconi 2008    | 0.938 | 14.599 | 0.023 | 626.54 |
| Sardanelli 2005  | 0.824 | 4.987 | 0.146 | 34.22 |
| Fobben 1995 (a)  | 0.786 | 4.000 | 0.084 | 194.86 |
| Fobben 1995 (b)  | 0.700 | 2.540 | 0.161 | 46.50 |
| Fobben 1995 (c)  | 0.886 | 7.500 | 0.161 | 46.50 |
| Goerres, 2003    | 0.944 | 14.143 | 0.227 | 62.33 |
| Helbig, 1997     | 0.816 | 5.235 | 0.047 | 111.11 |
| Kneeshaw, 2006   | 0.897 | 7.286 | 0.279 | 26.14 |
| Kneeshaw, 2008   | 1.000 | 9.444 | 0.556 | 17.00 |
| Knopp, 2003 (a)  | 1.000 | 13.429 | 0.540 | 24.88 |
| Knopp, 2003 (b)  | 0.846 | 3.521 | 0.542 | 6.50 |
| Martinich 2011 (a) | 0.978 | 36.432 | 0.192 | 208.72 |
| Martinich 2011 (b) | 0.982 | 51.356 | 0.056 | 920.00 |
| Martinich 2011 (c) | 0.969 | 30.280 | 0.050 | 611.70 |
| Pediconi 2005    | 0.875 | 7.826 | 0.025 | 315.00 |
| Pediconi 2007    | 0.714 | 3.430 | 0.028 | 122.50 |
| Pediconi 2008    | 0.938 | 14.599 | 0.023 | 626.54 |
| Sardanelli 2005  | 0.824 | 4.987 | 0.146 | 34.22 |
| Fobben 1995 (a)  | 0.786 | 4.000 | 0.084 | 194.86 |
| Fobben 1995 (b)  | 0.700 | 2.540 | 0.161 | 46.50 |
| Fobben 1995 (c)  | 0.886 | 7.500 | 0.161 | 46.50 |
| Goerres, 2003    | 0.944 | 14.143 | 0.227 | 62.33 |
| Helbig, 1997     | 0.816 | 5.235 | 0.047 | 111.11 |
| Kneeshaw, 2006   | 0.897 | 7.286 | 0.279 | 26.14 |
| Kneeshaw, 2008   | 1.000 | 9.444 | 0.556 | 17.00 |
| Knopp, 2003 (a)  | 1.000 | 13.429 | 0.540 | 24.88 |
| Knopp, 2003 (b)  | 0.846 | 3.521 | 0.542 | 6.50 |
| Martinich 2011 (a) | 0.978 | 36.432 | 0.192 | 208.72 |
| Martinich 2011 (b) | 0.982 | 51.356 | 0.056 | 920.00 |
| Martinich 2011 (c) | 0.969 | 30.280 | 0.050 | 611.70 |

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).
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.

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