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ORIGINAL ARTICLE

The role of magnetic resonance imaging in assessing residual disease and pathologic complete response in breast cancer patients receiving neoadjuvant chemotherapy: a systematic review

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Abstract
Objectives This systematic review aimed to assess the role of magnetic resonance imaging (MRI) in evaluating residual disease extent and the ability to detect pathologic complete response (pCR) after neoadjuvant chemotherapy for invasive breast cancer.
Methods PubMed, the Cochrane Library, MEDLINE, and Embase databases were searched for relevant studies published until 1 July 2012. After primary selection, two reviewers independently assessed the content of each eligible study using a standardised extraction form and predefined inclusion and exclusion criteria.
Results A total of 35 eligible studies were selected. Correlation coefficients of residual tumour size assessed by MRI and pathology were good, with a median value of 0.698. Reported sensitivity, specificity, positive predictive value and negative predictive value for predicting pCR with MRI ranged from 25 to 100 %, 50–97 %, 47–73 % and 71–100 %, respectively. Both overestimation and underestimation were observed. MRI proved more accurate in determining residual disease than physical examination, mammography and ultrasound. Diagnostic accuracy of MRI after neoadjuvant chemotherapy could be influenced by treatment regimen and breast cancer subtype.
Conclusions Breast MRI accuracy for assessing residual disease after neoadjuvant chemotherapy is good and surpasses other diagnostic means. However, both overestimation and underestimation of residual disease extent could be observed.
Main Messages
- *Breast MRI accuracy for assessing residual disease is good and surpasses other diagnostic means.*
- *Correlation coefficients of residual tumour size assessed by MRI and pathology were considered good.*
- *However, both overestimation and underestimation of residual disease were observed.*
- *Diagnostic accuracy of MRI seems to be affected by treatment regimen and breast cancer subtype.*

Keywords Breast cancer · MRI · Neoadjuvant chemotherapy · Residual disease

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Introduction

Neoadjuvant chemotherapy (NAC) is defined as the administration of chemotherapy to treat invasive breast cancer before local treatment (i.e. surgery). Although in breast cancer patients NAC was primarily used for treatment of locally advanced disease stages, its use has been extended to

the treatment of early stage breast cancers in order to enable breast-conserving therapy for patients who would otherwise undergo mastectomy. In a large meta-analysis by Mauri et al., no significant differences in survival or overall disease progression was observed between patients receiving adjuvant or neoadjuvant chemotherapy [1].

Some physicians prefer NAC instead of the adjuvant chemotherapy because of the ability to assess tumour response in vivo. In this situation, reliable assessment of pathological tumour response to NAC is vital in order to select the most appropriate surgical plan. An imaging modality that could assess tumour response to NAC would be beneficial, providing it could detect any residual disease present. This could result in a surgical treatment plan more tailored to the individual patient. In addition, pathological complete response (pCR, i.e. the absence of any residual invasive tumour cells) on NAC has shown to be a prognostic factor for overall better survival, disease-free survival and recurrence-free survival [2]. In the future, this latter information might also guide further adjuvant treatment recommendations.

Many examinations have been proposed to evaluate residual disease and/or complete response to therapy (such as clinical examination, mammography and ultrasound), but their accuracy was only of modest degree [3]. Parallel to these findings, (contrast-enhanced) magnetic resonance imaging (MRI) of the breast proved to be superior to mammography and ultrasound with respect to assessing tumour extent, presence of additional foci (i.e. multifocality and/or multicentricity) and the presence of contralateral breast tumours [4, 5]. Therefore, MRI might be a promising imaging tool to assess therapy response in the NAC setting and for assessing pCR.

Several reviews have been recently published that assessed the ability of breast MRI to predict pCR in patients receiving NAC [6–8]. However, pCR is only achieved by a minority of patients and as a consequence, the role of breast MRI in neoadjuvant chemotherapy was not investigated for a substantial number of patients that still have some degree of residual disease after treatment. In this systematic review, we aimed to address the role of breast MRI in assessing both residual disease extent and pCR after NAC in breast cancer patients. Our study purpose was to assess the role of magnetic resonance imaging (MRI) in the evaluation in *all* patients receiving neoadjuvant chemotherapy for invasive breast cancer.

Materials and methods

For this systematic review, Embase, the Cochrane library, MEDLINE and citations as provided by PubMed were searched until 1 July 2012, using the search terms *breast*, *breast neoplasms*, *breast neoplasm*, *breast cancer*, *breast carcinoma* and *breast lesion* combined with the search terms *magnetic resonance imaging*, *MRI*, *MR mammography* and *neoadjuvant therapy*, *neoadjuvant chemotherapy*, *neoadjuvant systemic therapy*, *neoadjuvant*, *chemotherapy*, *primary therapy* and *initial therapy*. Only original articles were considered for inclusion (i.e. no reviews, brief communications or letters to the editor). References of all retrieved articles were manually searched for additional relevant manuscripts. Studies found through these search terms were assessed for potential eligibility by reading the abstracts first and then applying inclusion and exclusion criteria.

Included were only those in which breast MRI was performed at baseline and prior to surgery (but after completion of neoadjuvant chemotherapy). In addition, the ability of MRI to assess pCR was one of our study aims. Rates of pCR to NAC may vary, depending on the treatment regime used: 6–15 % in antracycline-based therapies, up to 30 % when adding taxanes [9]. Therefore, in order to have some reliable information on the ability of MRI to assess residual disease and also pCR, eligible studies should have a sufficiently large study population. To be eligible for this review, we decided that a study should consist of at least 25 patients (in the final analysis) with newly diagnosed, histologically proven breast cancer undergoing neoadjuvant chemotherapy who were imaged using clinical MRI scanners (i.e. minimum 1.5 T).

Studies were not excluded if other imaging modalities were performed parallel to MRI in order to evaluate treatment response.

After this initial assessment, the publications were summarised separately by two radiologists using a standard extraction form. When discrepancies were encountered, consensus opinion was reached afterwards. Extracted data included: first author, year of publication, study design (retrospective or prospective), blinding procedures, population size, mean patient age and range, magnetic field strength, contrast agent/dose used, breast cancer stage at inclusion, tumour histology, breast cancer subtypes, chemotherapy regimen, imaging response assessment [World Health Organisation (WHO) criteria, Response Evaluation Criteria in Solid Tumours (RECIST) criteria or other] and histopathological response assessment.

While scoring the extraction forms in consensus, some studies were excluded if the study outcome proved not to contain information on residual disease evaluation by MRI. All reported P-values ≤ 0.05 were considered statistically significant. The large heterogeneity observed in the included studies precluded us from pooling data (see also 'Discussion' section), which is why we chose to use descriptive statistics in this review. Since this was a systematic review, no approval from our institutional review board was necessary.

Results

In the primary literature search, 3,119 potential studies were identified, of which 515 were double in various searches, leaving 2,604 studies after the primary search. After reading the abstracts, 2,444 were excluded from further evaluation, leaving 160 studies to be analysed using the inclusion and exclusion criteria. In these studies, two additional studies were identified by manually searching the references in the manuscripts. In this analysis, another 98 studies did not comply with our eligibility criteria and were subsequently excluded, leaving 64 studies to be reviewed using the extraction form and consensus reading. This led to the exclusion of another 29 studies, because they did not address the topic of residual disease assessment with MRI after neoadjuvant chemotherapy. Therefore, a total of 35 studies were eligible for this systematic review [10–45]. Figure 1 presents a more detailed overview of the study selection process.

The majority of studies (27) were prospective in design. A total of 2,359 patients were included in the studies (mean 65.5 patients per study, range 30–216). Median age of patients was 48.0 years (range 23–82 years). Three studies were performed on a 3-T MRI scanner, four on both 1.5- and 3-T scanners, and the remaining studies on 1.5-T MRI scanners. In all studies, a commercially available gadolinium-based contrast agent was used for breast MRI at regular clinical administration doses. Interestingly, there was a remarkable heterogeneity in breast cancer stages and subtypes, neoadjuvant chemotherapy regimens, and methods used for assessing response in both imaging and histopathological analyses (Tables 1 and 2). This heterogeneity precluded us from further pooling of data in a meta-analysis.

Seventeen studies calculated correlation coefficients for the comparison of MRI tumour measurements compared with histopathological results [13, 14, 17, 21, 22, 25, 27, 28, 31–35, 37, 39, 40, 43]. Correlation coefficients varied from poor to excellent, but the median value was 0.698 (range 0.21–0.982, Table 3). Nonetheless, two studies reported non-significant correlation coefficients. In the relatively small (n=59) retrospective study by Guarneri et al., the correlation coefficients were similar for MRI (0.53) and ultrasound (0.66) when compared to histopathology, and both were non-significant [35]. In the study of 86 women by Nakahara et al., the correlation coefficient of all included patients was remarkably low (0.21), but rose to a strikingly high and statistically significant value of 0.92 when only triple-negative breast cancer types were analysed [31]. A weak correlation coefficient (0.30) was also presented by Chen et al. However, when four cases with a size discrepancy larger than 5 cm were excluded (all HER2-negative tumours presenting as non-mass-like enhancement), the correlation coefficient increased remarkably to 0.76 (P<0.001) [39]. Furthermore, both overestimation and underestimation were observed by multiple studies [10, 13, 15, 16, 20, 22, 24, 32, 37].

Although correlation coefficients are useful tools to describe MRI's ability to assess response to NAC, it could mask the truth, since the same trend in all studies could result in excellent correlation between histopathological results and MRI measurements, yet the actual estimation

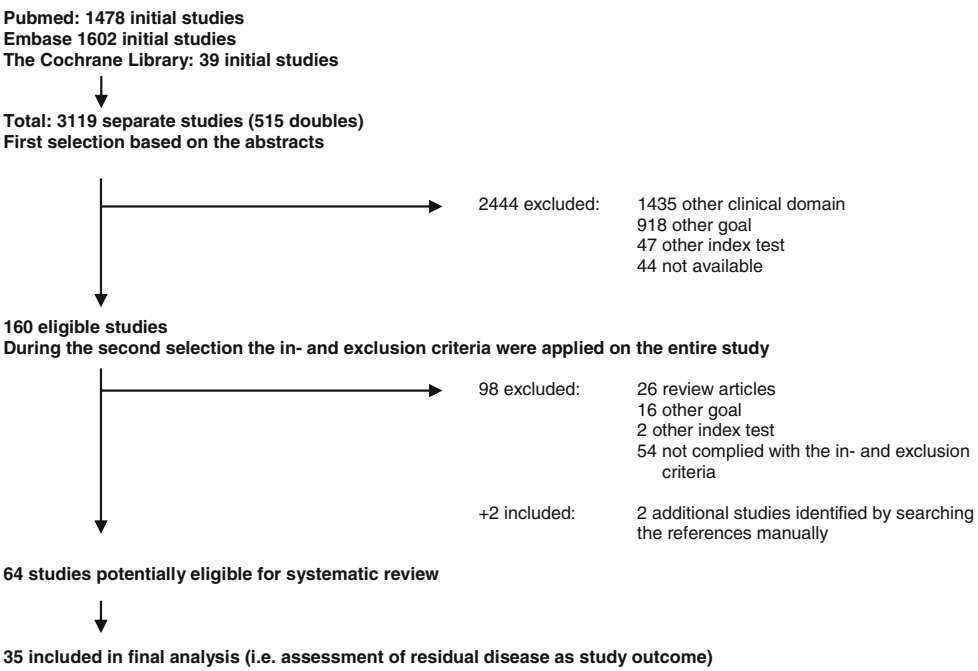

Fig. 1 Detailed overview of study selection

Table 1 Overview of included studies

Authors	Year	Study design	Population size	Age in years (range)	Breast cancer stage of included patients	Breast cancer types	Breast cancer subtypes
Abraham et al.	1996	Prospective	39	50 (31–73)	IIa, IIb,IIIa, IIIb	IDC, ILC, mixed ductal and lobular carcinoma	ER, PR
Esserman et al.	2001	Prospective	33	46 (32–75)	IIIa, IIIb, IIIc, to large for breast conserving therapy	IDC, ILC, inflammatory	ER, PR
Rieber et al.	2002	Prospective	58	51 (27–72)	Not reported	IDC, ILC, DCIS, mucinous carcinoma, ductolobular carcinoma	Not reported
Partridge et al.	2002	Prospective	52	47 (29–72)	Not reported	Not reported	Not reported
Cheung et al.	2003	Prospective	33	45 (29–63)	Not reported	IDC, ILC, mucinous carcinoma	Not reported
Denis et al.	2004	Prospective	40	48 (29–64)	LABC	Not reported	Not reported
Warren et al.	2004	Retrospective	67	46 (28–62)	Not reported	Not reported	ER, PR
Martincich et al.	2004	Prospective	30	49 (36–65)	II, III, inoperable locally-advanced breast cancer	IDC, ILC	ER, PR
Schott et al.	2005	Prospective	43	48 (26–66)	IIb, IIIa, T1N0/1, T2N0/1	IDC, ILC, mixed ductal and lobular carcinoma, anaplastic carcinoma	ER
Yeh et al.	2005	Prospective	31	45 (31–65)	IIb,IIIa, IIIb, IIIc	IDC, ILC, mixed ductal and lobular carcinoma, invasvive carcinoma n.o.s.	Not reported
Belli et al.	2006	Prospective	45	54 (30–76)	IIa, IIb, IIIa, IIIb,	IDC, ILC, mucinous carcinoma, tubular carcinoma	ER, PR
Segara et al.	2007	Prospective	68	50 (29–71)	Clinical stage I, II, and III	IDC, ILC, mixed ductal and lobular carcinoma; sometimes DCIS or LCIS present in lesions	ER, PR, HER2
Kim et al.	2007	Prospective	50	42 (25–68)	IIb, IIIa, IIIb, IIIc	IDC, ILC	ER, PR
Chen et al.	2007	Prospective	51	50 (31–77)	II, III, IV	IDC, ILC	HER2
Bhattacharyya et al.	2008	Prospective	32	42 (24–60)	>4 cm, large tumours in small breasts, node involvement	Not reported	Not reported
Moon et al.	2009	Prospective	195	46 (not reported)	Not reported	Not reported	ER, PR, HER2
Wright et al.	2010	Prospective	48	47 (30–72)	IIb, IIIa, IIIb	IDC, ILC, invasive micropapillary carcinoma	ER, PR, HER2
Woodhams et al.	2010	Prospective	69	Not reported	Not reported	IDC, ILC, DCIS, LCIS, mucinous carcinoma, other	Not reported
Park et al.	2010	Retrospective	53	44 (24–65)	IIa,IIb, IIIa, IIIb	IDC, mucinous carcinoma, mixed ductal and lobular carcinoma	ER, PR, HER2
De Los Santos et al.	2010	Retrospective	81	50 (27–73)	Not reported	IDC, ILC, mixed ductal and lobular carcinoma, carcinoma n.o.s.	ER, PR, HER2
Straver et al.	2010	Retrospective	208	46 (23–76)	>3 cm and/or N+	IDC, ILC, carcinoma n.o.s.	ER, PR, HER2
Nakahara et al.	2010	Prospective	86	48 (24–62)	Not reported	IDC, papillotubular carcinoma, solid-tubular carcinoma, scirrhous carcinoma	ER, HER2
Wang et al.	2010	Prospective	43	48 (34–69)	II, III	IDC	Not reported
Dongfeng et al.	2011	Prospective	60	55 (not reported)	I, IIa, IIb, IIIa, IIIb, IIIc	IDC, mucinous carcinoma	ER, HER2
Fangberget et al.	2011	Prospective	31	51 (37–72)	Not reported	IDC, ILC	ER, PR, HER2

Table 1 (continued)

Authors	Year	Study design	Population size	Age in years (range)	Breast cancer stage of included patients	Breast cancer types	Breast cancer subtypes
Guarneri et al.	2011	Retrospective	59	48 (30–70)	IIa, IIb, IIIa, IIIb, IIIc	IDC, ILC, other n.o.s.	ER, PR, HER2
Loo et al.	2011	Prospective	118	46 (23–76)	>3 cm	IDC, ILC, adenocarcinoma n.o.s.	ER, HER2
Shin et al.	2011	Prospective	43	43 (25–62)	LABC/inflammatory breast cancer and at least N1, or unsuitable for BCT, or skin/chest wall involvement	IDC, micropapillary carcinoma	ER, HER2
Lyou et al.	2011	Retrospective	57	44 (24–64)	Not reported	IDC, ILC	Not reported
Chen et al.	2011	Prospective	50	49 (28–82)	Not reported	IDC, ILC, invasive cancer with squamous differentiation	ER, PR, HER2, Ki-67
Kim et al.	2012	Prospective	55	49 (28–82)	IIa, IIb, IIIa, IIIb, IIIc, IV	IDC, ILC, mucinous carcinoma	Not reported
Kuzucan et al.	2012	Retrospective	54	46 (29–63)	Not reported	IDC, ILC, mixed ductal carcinoma with lobular features	ER, PR, HER2, Ki-67
Takeda et al.	2012	Prospective	37	51 (30–78)	Not reported	Not reported	Not reported
Shin et al.	2012	Retrospective	90	46 (24–68)	IIa, IIb, IIIa, IIIb, IIIc	IDC, ILC, metaplastic carcinoma, micropapillary carcinoma	ER, PR, HER2
Hylton et al.	2012	Prospective	216	48 (26–68)	T3 tumour of at least 3 cm	IDC, ILC, mixed ductolobular carcinoma, mucinous carcinoma	ER, PR, HER2
Park et al.	2012	Retrospective	34	44 (27–60)	Tumour size >2	IDC, mucinous carcinoma, mixed ductolobular carcinoma	HER2

Overview of included studies regarding year of publication, study design, size of study population, age of population, breast cancer stages of patients included, breast cancer types observed in the respective studies and their subtypes

LABC locally advanced breast cancer, *BCT* breast-conserving therapy, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *DCIS* ductal carcinoma in situ, *n.o.s.* not otherwise specified, *ER* estrogen receptor, *PR* progesterone receptor, and *HER* human epidermal growth factor receptor

of pCR might not be accurate. Therefore, the variation of size evaluation between MRI and pathology yields additional information. Bhattacharyya et al. reported an overestimation of >10 mm in 4 of 32 cases [24]. Belli et al. described a mean overestimation and underestimation of 2.1 and 2.0 mm, respectively [20]. These numbers were 20.2 and 13.8 mm in the study by Denis et al. [15]. Partridge et al. found the smallest deviation with an overestimation of MRI measurements of only 0.9 mm [13]. The studies by Guarneri et al. and Lyou et al. found a mean size difference of 1.6 and 6.0 mm, respectively [35, 38].

With respect to pCR prediction with MRI, sensitivity was considered to be the proportion of patients with pCR that were correctly classified with MRI as complete responders. Specificity was considered to be the proportion of patients with non-pCR correctly classified by MRI as non-responders. To illustrate, a sensitivity of 62 % in these studies meant that in 62 out of 100 patients, MRI was able to correctly identify patients with pCR (i.e. MRI did not show any residual enhancement). Eight studies calculated the diagnostic accuracies for MRI in predicting pCR (Table 4) [12, 18, 24, 25, 29, 34, 43, 45]. Two studies reported diagnostic accuracies for diffusion-weighted MR imaging, and both reported a sensitivity of 100 % [43, 45]. Specificity was 70 % and 91 %. Only one study evaluated the potential of MR spectroscopy parameters (total choline-containing compounds, tCho) and reported a sensitivity of 53 % and a specificity of 70 % [43]. The remaining studies used dynamic, contrast-enhanced MR imaging. Median (and range) sensitivity and specificity were 42 % (25–92 %) and 89 % (50–97 %), respectively. If reported, median (and range) PPV and NPV were 64 % (50–73 %) and 87 % (71–96 %), respectively.

Interestingly, only three studies compared diagnostic accuracy of MRI and ultrasound for assessing residual disease [19, 21, 25]. In these studies, ultrasound was less accurate than MRI. MRI was also more accurate than mammography in assessing residual disease, but only one study performed this comparison [19]. Finally, MRI was more accurate than physical examination for assessing residual disease, which was examined by three studies [19, 21, 44].

Table 2 Overview of included studies

Author	Chemotherapy regimen	Response assessment	Field strength (Tesla)	Pathologic assessment
Abraham et al.	4–5 cycles of doxorubicin	WHO	1.5	4 categories: (1) no residual disease; (2) disease in a single quadrant only; (3) multiquadrant small residual disease; (4) multiquadrant extensive disease
Esserman et al.	4 cycles of doxorubicin/cyclophosphamide	WHO	1.5	Correlation with tumour size measurements
Rieber et al.	3–5 cycles of anthracyclines and epirubicine/ paclitaxel, or anthracyclines and cyclophosphamide	No WHO or RECIST	1.5	Correlation with tumour size measurements
Partridge et al.	4 cycles of doxorubicin and cyclophosphamide followed by up to 12 cycles of paclitaxel	No WHO or RECIST	1.5	Correlation with tumour size measurements
Cheung et al.	3 cycles of paclitaxel and epirubicin	RECIST	1.5	Correlation with tumour size measurements
Denis et al.	5-fluorouracil/epirubicine, or 6 cycles of docetaxel or 8 cycles of docetaxel/epirubicine	RECIST	1.5	Correlation with tumour size measurements
Warren et al.	6 cycles of doxorubicin/cyclophosphamide, or 6 cycles of doxorubicin/docetaxel, or 4 cycles epirubicin then 4 cycles cyclophosphamide, or 4 cycles epirubicin, or docetaxel/herceptin	No WHO or RECIST	1.5	UICC response criteria/NHSBSP guidelines
Martincich et al.	4 cycles of doxorubicin bolus, followed by paclitaxel (n=29). In one case, doxorubicin was omitted because of low baseline left ventricular ejection fraction	WHO	1.5	5 grades: (1) some alteration in individual cells but no reduction in overall number of tumour cells; (2) mild loss of invasive tumour cells but still high cellularity; (3) estimated >90 % loss of tumour cells; (4) only small clusters of disease remaing, or only in situ component, or only tumour stroma remaining; (5) pathologic complete response
Schott et al.	4 cycles of doxorubicin/docetaxel	No WHO or RECIST	1.5	Definitions of response: pCR: no viable invasive cancer or DCIS. Stable disease/non-complete response: does not meet criteria for pCR. Partial response and progressive disease: not defined
Yeh et al.	4 cycles of doxorubicin, then 9 cycles of paclitaxel (or vice versa)	RECIST	1.5	Equal to pathology if longest tumour diameter was within 30 % of pathology tumour size. Not equal if tumour diameter was less than 70 % of pathology tumour size (underestimation) or more than 130 % of pathology tumour size (overestimation)
Belli et al.	3 cycles of cyclophosphamide, methotrexate, and 5-fluorouracil alternated with adriamycine, or 6 cycles of epirubicin and taxole	WHO	1.5	Correlation with tumour size measurements
Segara et al.	ER/PR/HER2 negative: 4 cycles cisplatin. ER positive: 4 cycles capecitabine. HER2 positive: either trastuzumab/vinorelbine or trastuzumab/carboplatin/docetaxel	RECIST	1.5	5 grades: (1) some alteration in individual cells but no reduction in overall number of tumour cells; (2) mild loss of invasive tumour cells but still high cellularity; (3) estimated

Table 2 (continued)

Author	Chemotherapy regimen	Response assessment	Field strength (Tesla)	Pathologic assessment
				>90 % loss of tumour cells; (4) only small clusters of disease remaing, or only in situ component, or only tumour stroma remaining; (5) pathologic complete response
Kim et al.	3 cycles of doxorubicine/docetaxel	WHO	1.5	Equal to pathology if tumour size was within 50 % of pathology tumour size. Not equal if tumour size was less than 50 % of pathology tumour size (underestimation) or more than 150 % of pathology tumour size (overestimation)
Chen et al.	2 cycles of doxorubicin and cyclophosphamide, then either 2 cycles of additional cyclophosphamide or taxane-based regimen (paclitaxel or Nab-paclitaxel combined with carboplatin. HER2+ also received trastuzumab, HER2- also received bevacizumab	RECIST	1.5	3 categories: (1) no residual malignancy or cancer cells; (2) no residual invasive cancer, but DCIS present; (3) residual invasive cancer. Categories 1 and 2 are considered pCR
Bhattacharyya et al.	6 cycles of doxorubicin or epirubicin and cyclophosphamide	RECIST	1.5	Correlation with tumour size measurements
Moon et al.	Taxane/anthracycline regimen, or anthracycline regimen, or trastuzumab	No WHO or RECIST	1.5	Correlation with tumour size measurements
Wright et al.	Epirubicin/taxotere (n=30); doxorubicin/ cyclophosphamid (n=17); cyclophosphamide/ taxotere/herceptin (n=1)	No WHO or RECIST	1.5	5 grades: (1) some alteration in individual cells but no reduction in overall number of tumour cells; (2) mild loss of invasive tumour cells but still high cellularity; (3) estimated >90 % loss of tumour cells; (4) only small clusters of disease remaing, or only in situ component, or only tumour stroma remaining; (5) pathologic complete response
Woodhams et al.	4 cycles of anthracycline/cyclophosphamide, followed by 4 cycles of paclitaxel	Not applicable	1.5	4 categories: (1) no residual disease; (2) disease in single quadrant only; (3) multiple residual diseases including EIC limited to one quadrant; (4) multiple residual disease including EIC in 2 or more quadrants
Park et al.	3 cycles of docetaxel/doxorubicin	RECIST	1.5	Correlation with tumour size measurements
De Los Santos et al.	4 cycles of doxorubicin, then 4 cycles of paclitaxel, then 4 cycles of cyclophosphamide	RECIST	1.5	Assessment for pCR
Straver et al.	HER2-: 6 cycles of doxorubicin/cyclophosphamide, 6 cycles of doxorubicin/docetaxel, or 6 cycles of capecitabine/docetaxel, or the combination of 3 cycles of doxorubicin/cyclophosphamide plus 3 cycles of capecitabine/docetaxel. HER2+: doxorubicin/ cyclophosphamide and after 2005 paclitaxel, trastuzumab, carboplatin	No WHO or RECIST	1.5/3	Assessment for pCR

Table 2 (continued)

Author	Chemotherapy regimen	Response assessment	Field strength (Tesla)	Pathologic assessment
Nakahara et al.	4–6 cycles of epirubicin/cyclophosphamide, with or without doxifluridine. In 17 cases continuation with 4–6 cycles docetaxel or 12 cycles paclitaxel. In 15 cases 6 cycles of docetaxel/epirubicin/cyclophosphamide. In HER2+, also taxanes (n=7) or taxanes/trastuzumab (n=4)	RECIST	1.5	Japanese Breast Cancer Society classification system
Wang et al.	Taxol/carboplatin n.o.s.	No WHO or RECIST	1.5	Correlation with tumour size measurements
Dongfeng et al.	4 cycles of paclitaxel/pirarubicin	RECIST	3	Correlation with tumour size measurements
Fangberget et al.	Letrozol therapy (n=2); or 4 cycles 5-fluorouracil/epirubicin/cyclophosphamide, followed by 2 additional cycles (n=10), or switch to taxans (n=10) or taxans/trastuzumab (n=8)	RECIST	1.5	Correlation with tumour size measurements
Guarneri et al.	4–8 cycles of either epirubicin/paclitaxel or paclitaxel, followed by 5-fluorouacil/epirubicin/cyclophosphamide. Some HER2+ patients also received trastuzumab (n=25)	No WHO or RECIST	1.5	Correlation with tumour size measurements
Loo et al.	Different regimes: majority of HER2-recieved 6 cycles of cyclosphosphamide/doxorubicin, some HER2-6 cycles of capecitibine/docetaxel, or doxorubicin/docetaxel; if no response, switch to 3 cycles of cyclophosphamide/doxorubicin, followed by 3 cycles of capecitibine/docetaxel; HER2+ recieved 8 weeks of paclitaxel/trastuzumab/carboplatin, followed by either 2×8 weeks paclitaxel/trastuzumab/carboplatin, or 4 cycles of trastuzumab/fluorouacil/cyclophosphamide	Two approaches: Breast Response Index, and dichotomously (presence or absence of residual disease). PCR and near-pCR were considered on category (pCR)	1.5/3	World Health Organisation grading of tumours
Shin et al.	8 cycles of adriamycin/cyclophosphamide/docetaxel, or 8 cycles of capecitabine/vinorelbine/docetaxel	RECIST	1.5	5 grades: (1) some alteration in individual cells but no reduction in overall number of tumour cells; (2) mild loss of invasive tumour cells but still high cellularity; (3) estimated >90 % loss of tumour cells; (4) only small clusters of disease remaining, or only in situ component, or only tumour stroma remaining; (5) pathologic complete response
Lyou et al.	3–6 cycles of taxane/anthracycline, or 3–4 cycles of anthracycline-based regimen, or 6 cycles of trastuzumab/taxane regimen	RECIST	1.5	Correlation with tumour size measurements
Chen et al.	2 cycles of doxorubicin, followed by cyclophosphamide biweekly, followed by 12 weeks of taxane based regimen; or only taxane-based regimen	Not reported	3	3 grades: (1) no residual cancer cells; (2) no residual invasive cancer cells but ductal carcinoma in situ; (3) residual invasive cancer. PCR was defined as being category 1 and 2
Kim et al.	Taxane/anthracycline based regimen, or	RECIST	1.5/3	5 grades: (1) some alteration in individual cells but no reduction in overall number of tumour cells; (2) mild loss of invasive

Table 2 (continued)

Author	Chemotherapy regimen	Response assessment	Field strength (Tesla)	Pathologic assessment
				tumour cells but still high cellularity; (3) estimated >90 % loss of tumour cells; (4) only small clusters of disease remaining, or only in situ component, or only tumour stroma remaining; (5) pathologic complete response
Kuzucan et al.	Combination of doxorubicin and cyclophosphamide and taxane based regimen; or only cyclophosphamide; or only taxane-based regimen	Not reported	1.5/3	Pathologic complete response defined as the absence of invasive cancer
Takeda et al.	Docetaxel and cyclophosphamide for 3–6 cycles	No WHO or RECIST	3	Pathologic complete response defined as the absence of invasive cancer
Shin et al.	4 cycles of doxorubicin/cyclophosphamide; or 4 cycles of cyclophosphamide followed by 4 cycles of docetaxel; or doxorubicin/ docetaxel; or 5-fluorouracil/epirubicin/ cyclophosphamide; or 6 cycles of trastuzumab/paclitaxel	RECIST	1.5	PCR classified into two categories: (1) no residual disease, or (2) absence of invasive cancer, but DCIS present
Hylton et al.	Anthracycline-cyclophosphamide regimen alone or followed by a taxane	RECIST	1.5	Residual cancer burden and pathologic complete response; pCR defined as the absence of invasive cancer
Park et al.	3 cycles of doxorubicin/docetaxel; or (if HER2-positive) 6 cycles of paclitaxel/ gemcitabine/trastuzumab	No WHO or RECIST	1.5	5 grades: (1) some alteration in individual cells but no reduction in overall number of tumour cells; (2) mild loss of invasive tumour cells but still high cellularity; (3) estimated >90 % loss of tumour cells; (4) only small clusters of disease remaining, or only in situ component, or only tumour stroma remaining; (5) pathologic complete response Pathologic complete response defined as the absence of invasive cancer. Pathologic complete response defined as the absence of invasive cancer PCR classified into two categories: (1) no residual disease, or (2) absence of invasive cancer, but DCIS present. Residual cancer burden and pathologic complete response; pCR defined as the absence of invasive cancer

Overview of included studies regarding chemotherapy regimen(s) that were used in the study, method of response evaluation, field strength of the MRI scanner used, method of pathologic response assessment

n.o.s. not otherwise specified, *ER* estrogen receptor, *PR* progesterone receptor, *HER* human epidermal growth factor receptor, *RECIST* Response Evaluation Criteria In Solid Tumours, *WHO* World Health Organisation, *pCR* pathologic complete response, *DCIS* ductal carcinoma in situ, *EIC* extensive intraductal component, *UICC* Union for International Cancer Control and *NHSBSP* National Health Service Breast Screening Programme

Table 3 Correlation coefficients of MRI and histopathological tumour measurements

Author	Correlation coefficient	P-value
Partridge et al.	0.89	<0.001
Cheung et al.	0.982	<0.001
Martincich et al.	0.72	<0.001
Segara et al.	0.749	<0.0001
Kim et al.	0.645	<0.001
Moon et al.	0.584	NA
Wright et al.	0.49	NA
Park et al.	0.667	NA
Nakahara et al.	0.21	NS
Wang et al.	0.866	<0.01
Dongfeng et al.	0.698	<0.001
Fangberget et al.	0.87	<0.001
Guarneri et al.	0.53	NS
Shin et al.[a]	0.97	NA
Chen et al.	0.30	0.03
Kim et al.	0.619	<0.0001
Shin et al.[b]	0.781	NA

NA not available, *NS* not significant

[a] 2011 paper, [b] 2012 paper

Discussion

In this systematic review, we aimed to analyse the available data on MRI accuracy for assessing residual disease and pCR after neoadjuvant chemotherapy in breast cancer patients.

Many studies compared the measured tumour diameter or volumes on MRI with pathological results as the gold standard. Correlation coefficients for these comparisons were good to excellent, but both overestimation and underestimation of the MRI size measurements were frequently observed. Although these correlation coefficients were good, it does not necessarily mean that agreement between these measurements is good. The majority of studies did not investigate the agreement between these measurements, for instance by using Bland-Altman plots [46].

Contrast-enhanced breast MRI is superior to other imaging modalities to assess breast tumour extent and the presence of multicentricity or multifocality [4, 5]. However, overestimation of tumour extent is a well-known phenomenon in (preoperative) breast MRI [47, 48] and was also observed in the NAC setting. Confounding factors in overestimating tumour size might be: reactive inflammation caused by tumour response and healing, surrounding sclerosis and necrosis, multiple scattered lesions and presence of accompanying ductal carcinoma in situ [19, 20, 22]. In theory, overestimation of tumour size by MRI could result in an altered surgical treatment plan for the individual patient, with the risk of achieving wider resection margins (with poorer cosmetic results) or performing unnecessary mastectomy (where breast-conserving therapy would have been possible).

In contrast to overestimation of tumour size by MRI, underestimation was also observed in the NAC setting. Causes might be antivascular effects of docetaxel (resulting in less tumour enhancement), lack of inflammatory response surrounding the tumour in docetaxel patients, more extensive ductal carcinoma in situ components and partial volume effects in very small foci of residual disease [13, 15, 21]. Underestimation of residual disease could lead to positive resection margins with viable residual tumour cells, necessitating re-surgery. In addition, positive resection margins are associated with an increased long-term risk of disease recurrence in patients who have undergone breast-conserving therapy [49]. Straver et al. attempted to create an MRI-based model that could help in surgical decision making. In this study, MRI underestimated tumour size >20 mm in 17 % of the patients, in 13 % leading to an incorrect decision to perform breast-conserving surgery. From their study, they

Table 4 Diagnostic accuracies of MRI for predicting pathologic complete response

Author	Sensitivity (%)	Specificity (%)	PPV (%	NPV (%)	Accuracy (%)	Prevalence
Rieber et al.	42	89	73	71	72	0.21
Schott et al.	25	97	50	94	89	0.10
Bhattacharyya et al.	80	89	56	96	NA	0.13
Moon et al.	38	96	NA	NA	NA	0.15
De Los Santos et al.	92	50	72	80	NA	0.40
Fangberget et al.	38	96	NA	NA	NA	0.37
Park et al.	100[a]	70[a]	47[a]	100[a]	77[a]	0.21
Shin et al.	77	70	NA	NA	NA	0.33
	100[a]	91[a]	NA[a]	NA[a]	NA[a]	
	53[b]	70[b]	NA[b]	NA[b]	NA[b]	

PPV positive predictive value, *NPV* negative predictive value, *NA* not available, *tCho* total choline-containing compounds

The results are presented for dynamic, contrast-enhanced MRI, with the exception of: [a]diffusion-weighted imaging and [b]MR spectroscopy parameters

concluded that baseline tumour size, tumour size reduction and cancer subtype should be taken into account in the optimal selection of patients eligible for breast-conserving therapy [30].

Seven studies provided an overview of the diagnostic accuracy of MRI to predict pCR. Median sensitivity and specificity were 42 % and 89 %, respectively. If reported, median PPV and NPV were 64 % and 87 %, respectively. In a meta-analysis of 25 studies, Yuan et al. showed that pooled weighted estimates of sensitivity and specificity of MRI for demonstrating pCR were 63 % (range 56–70 %) and 91 % (range 89–92 %) [6]. These findings were concordant with the observations made by Wu et al., who performed a meta-analysis of 34 studies [7]. They concluded that the sensitivity and specificity of contrast-enhanced breast MRI to predict pCR were 68 % and 91 %, respectively. These values are slightly discrepant with the observations of our current review. The variation in these findings, especially in specificity, might be explained by the differences in included studies, since these recent publications additionally included studies with smaller populations and lower MRI field strengths. Since pCR is only achieved in up to 30 % of patients, we think that a minimum number of ten patients is too low to accurately use pCR as a study outcome. Therefore, we chose a minimum number of 25 patients to be included in our final analysis. Despite the differences in these reviews and our current study, the diagnostic accuracy of breast MRI to predict pCR seems to have a high specificity and NPV versus only moderate sensitivity and PPV. Nevertheless, the varying results in the separate studies (and their range) of the recent reviews show that MRI's accuracy for assessing pCR is still under debate and that it is too early to use it as a decision-making tool in studies that investigate other treatment strategies after pCR besides surgery.

Although the number of studies was small, contrast-enhanced MRI outperformed physical examination, ultrasound and mammography in accurately assessing residual disease. In physical examination, this is most likely explained by fibrosis surrounding the tumour bed as a result of the therapy. This fibrotic tissue remains hard, and as such it could lead to misinterpretation of residual disease. These fibrotic changes can also be observed in mammography and ultrasound and cannot be easily discerned from residual tumour tissue, but can be excluded by MRI since this fibrotic tissue does not show any enhancement after contrast administration. In addition, the diagnostic accuracy of mammography is strongly dependent on breast density, being lower in breasts with extremely dense fibroglandular tissue [50]. If performed in the right period of the menstrual cycle (day 3–14 in premenopausal women), the accuracy of breast MRI was less influenced by breast density [51].

Almost all papers used contrast-enhanced breast MRI for the evaluation of residual disease and pCR after NAC. Some studies additionally investigated the ability of diffusion-weighted imaging (DWI) for assessing pCR after NAC. In DWI, MRI is used to assess the Brownian motions of water molecules within a certain tissue of interest. In the cell-rich environment of tumours, the motion of these molecules is restricted and can be measured with DWI. This results in increased signal intensity on so-called diffusion-weigted images, with corresponding low values for the apparent-diffusion coefficient or ADC. Woodhams et al. demonstrated that the sensitivity, specificity and accuracy of DWI for assessing pCR was higher than contrast-enhanced breast MRI, but the differences observed were not significant with p-values of 0.31, 0.08 and 0.06, respectively [26]. In the study by Park et al., DWI was compared to positron emission computed tomography (PET-CT) and showed a slightly higher AUC for predicting pCR when compared to PET-CT, although this difference was not statistically significant in their population of 34 patients, of which 7 achieved pCR after therapy [45]. In the study by Shin et al., three different MRI techniques were compared: dynamic contrast-enhanced MRI, DWI and MR spectroscopy. They concluded that the change in ADC after treatment was the most accurate predictor of pCR. With an AUC of 0.96, they found that the optimal cutoff value for percentage ADC change was 40.7 %, yielding a sensitivity of 100 % and a specificity of 91 % [43].

This review has some important limitations. First, publication bias is a study limitation that merits attention in each systematic review. Small studies with less favorable results tend to be published less frequently or not at all. With this potential bias in mind, one should realise that the current positive findings of MRI accuracy after NAC might be overestimated.

Second, the lack of study uniformity prevented us from performing a meta-analysis. Therefore, we chose to perform a systematic review of the selected studies and provide a descriptive presentation of the observed findings instead of performing a meta-analysis that uses statistical models to adjust for this heterogeneity to some extent. Variations in study aim, chemotherapy regimens, response assessment criteria in both imaging and pathological analysis, patient populations and breast cancer subtypes precluded us from drawing more definitive conclusions. For example, Chen et al. showed in their study that MRI can predict pCR accurately in HER2-positive patients, but a high false-negative rate was observed in HER2-negative patients, especially when they received anti-angiogenic drugs [23]. Loo et al. showed in their study of 118 patients that response monitoring after NAC is effective in triple-negative or HER2-positive breast cancer subtypes, but is inaccurate in ER-positive/HER2-negative subtypes [36]. In their 2011 publication, Chen et al. demonstrated that MR imaging accuracy was higher for HER2-positive cancer types than for HER2-negative tumours (88 % versus 82 %). In the same study,

they showed that the average size discrepancy in cases with Ki-67 staining of <10 % was greater than in cases with Ki-67 staining of >40 % [39]. But also the choice of chemotherapeutic regimen can influence MRI accuracy. Denis et al. showed that MRI frequently underestimated residual tumour size in taxane-containing treatments, most likely because of the antivascular effects of these drugs, resulting in less enhancement on contrast-enhanced MRI [15].

Third, the method of evaluating treatment response in imaging and pathology is important. Although no significant differences between WHO and RECIST criteria in imaging response assessment were observed in other cancer types, multiple response criteria were used in the selected studies [52, 53]. Similarly, there are no widely accepted response assessment criteria for pathology. The most important issue in this assessment is the extent of residual DCIS. Whether or not DCIS is included in the analysis might partly explain the differences observed in MRI over- and underestimation. From a clinical point of view, it would be most interesting to assess MRI accuracy if DCIS were included in the definition of pCR, since DCIS should also be excised during surgery and identification of DCIS extension by MRI remains challenging [54].

Fourth, the population size of the majority of studies is relatively small. Only four studies had a population size >100 subjects [25, 30, 36, 44] and most of the studies were single-centre studies. The statistical noise will be smaller if the sample sizes are increased in (future) multicentre studies in order to assess the true accuracy of MRI in the NAC setting with greater confidence.

In summary, breast MRI accuracy for assessing residual disease after neoadjuvant chemotherapy is good, but multiple factors, such as cancer subtype and treatment regimen, can influence MRI accuracy and should be considered in clinical decision making. Both overestimation and underestimation can be observed and might have important clinical impact. Clinical decision making based on MRI results should therefore be made prudently with these limitations in mind. Regardless of the many potential confounders described in this review, we feel that assessment of NAC response with MRI is promising and ready for more multicentre studies that are able to address these shortcomings.

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