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Original article

Early prediction of pathologic response to neoadjuvant therapy in breast cancer: Systematic review of the accuracy of MRI

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ABSTRACT

Magnetic resonance imaging (MRI) has been proposed to have a role in predicting final pathologic response when undertaken early during neoadjuvant chemotherapy (NAC) in breast cancer. This paper examines the evidence for MRI's accuracy in early response prediction. A systematic literature search (to February 2011) was performed to identify studies reporting the accuracy of MRI during NAC in predicting pathologic response, including searches of MEDLINE, PREMEDLINE, EMBASE, and Cochrane databases. 13 studies were eligible (total 605 subjects, range 16–188). Dynamic contrast-enhanced (DCE) MRI was typically performed after 1–2 cycles of anthracycline-based or anthracycline/taxane-based NAC, and compared to a pre-NAC baseline scan. MRI parameters measured included changes in uni- or bidimensional tumour size, three-dimensional volume, quantitative dynamic contrast measurements (volume transfer constant [Ktrans], exchange rate constant [k_{ep}], early contrast uptake [ECU]), and descriptive patterns of tumour reduction. Thresholds for identifying response varied across studies. Definitions of response included pathologic complete response (pCR), near-pCR, and residual tumour with evidence of NAC effect (range of response 0–58%). Heterogeneity across MRI parameters and the outcome definition precluded statistical meta-analysis. Based on descriptive presentation of the data, sensitivity/specificity pairs for prediction of pathologic response were highest in studies measuring reductions in Ktrans (near-pCR), ECU (pCR, but not near-pCR) and tumour volume (pCR or near-pCR), at high thresholds (typically >50%); lower sensitivity/specificity pairs were evident in studies measuring reductions in uni- or bidimensional tumour size. However, limitations in study methodology and data reporting preclude definitive conclusions. Methods proposed to address these limitations include: statistical comparison between MRI parameters, and MRI vs other tests (particularly ultrasound and clinical examination); standardising MRI thresholds and pCR definitions; and reporting changes in NAC based on test results. Further studies adopting these methods are warranted.

Introduction

Neoadjuvant chemotherapy (NAC) has a well-established role in the management of breast cancer.[1] A number of theoretical advantages of NAC over adjuvant therapy have been identified[2]; however, for women with operable disease at presentation, the primary aim of NAC is the achievement of pathologic complete response (pCR) prior to surgery,[3,4] which has been shown to confer improvements in long-term disease-free and overall survival.[5,6] A secondary objective in these patients is an improvement of surgical options (conversion from mastectomy to breast conservation surgery [BCS], or performance of more cosmetic BCS). For women with inoperable locally advanced disease, the emphasis placed on these aims is reversed.[4]

A key advantage of NAC is the opportunity to assess response early during treatment as a predictor of final pathologic response,[2] with the potential for modification of therapy to increase rates of pCR, tumour volume reduction, and treatment tolerability.

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Randomised controlled trials (RCTs) have indicated potential advantages of therapy modification in both early responders and non-responders, where response was assessed primarily by clinical examination and ultrasound (US). Significantly increased rates of pCR (34% vs 16%, $p < 0.04$), BCS (67% vs 48%, $p < 0.01$) and improved overall survival (OS) were found in clinical responders randomised to taxanes after 4 cycles of anthracycline-based NAC relative to those continuing treatment.[7,8] A further RCT randomising early responders to standard (i.e. 6 cycles) or extended (i.e. 8 cycles) anthracycline/taxane-based NAC found significantly longer disease-free survival (DFS) (hazard ratio [HR] 0.79, $p = 0.03$) and a trend towards longer OS (HR 0.76, $p = 0.06$) when NAC was extended.[9] Additionally, improved DFS (HR 0.6, $p = 0.001$) and treatment tolerability has been demonstrated in early non-responders after a switch to vinorelbine and capecitabine, with similar rates of pCR (6.0% vs 5.3%) and BCS (60% vs 57%) as continued anthracycline/taxane-based NAC.[9,10]

Among other applications in the NAC setting, magnetic resonance imaging (MRI) has been proposed to have a role in early response assessment. Quantitative imaging by dynamic contrast enhanced (DCE) MRI has theoretical advantages over conventional assessment methods (mammography, US, clinical examination) in measuring angiogenic changes in response to NAC which may occur prior to reductions in tumour size.[11] Consensus recommendations specify that early response assessment with MRI is worthy of further investigation.[12] This paper systematically examines the evidence on MRI's accuracy in early prediction of pathologic response, including comparisons with alternative assessment methods.

Methods

Identification of studies

A systematic search of the biomedical literature up to February 2011 was undertaken to identify studies assessing the accuracy of MRI during NAC in predicting pathologic response. MEDLINE and EMBASE were searched via EMBASE.com; PRE-MEDLINE, Database of Abstracts of Reviews of Effects (DARE), Heath Technology Assessment (CLHTA), and Cochrane databases were searched via Ovid. Keywords and medical subject headings included 'breast cancer', 'nuclear magnetic resonance imaging', 'MRI', 'neoadjuvant', and 'response'. The full search strategy is available in Table S1 (online Appendix). Reference lists were also searched and content experts consulted to identify additional studies.

Review of studies and eligibility criteria

A total of 2107 non-duplicate citations were identified. All abstracts were screened for eligibility by one author (LM). A sample of 252 abstracts (12%) was assessed independently by a second reviewer (NH) to ensure consistent application of the eligibility criteria. Eligible studies were required to have enrolled patients with newly diagnosed breast cancer undergoing NAC prior to surgery, with MRI undertaken at any point *during* NAC to predict in-breast pathologic response (with or without response in axillary lymph nodes) after completion of the last NAC cycle. Studies must have provided estimates of the accuracy of MRI, or sufficient data to allow calculation of accuracy. Pathologic response based on surgical excision was the reference standard, but studies were not excluded if alternative reference standards were used in a minority of patients. Where comparisons with alternative assessment methods were presented, estimates of accuracy were also extracted or derived for these tests. Studies in which MRI was undertaken only after completion of NAC, or which enrolled fewer than 10 patients, were ineligible.

Potentially eligible citations were retrieved in full. One author (LM) determined final inclusion; studies with unclear eligibility were reviewed by a second author (NH). The screening and inclusion process is summarised in Fig. S1 (online Appendix).

Data extraction

Data on test accuracy, study design, patient characteristics, technical details of MRI, comparator tests, and the reference standard were extracted independently by two authors (LM, and either SC, MB, or FS). Study-level definitions of pathologic response were categorised according to the criteria in Table 1. Quality appraisal was undertaken using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist (modified for application to studies of response prediction in this setting).[13,14] Disagreements were resolved by discussion and consensus, with arbitration by a third author (NH) when required.

Statistical analysis

Study-specific estimates of pathologic response, and sensitivity and specificity for predicting pathologic response were calculated for MRI and comparator tests. Sensitivity was defined as the proportion of pathologic responders classified as early responders to NAC by the relevant test; specificity was defined as the proportion of pathologic non-responders in whom no early response was detected. Exact 95% confidence intervals for proportions were computed (SAS version 9.2). Sensitivity/specificity pairs for MRI were plotted in receiver operating characteristics (ROC) space, and points were joined where variation of the MRI or pathologic response threshold resulted in multiple estimates within studies. For each study, when paired data were available, differences in sensitivity and specificity between MRI parameters or MRI and other technologies were tested with McNemar's test. Major

Table 1
Classification of pathologic response definitions.

1 No invasive cancer, but DCIS may be present
This category includes classifications such as:

- Smith et al. (2002), Ogsten, Miller, Payne et al. (2003) grading systems – grade 5 (no malignant cells identifiable in sections from the site of the tumour; only vascular fibroelastotic stroma remains often containing macrophages. However, ductal carcinoma *in situ* (DCIS) may be present)
- Sinn et al. (1994) – combination of score 4 (No residues at all) and score 3 (no invasive residues but persistent intraductal tumour)

2 No invasive cancer (not further specified)

3 Near pCR, minimal residual disease
This category includes classifications such as:

- Ogsten, Miller, Payne et al. (2003) – grade 4 (a marked disappearance of tumour cells such that only small clusters or widely dispersed individual cells remain; more than 90% loss of tumour cells), or variants of this classification
- Sataloff (1995) – grade A (total or near total therapeutic effect)

4 More than minimal residual disease, but evidence of chemotherapeutic effect

- Miller/Payne modifications: Macroscopic residual cancer with chemo-induced changes and/or histological tumour response.
- Sataloff (1995) – grade B (>50% therapeutic effect)

inconsistencies between studies across several levels (MRI parameters, thresholds, and pathologic outcome definitions; see Results) precluded pooled analysis; hence, a descriptive summary of the results is provided.

Results

Thirteen studies met our eligibility criteria. A summary of included studies and study quality is presented in Tables S2 and S3 (online Appendix).

Study and patient characteristics

Patients were enrolled between 1995 and 2009. Study sample sizes ranged from 16 to 188 patients (median 28). Mean ages ranged from 43 to 53 years (median 49). Invasive ductal carcinoma (IDC) was the main tumour type, reported in 56–100% (median 83%). In six of the seven studies presenting stage categories, most patients were stage II; in the other, the majority were stage III; and two studies included a small number with stage IV (4%, 11%). Between 60% and 100% of patients presented with operable disease (median 88%; nine studies), according to the National Surgical Adjuvant Breast and Bowel Project (NSABP) definition of operability (stages IIa, IIb, IIIa).[15]

NAC characteristics

NAC regimens were primarily anthracycline-based and/or anthracycline/taxane-based (sequential or in combination). In two studies, other regimens were delivered in 68% and 44% of patients, respectively.[17,18] The number of planned NAC cycles varied between 3 and 8, although one study delivered a minimum of two cycles.[18] Three studies used trastuzumab in HER2-positive patients.[19,20]

MRI characteristics and timing

All studies used DCE-MRI with a 1.5 T magnet. Dedicated bilateral breast coils were used in all studies. Of 11 studies providing detail on contrast materials and dose, all employed gadolinium-based materials with R1 relaxivity ranging from 3.6 to 4.3 L/mmol s^{-1} and 0.5-M concentration,[21] typically at the standard dosage of 0.1 mmol/kg body weight.

MRI was most commonly performed after one or two NAC cycles (nine studies). Two studies performed MRI after four (of six-to-eight planned) cycles,[16,22] and in another, MRI was performed after 12 weekly taxane cycles, followed by four cycles of FEC.[23] One further study performed MRI after one cycle in patients receiving three-to-five cycles of trastuzumab, and for the majority of patients, after three of six planned cycles of an anthracycline-based regimen.[20] All studies compared mid-NAC MRI to pre-NAC baseline scans.

There was variability in the MRI parameter measured: nine studies considered reductions in uni- or bidimensional tumour size[16–19,22–26]; three considered three-dimensional tumour volume[22,27,28]; four measured dynamic contrast characteristics (volume transfer constant [Ktrans], exchange rate constant [k_{ep}], early contrast uptake)[18,25,27,29]; and one study reported patterns of MRI tumour reduction (shrinking mass, diffuse decrease, small foci, no enhancement, no change).[20] Thresholds applied to identify MRI response also varied (Table 2), and were data-driven (i.e. derived retrospectively to obtain the highest sensitivity and specificity pair) in seven studies.

Definitions of pathologic response

The definition of pathologic response after NAC was not standardised. Hence, where multiple definitions were possible within studies, these have been presented individually. Four studies defined the outcome as pCR (absence of invasive cells, with or without ductal carcinoma *in situ* [DCIS]).[16,19,22,27] Two studies defined response as no residual invasive disease in the breast and axilla, and were the only studies to include nodal status in the outcome.[23,28] Response was defined as "near-pCR" (small clusters of microscopic invasive cells, or similar definitions of minimal residual disease) in seven studies.[16,17,20,24,26,27,29] Definitions which allowed for more than minimal residual disease (e.g. macroscopic residual cancer with evidence of chemotherapeutic effect) were presented in three studies.[18,25,26]

In three studies, pathologic verification from surgery was not obtained in a minority of patients (range 7–18%)[17,18,25]; in one of these studies, an alternative reference standard was used in a larger proportion of patients for ROC analyses only (28%).[17] Alternative reference standards were biopsy, clinical and/or radiological examination, and long-term follow-up.

Study-specific rates of pathologic response ranged between 0% and 58%, and are presented in Fig. 1, stratified by response definition. Although the prevalence of pathologic response varied within strata, estimates were observed to increase as more residual invasive disease was permitted in the response definition.

Accuracy of MRI to predict final pathologic response

Tables 2–4 summarise accuracy estimates according to the MRI parameters measured and the pathologic response definitions applied. Data on MRI's sensitivity (proportion of pathologic responders correctly classified as early responders) and/or specificity (proportion of pathologic non-responders correctly classified as early non-responders) were derived from 11 studies. Figs. 2 and 3 present study-specific sensitivity/specificity pairs for the prediction of pCR and near-pCR in ROC space, with estimates labelled by MRI parameter and threshold. For both outcome definitions, sensitivity/specificity pairs appeared to be highest for reductions in three-dimensional tumour volume[22,27] and quantitative DCE-MRI parameters[27,29] during NAC relative to baseline. Thresholds to declare response were relatively high for tumour volume (65% or 83%) and Ktrans (85%). For one study comparing reductions in volume and early contrast uptake (ECU), with separate ECU thresholds applied to homogenous (58%) and peripheral ring-like lesions (38%), comparable sensitivity (100% vs 100%, $p = 1.0$) and specificity (71% vs 79%, $p = 0.48$) were reported for the prediction of pCR (Fig. 2); for the prediction of near-pCR, sensitivity for volume reduction was higher than for ECU (91% vs 64%, $p = 0.08$), with comparable specificity (84% vs 79%, $p = 0.65$)[27] (Fig. 3). Significance tests were not presented in the remaining studies. For each of these studies, data-driven thresholds were applied to derive the highest sensitivity/specificity pair.

For the prediction of both pCR and near-pCR by reductions in uni- or bidimensional tumour size, between-study comparisons suggested that any possible gains in sensitivity over volumetric or quantitative DCE-MRI parameters were offset by large reductions in specificity (or vice versa) (Figs. 2 and 3). Three comparisons of Ktrans (and the related parameter k_{ep}), volumetric and size measurements found similar AUCs for these parameters within studies[18,19,22]; in one study, the AUC for Ktrans appeared to be greater than for bidimensional size[25] (Table 4). Significance tests for differences in AUCs between parameters were not reported.

Variable sensitivity/specificity estimates were evident for patterns of MRI tumour reduction to predict near-pCR (Fig. 3),[20] but

Table 2
All studies reporting the sensitivity and/or specificity of MRI.

Author [reference] (date)	*N*	pCR category	MRI timing		Treatment change (%)		MRI response parameter	Threshold reduction	Data driven threshold	MRI accuracy			
			Cycles	(Weeks)						TP/pCR	Sn (95% CI)	TN/no-pCR	Sp (95% CI)
Ah-See[25] (2008)	28	4	2	(6)	Yes	(13)	Bidimensional size	>26.5%	Yes	NR	NR	10/17	0.59 (0.33–0.82)
							Ktrans	>42.4%	Yes	8/11	0.73 (0.39–0.94)	16/17	0.94 (0.71–1.00)
Baek[19] (2009)	34	1	1–2[a]	(2–4)	Yes	(NR)	Bidimensional size[b]	≥30%	No[c]	8/17	0.47 (0.23–0.72)	12/17	0.71 (0.44–0.90)
							Bidimensional size[b]	≥50%	No[c]	5/17	0.29 (0.10–0.56)	13/17	0.76 (0.50–0.93)
							Bidimensional size[b]	≥65%	No[c]	3/17	0.18 (0.04–0.43)	16/17	0.94 (0.71–1.00)
Corcioni[16] (2008)	16	1	4	(NR)	NR	(NR)	Unidimensional size[d]	>0%	?Yes	0/0	–	4/16	0.25 (0.07–0.52)
	16	3	4	(NR)	NR	(NR)	Unidimensional size[d]	>0%	?Yes	5/5	1.00 (0.48–1.00)	4/11	0.36 (0.11–0.69)
Fangberget[22] (2011)	26	1	4	(12)	Yes	(63)	Volume	≥83%	Yes	NR	0.91 (NR)	NR	0.80 (NR)
Kim[23] (2009)[e]	115	2	12	(12)	NR	(NR)	Unidimensional size	≥30%	No	25/29	0.86 (0.68–0.96)	26/86	0.30 (0.21–0.41)
							Bidimensional size	≥50%	No	27/29	0.93 (0.77–0.91)	21/86	0.24 (0.16–0.35)
							Bidimensional size	≥80%	Yes	22/29	0.76 (0.56–0.90)	54/86	0.63 (0.52–0.73)
Loo[24] (2008)	54	3	2	(6)	No	(0)	Unidimensional size	≥25%	Yes	14/15	0.93 (0.68–1.00)	21/39	0.54 (0.37–0.70)
Loo[20] (2011)	188	3	1,3	(6,8)	Yes	(NR)	MRI pattern: shrinking mass	NA	NA	13/38	0.34 (0.20–0.51)	83/150	0.55 (0.47–0.63)
							MRI pattern: diffuse decrease	NA	NA	5/38	0.13 (0.04–0.28)	110/150	0.73 (0.66–0.80)
							MRI pattern: small foci	NA	NA	8/38	0.21 (0.10–0.37)	141/150	0.94 (0.89–0.97)
							MRI pattern: no enhancement	NA	NA	11/38	0.29 (0.15–0.46)	139/150	0.93 (0.87–0.96)
							MRI pattern: any change above	NA	NA	37/38	0.97 (0.86–1.00)	23/150	0.15 (0.10–0.22)
Martincich[27] (2004)	30	1	2	(NR)	NR	(NR)	Volume	>65%	Yes	6/6	1.00 (0.54–1.00)	17/24	0.71 (0.49–0.87)
							Early contrast uptake	≥58%, ≥38%[f]	Yes	6/6	1.00 (0.54–1.00)	19/24	0.79 (0.58–0.93)
	30	3	2	(NR)	NR	(NR)	Volume reduction	>65%	Yes	10/11	0.91* (0.59–1.00)	16/19	0.84 (0.60–0.97)
							Early contrast uptake	≥58%, ≥38%[f]	Yes	7/11	0.64* (0.31–0.87)	15/19	0.79 (0.54–0.94)
Padhani[17] (2006)	20	3	1	(3)	No	(0)	Bidimensional size	>10%	No	6/11	0.55 (0.23–0.83)	8/9	0.89 (0.52–1.00)
	15	3	2	(6)	No	(0)	Bidimensional size	>10%	No	5/9	0.56 (0.21–0.86)	5/6	0.83 (0.36–1.00)
Tozaki[26] (2010)	16	3	2	(NR)	No	(0)	Unidimensional size	≥30%	No[c]	3/4	0.75 (0.19–0.99)	8/12	0.67 (0.35–0.90)
							Unidimensional size	≥50%	No[c]	2/4	0.50 (0.07–0.93)	11/12	0.92 (0.62–1.00)
							Unidimensional size	≥65%	No[c]	0/4	0.00 (0.00–0.70)	12/12	1.00 (0.74–1.00)
	16	4	2	(NR)	No	(0)	Unidimensional size	≥30%	No[c]	6/8	0.75 (0.35–0.97)	7/8	0.87 (0.47–1.00)
							Unidimensional size	≥50%	No[c]	2/8	0.25 (0.03–0.65)	7/8	0.87 (0.47–1.00)
							Unidimensional size	≥65%	No[c]	0/8	0.00 (0.00–0.37)	8/8	1.00 (0.63–1.00)
Yu[29] (2010)	33	3	2	(6)	No	(0)	Ktrans	≥85%	Yes	14/17	0.82 (0.57–0.96)	14/16	0.87 (0.62–0.98)

Abbreviations: AUC = area under the receiver operating characteristics curve, CI = confidence interval, Ktrans = volume transfer constant, MRI = magnetic resonance imaging, NA = not applicable, NR = not reported, pCR = pathologic complete response, Sn = sensitivity, Sp = specificity, TN = true negative, TP = true positive.

*$p = 0.08$.

[a] Data also presented for MRI at 3 or 4 cycles; unclear whether these scans were truly "mid-cycle", so have been excluded from this analysis.

[b] Data presented are square-roots of the product of bidimensional tumour sizes. Values were squared to be consistent with WHO criteria.

[c] No threshold presented in paper; thresholds applied to individual patient data.

[d] With malignant indeterminate T/SI curve.

[e] Ultrasound performed instead of MRI in 17/115 (15%).

[f] Different thresholds applied to homogenous (58%) and peripheral ring-like lesions (38%).

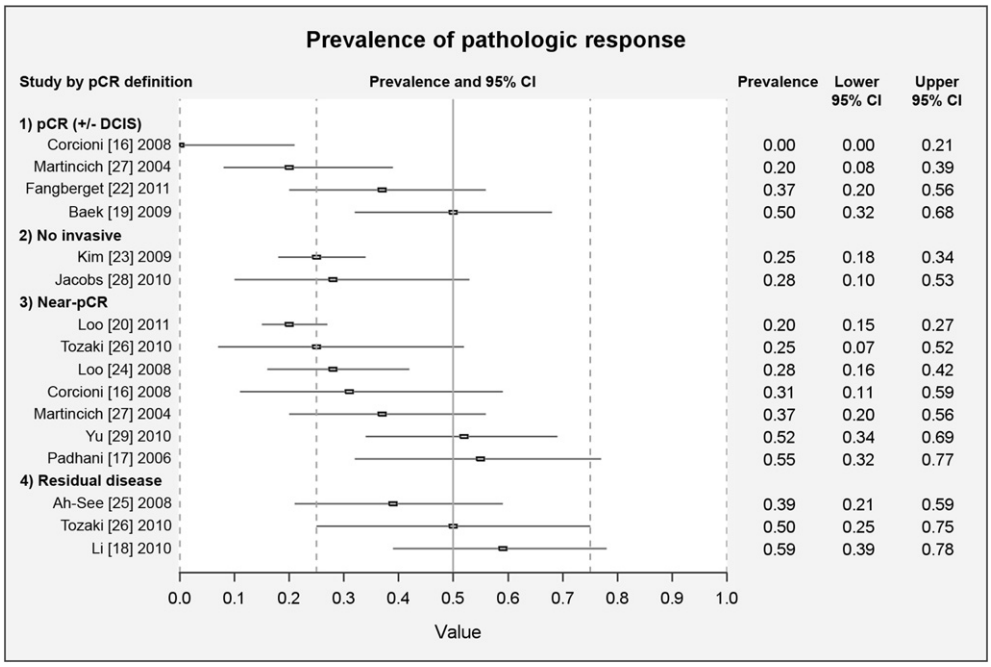


Fig. 1. Study-specific rates of pathologic response by response definition.

no individual pattern provided a higher sensitivity/specificity pair than those from size, volume or quantitative DCE-MRI measurements.

In two studies reporting reductions in bidimensional tumour size to predict pCR (Fig. 2), similar MRI thresholds produced different estimates, reflecting the inclusion[19] or exclusion[23] of axillary lymph nodes in the pCR definition. Sensitivity was observed to be higher (and specificity lower) when nodes were included. MRI sensitivity and specificity were presented for more than one outcome definition in two studies[26,27] (Fig. 4). Estimates varied by the outcome definition applied, but the effect was not consistent across MRI parameters, thresholds and changes in outcome.

Comparison of the accuracy of MRI and alternative tests

Four studies compared sensitivities and specificities for MRI and another test (Table 3). Identical sensitivities (100%) and specificities (36%) for the prediction of near-pCR were observed in a small study applying a low threshold (>0% unidimensional size reduction) to MRI and contrast-enhanced US; both tests categorised the same patients as responders or non-responders.[16] In another study, no significant differences in sensitivity and specificity between MRI (30% unidimensional size reduction) and proton MR spectroscopy (^{1}H-MRS; 40–50% normalised choline signal reduction) were found for the prediction of both near-pCR and more-than-minimal residual disease (all $p > 0.15$).[26] MRI was significantly more specific than ^{1}H-MRS for predicting near-pCR (but not pCR) when higher thresholds (≥50% or ≥65%) were applied to the data; MRI was significantly less sensitive at higher thresholds (≥65% for near-pCR; ≥50% for pCR) (all $p < 0.05$). Sensitivities and specificities for MRI appeared to be higher than for a combination of clinical examination, mammography and/or US for the prediction of pCR,[27] and similar to DW-MRI for the prediction of pCR or near-pCR[22] using a range of parameters and thresholds, but no statistical comparisons were possible.

A small study comparing AUCs for MRI (volume) and clinical examination (unidimensional size) appeared to report a higher AUC for MRI, though no significance testing was undertaken[28] (Table 4). Similar AUCs for DCE-MRI and alternative MR technologies were generally reported in studies comparing these tests.[18,19,22,28]

Discussion

This systematic review identified 13 studies assessing the accuracy of mid-NAC MRI in predicting pathologic response; that is, MRI's capability (when performed during NAC) to distinguish responders from non-responders at completion of treatment. Variability across the MRI parameters measured, thresholds applied to identify (non)responders, and definitions of pathologic response precluded formal pooled analysis. However, a descriptive summary of the evidence suggested several findings of relevance to future research and imaging in the NAC setting.

Firstly, while definitive conclusions are limited by small sample sizes and a lack of significance testing, certain MRI parameters may hold greater potential for the accurate identification of (non) response to NAC. Between-study comparisons suggested that MRI sensitivity (correct identification of responders) and specificity (correct identification of non-responders) were higher for reductions in tumour volume (to predict pCR and near-pCR),[22,27] Ktrans (to predict near-pCR),[29] and ECU (to predict pCR, but not near-pCR),[27] compared with uni- or bidimensional size. Quantitative DCE-MRI parameters and volumetric measurements have theoretical advantages over the assessment of tumour size, with the former measuring angiogenic changes which may occur prior to size reductions,[11] and the latter potentially providing a more complete depiction of tumour burden.[30] Hence, it is plausible that both Ktrans and three-dimensional volume reduction may be more accurate markers for early response than uni- or bidimensional size measurement, particularly when the threshold set for each of these parameters is high (above 50% reduction). ECU may also hold promise for this purpose, but the use of multiple thresholds may limit its clinical application.

Support for this finding was evident in studies suggesting higher AUCs for Ktrans than MRI tumour size (though significance tests were not performed),[25] and for MRI volume compared with clinical

Table 3
Studies comparing the sensitivity and/or specificity of MRI to another test.

Author [reference] (date)	*N*	pCR category	MRI				Comparator				
			Response parameter	Threshold reduction	Sn (95% CI)	Sp (95% CI)	Test	Response parameter	Threshold reduction	Sn (95% CI)	Sp (95% CI)
Corcioni[16] (2008)	16	1	Unidimensional size[a]	>0%	–	0.25 (0.07–0.52)	CE-US	Unidimensional size[a]	>0%	–	0.25 (0.07–0.52)
	16	3	Unidimensional size[a]	>0%	1.00 (0.48–1.00)	0.36 (0.11–0.69)	CE-US	Unidimensional size[a]	>0%	1.00 (0.48–1.00)	0.36 (0.11–0.69)
Fangberget[22] (2011)	26[b]	1	Volume	≥83%	0.91 (NR)	0.80 (NR)	DW-MRI	ADC[c]	≥1.42×10^{-3} mm^2/s	0.88 (NR)	0.80 (NR)
Martincich[27] (2004)	30	1	Volume	>65%	1.00 (0.54–1.00)	0.71 (0.49–0.87)	Conventional[e]	Bidimensional size	≥50%	0.83 (0.36–1.00)	0.42 (0.22–0.63)
			Early contrast uptake	≥58%/≥38%[d]	1.00 (0.54–1.00)	0.79 (0.58–0.93)					
	30	3	Volume	>65%	0.91 (0.59–1.00)	0.84 (0.60–0.97)	Conventional[e]	Bidimensional size	≥50%	0.91 (0.59–1.00)	0.53 (0.29–0.76)
			Early contrast uptake	≥58%/≥38%[d]	0.64 (0.31–0.87)	0.79 (0.54–0.94)					
Tozaki[26] (2010)	16	3	Unidimensional size	≥30%	0.75 (0.19–0.99)	0.67 (0.35–0.90)	^{1}H-MRS	Normalised Cho signal	≥40–50%	1.00[f] (0.40–1.00)	0.58[g] (0.28–0.85)
			Unidimensional size	≥50%	0.50 (0.07–0.93)	0.92[g] (0.62–1.00)					
			Unidimensional size	≥65%	0.00[f] (0.00–0.70)	1.00[g] (0.74–1.00)					
	16	4	Unidimensional size	≥30%	0.75 (0.35–0.97)	0.87 (0.47–1.00)	^{1}H-MRS	Normalised Cho signal	≥40–50%	1.00[f] (0.63–1.00)	0.87 (0.47–1.00)
			Unidimensional size	≥50%	0.25[f] (0.03–0.65)	0.85 (0.47–1.00)					
			Unidimensional size	≥65%	0.00[f] (0.00–0.37)	1.00 (0.63–1.00)					

Abbreviations: ADC = apparent diffusion coefficient, AUC = area under the receiver operating characteristics curve, CE-US = contrast-enhanced ultrasound, Cho = choline, CI = confidence interval, DW = diffusion weighted, ^{1}H-MRS = proton magnetic resonance spectroscopy, MRI = magnetic resonance imaging, NR = not reported, pCR = pathologic complete response, Sn = sensitivity, Sp = specificity.

[a] With malignant indeterminate T/SI curve.
[b] *N* = 22 for DW-MRI.
[c] ADC value after 4 cycles, not a reduction compared with baseline.
[d] Different thresholds applied to homogenous (58%) and peripheral ring-like lesions (38%).
[e] Combination of clinical exam, mammography and/or US.
[f] Significant difference between MRI and comparator sensitivity at $p < 0.05$.
[g] Significant difference between MRI and comparator specificity at $p < 0.05$.

size assessment (though differences in parameters and assessment methods may be confounded).[28] Most within-study comparisons, however, found similar AUCs for Ktrans (and the related parameter k_{ep}), tumour volume and size measurement.[18,19,22] A further caveat regarding the value of quantitative parameters and tumour volume measurement is that studies reporting these parameters retrospectively selected study-specific thresholds to derive the highest sensitivity/specificity pair. While this seems a reasonable initial approach, the application of data-driven thresholds will provide overly optimistic estimates of test performance. These thresholds require further validation.[31]

More generally, there was a lack of consistency between studies in the thresholds applied to specific MRI parameters. Unlike for dynamic contrast- or volume-based measurements, there are standard response criteria for percentage reductions in uni- or bidimensional tumour size.[32,33] Future studies should consider, at minimum, reporting accuracy at these thresholds.

A further apparent difference in the accuracy of MRI parameters was evident in one study assessing various MRI patterns of tumour reduction as indicators of response.[20] Though no studies directly compared patterns of tumour reduction to size, volume or quantitative DCE-MRI parameters, between-study comparisons suggest that the former are less informative in assessing early response during NAC. This does not discount the potential relevance of pattern of tumour reduction for surgical planning after completion of NAC, where this information may inform eligibility for BCS or mastectomy.[34]

Definitions of pathologic response in this setting are a critical determinant of test accuracy. The choice of an appropriate outcome definition depends on the aims of NAC; given that pCR is considered desirable in all patients,[3,4] studies should, at minimum, apply a pCR definition to capture this treatment aim. Several studies addressed the aim of improving surgical options by defining pathologic response as a reduction in tumour burden, allowing for the presence of some residual invasive disease. Such definitions are likely to be an imperfect surrogate for a change in surgical extent. For example, near-pCR may not indicate reduced resection volume if residual cells are widely dispersed; similarly, the degree to which macroscopic residual tumour is a surrogate for improved surgical options depends on the pattern of tumour reduction. However, near-pCR is more likely to capture improvements in surgical options in women with operable disease at presentation; conversely, the presence of more extensive residual disease may more appropriately capture this aim in patients with inoperable disease. Therefore, studies should carefully define the eligible patient population with reference to clinical stage, and consider applying non-pCR outcomes according to operability pre-NAC, acknowledging the inherent limitations of these definitions.

Definitions of pCR are not standardised,[35] varying in the inclusion or exclusion of response in the axillary nodes, and the presence or absence of residual DCIS. Between-study comparisons suggest that inclusion or exclusion of nodes in the pCR definition affects test performance. There was insufficient data to investigate the impact on accuracy of inclusion or exclusion of DCIS in the pCR definition, but this could plausibly be expected to affect accuracy given different sensitivity for DCIS detection with various imaging tests and lower MRI sensitivity for DCIS relative to invasive cancer.[36] Recent findings that residual DCIS and nodal disease may be of prognostic significance suggest that these aspects are an important consideration,[37] and highlight the need for research to inform standardisation.

In several studies, changes to patient management occurred based on mid-NAC response assessment, potentially confounding the accuracy of MRI to predict response. In circumstances when it is not feasible to avoid such treatment changes, studies should

Table 4
All studies reporting AUCs for MRI (and comparator tests when reported).

Author [reference] (date)	*N*	pCR category	Timing of test		Treatment change (%)		MRI		Comparator		
			Cycles	(Weeks)			Parameter	AUC (95% CI)	Test	Parameter	AUC (95% CI)
Baek[19] (2009)	34	1	1–2[a]	(2–4)	Yes	(NR)	Bidimensional size[b]	0.66	^{1}H-MRS	tCho level	0.67
							Ktrans	0.65	^{1}H-MRS	tCho peak area	0.68
							k_{ep}	0.66	^{1}H-MRS	Water peak area	0.65
Fangberget[22] (2011)	26[c]	1	4	(12)	Yes	(63)	Unidimensional size	0.78	DW-MRI	ADC	0.80
							Volume	0.82			
							Segmental volume	0.76			
Jacobs[28] (2010)	18	2	1	(3–5)	No	(0)	Volume	0.73	Clinical exam	Bidimensional size	0.56
									^{1}H-MRS	Cho SNR	0.82
									^{23}Na-MRI	Tissue Na concentration	0.83
Li[18] (2010)	27	3	2	(6)	Yes	(4)	Unidimensional size	0.86 (0.27–1.00)	ISW-MRI	R2*	0.62 (0.40–0.84)
							Ktrans	0.84 (0.27–1.00)	DSC-MRI	rBV	0.83 (0.23–1.00)
							k_{ep}	0.90 (0.25–1.00)		rBF	0.84 (0.23–1.00)
							v_e	0.59 (0.32–0.87)		MTT	0.53 (0.27–0.79)
							$IAUGC_{60}$	0.83 (0.28–1.00)			
Ah-See[25] (2008)	28	4	2	(6)	Yes	(13)	Bidimensional size	0.68	–	–	–
							Ktrans	0.93	–	–	–
Loo[24] (2008)[d]	54	3	1,3	(6,8)	Yes	(NR)	Unidimensional size (late enhancement)	0.85	–	–	–
Padhani[17] (2006)	20	4[e]	1	(3)	No	(0)	Bidimensional size	0.90	–	–	–
							Ktrans	0.76	–	–	–
	15	4[e]	2	(6)	No	(0)	Bidimensional size	0.93	–	–	–
							Ktrans	0.94	–	–	–

Abbreviations: ADC = apparent diffusion coefficient, AUC = area under the receiver operating characteristics curve, Cho = choline, CI = confidence interval, DSC = dynamic susceptibility contrast-enhanced, DW = diffusion weighted, ^{1}H-MRS = proton magnetic resonance spectroscopy, $IAUGC_{60}$ = initial area under the gadolinium concentration–time curve at 60 s, ISW = intrinsic susceptibility weighted, k_{ep} = exchange rate constant, Ktrans = volume transfer constant, MRI = magnetic resonance imaging, MTT = mean transit time, pCR = pathologic complete response, ^{23}Na = sodium, R2* = transverse relaxation rate, rBF = relative blood flow, rBV = relative blood volume, SNR = signal-to-noise ratio, tCho = signal intensity of choline-containing compounds, v_e = volume of extravascular extracellular space.

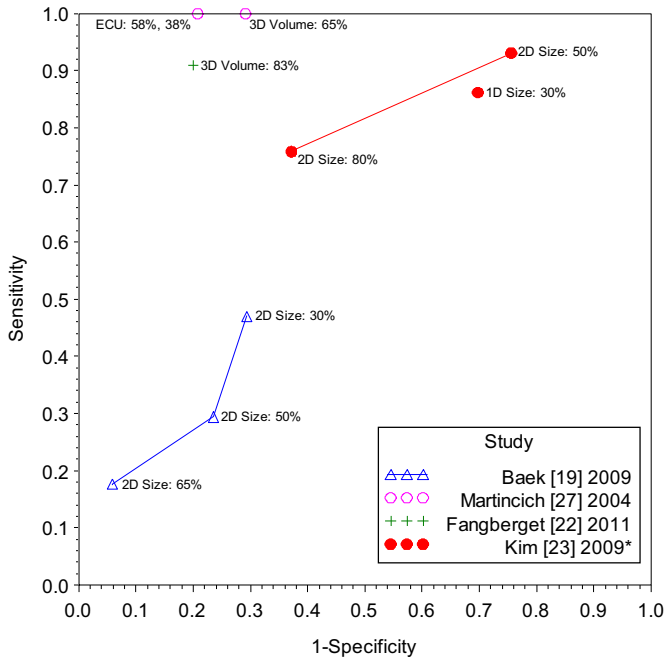
[a] Data also presented for MRI at 3 or 4 cycles; unclear whether these scans were truly "mid-cycle", so have been excluded from this analysis.

[b] "Equivalent one-dimensional tumour size" (square root of the product of the longest dimension and the longest perpendicular dimension).

[c] *N* = 22 for DW-MRI.

[d] Only largest univariate AUC presented.

[e] Outcome definition for AUC different than for Sn/Sp (response = pCR *or* clinical response).



* pCR defined as no residual invasive disease (with no reference to DCIS) in breast *and* axilla.

Fig. 2. Studies of MRI accuracy during NAC to predict pCR (with or without DCIS) or absence of invasive disease (not otherwise specified) [data points are labelled with parameter measured and percentage threshold reduction applied].

declare the proportion of patients for which management was changed; the results of MRI, comparator tests and pathology; and the nature of the management. This information makes transparent the potential for management changes to bias estimates of accuracy for MRI and comparators tests.

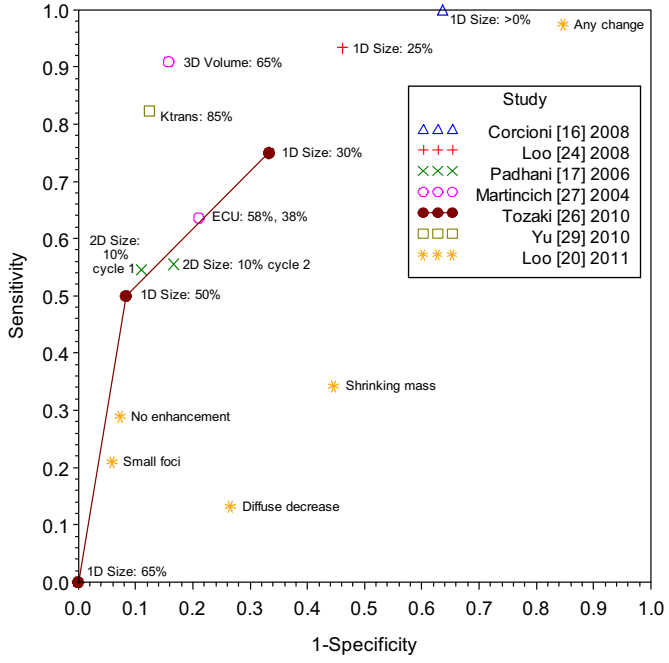


Fig. 3. Studies of MRI accuracy during NAC to predict near-pCR (minimal residual disease) [data points are labelled with parameter measured and percentage threshold reduction applied].

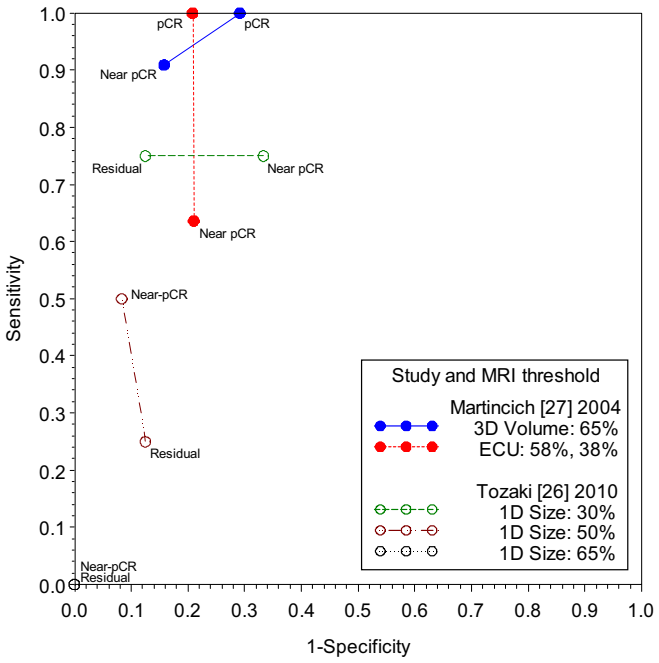


Fig. 4. Studies of MRI during NAC reporting multiple pathologic response thresholds.

Though RCTs have shown that modification of therapy may result in increased rates of pCR and BCS and improved OS and DFS in mid-NAC responders,[7–9] and improvements in DFS and treatment tolerability in non-responders,[9,10] response in these RCTs was assessed primarily by clinical examination or US rather than MRI. Few comparisons of MRI's accuracy to that of US or clinical examination were identified, and those presented are problematic in the applicability of comparator tests (US with contrast enhancement; composites of clinical examination and other tests), non-standardised response thresholds (any unidimensional size reduction), and a lack of significance testing between estimates. Further research comparing the test performance of MRI, US and clinical examination is warranted to inform assumptions about the applicability of RCT data to patients with MRI-determined response or non-response.[38]

MRI technology is rapidly evolving, including new contrast materials with higher relaxivity[21] and concentration[39] with potential implications for DCE-MRI performance, and developments in diffusion weighted imaging (DWI) which may increase accuracy in the NAC setting.[40,41] Similar sensitivities, specificities, and AUCs were reported for DCE-MRI and DW-MRI in the only study directly comparing the technologies in this review[22]; further research comparing these modalities is warranted. MRI shows promise as an imaging tool for early response assessment in women undergoing NAC, however the lack of standardisation in measurements and applied parameters, small sample sizes, methodological limitations, and a paucity of statistical comparisons between MRI and other tests limit definitive conclusions about MRI's capability in this setting. Notwithstanding these limitations, there is some evidence that substantial reductions in tumour volume or Ktrans may be accurate parameters for differentiating, early in the course of NAC, women likely to respond from those in whom response is unlikely. Future studies adopting methods we have recommended are required.

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Conflict of interest statement

None declared.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.breast.2012.07.006.

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