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BREAST CANCER IMAGING AND SCREENING (N SHARMA, SECTION EDITOR)

Diffusion-Weighted Magnetic Resonance Imaging of the Breast: an Accurate Method for Measuring Early Response to Neoadjuvant Chemotherapy?

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Abstract

Purpose of Review Accurate prediction of early treatment response in patients receiving neoadjuvant chemotherapy for breast cancer is essential to provide patients with the best care. Diffusion-weighted magnetic resonance imaging (DWI) provides a novel approach to distinguishing responders from non-responders. This article aims to review the literature regarding the accuracy of DWI in predicting patients who will respond to neoadjuvant chemotherapy at an early stage within their treatment pathway.
Recent Findings The initial search yielded 11,171 articles. After careful review, 19 of these articles were found to adhere to the inclusion criteria. Despite the varied research methods and data analysis across the studies, 16 out of 19 of these studies (84%) demonstrated DWI to be an accurate predictor of neoadjuvant chemotherapy response.
Summary These results are promising; however, further multi-centre studies with larger sample sizes, homogenous imaging and treatment parameters and formal assessment of pathological response are required to accurately evaluate the use of DWI as an early predictor of neoadjuvant chemotherapy response in patients with breast cancer.

Keywords Breast MRI · Diffusion-weighted imaging · Neoadjuvant chemotherapy · Apparent diffusion coefficient · Breast cancer

Introduction

Breast Cancer and Neoadjuvant Chemotherapy

Breast cancer is a significant cause of female morbidity and mortality [1]. This puts a significant strain on healthcare systems for the accurate diagnosis and measurement of response to treatment in patients across the world. Early breast cancer management traditionally involved surgery, plus radiotherapy and adjuvant systematic therapy as required [2]. The development of neoadjuvant chemotherapy (NACT) towards the end of the twentieth century provided the ability to reduce tumour size and potentially downstage the tumour before surgical intervention. Mortality rates have steadily declined due to these new treatment regimens, and developments in medical imaging have provided the clinician with information on clinical response to NACT whilst the patient received ongoing treatment [3]. Currently in England, patients with locally advanced breast cancer may undergo three cycles of NACT before their response to treatment is examined [4]. NACT carries great benefit to patients; complete responders to NACT are associated with a more favourable prognosis. However, it can carry common debilitating side effects such as vomiting, diarrhoea, sensory neuropathy and high-risk haematological toxicities such as neutropoenia and leucopoenia [5]. NACT regimens can lead to cardiotoxicity, severe sepsis and even death. Only 39% of patients on NACT have a complete pathological response, with 12% of a large studied population having no response at all to the treatment [2]. It is therefore important to determine non-responders to NACT early within the treatment pathway to avoid these harmful side effects.

Traditionally, tumour response during neoadjuvant treatment has been assessed using calliper measurements and mammography; however, advances in magnetic resonance imaging (MRI) have enabled the potential for more accurate measurements earlier in the treatment pathway. Current

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practice within NHS England utilises standard breast MRI protocols to monitor response to treatment in patients undergoing NACT by measuring maximal tumour length pre- and post-treatment [4]. Diffusion-weighted MRI (DWI) introduces the ability for radiologists to non-invasively assess other tumour markers such as the ADC (apparent diffusion coefficient). Such measures may be able to demonstrate, and quantify, tumour response before morphological changes appear on conventional MRI scans.

Diffusion-Weighted Imaging

DWI differs to conventional MRI as it uses motion-sensitising gradients to characterise the Brownian motion of water within intracellular and extracellular compartments [6]. This provides information on cell membrane integrity and tumour cellularity [7]. DWI is most commonly performed using a single-shot diffusion-weighted echo planar technique for breast imaging due to its insensitivity to gross patient motion and high signal-to-noise ratio [8].

The performance of DWI in improving the detection and tumour characterisation of benign and malignant breast tumours has been greatly explored [1, 9, 10]. The ADC is the most commonly measured parameter in these studies. ADC is a quantitative measurement of water diffusion obtained from a series of images with increasing 'b values' (a measure of the amplitude of the motion-sensitising gradients). An increase in ADC following cytotoxic treatment is hypothesised to reflect the loss of cell membrane integrity or increase in extracellular space within a tumour [11]. This would be in keeping with a positive tumour response to treatment.

A number of animal models have indicated the potential benefits in the measurement of ADC using DWI techniques to predict tumour response to a variety of chemotherapy [12–14] and radiotherapy regimens [15]. Measuring NACT treatment response using DWI techniques has been studied with varying results in humans. Some researchers have found that a lower initial ADC of the breast tumour correlates with a positive clinical response to NACT [16]; some researchers concluded that treatment responders demonstrate a greater change in ADC after the first cycle of chemotherapy compared with non-responders [17], and other researchers found that ADC values were not an accurate discriminator between responders and non-responders [18]. A recent meta-analysis [19] demonstrated strong evidence for the use of DWI in identifying pathological response to NACT.

Objective

With varying results from numerous studies, this systematic review aims to bring together the relevant papers and assess the accuracy of quantitative tumour imaging biomarkers gained from DWI in evaluating breast tumour NACT response early in the treatment pathway. Considering that NACT does not provide benefit to all patients, the cost of chemotherapy is high and there are significant associated side effects; this an important topic. Patients who do not respond to the therapy can be detected earlier and provided with alternative and more appropriate treatment options.

Methods

Identification of Studies and Eligibility Criteria

An electronic search of PubMed, Google Scholar and the Cochrane Libraries was undertaken from database inception to December 2018 to identify all potential publications. Articles relevant to assessing early breast tumour response to NACT using DWI techniques were reviewed. Keywords used for the search included the following: 'breast cancer' or 'breast tumour' or 'breast tumor', 'diffusion-weighted imaging' or 'DWI' or 'DWI-MRI', 'early response' or 'early prediction' or 'treatment response' and 'neoadjuvant chemotherapy' or 'NACT'.

Inclusion Criteria

Articles were included if they met the following criteria:

1. *Original* research articles,
2. Enrolling *newly diagnosed patients with primary breast cancer* with a DWI scan undertaken,
3. *Before* treatment and again at an *early stage* of the treatment pathway, (early stage defined as prior to the third cycle of chemotherapy),
4. With *clear statistical analysis* of the measured data.

Early in the treatment pathway was defined as a DWI scan being performed before the third cycle of NACT. All patients diagnosed with breast cancer, regardless of their TNM staging, were included. Studies that included both male and female patients were included. Prospective and retrospective studies of any sample size were included. There were no criteria for the definition of reference standard within the articles.

Exclusion Criteria

The majority of studies were excluded as they did not fit the criteria for 'early treatment response'. Studies that included case reports and other non-related research articles were excluded. Numerous duplicate studies were found across all the research databases. These studies were individually reviewed and discarded based on the exclusion criteria, Fig. 1 demonstrates the reasons for exclusion of articles and the number of articles excluded.

Data Extraction

The following information was extracted from the included studies: study design, first author, year of publication, sample size, clinical characteristics (disease stage and histological subtype if available), chemotherapy regimens, time points of DWI scans, strength of the magnetic field used for DWI, index tests, reference standards and statistical tests conducted.

Quality Assessment

Potentially eligible studies were critically appraised against the QUADAS-2 proforma [20]. This proforma was specifically designed for systematic reviews to assess the risk of bias and applicability of each enrolled study to the research question.

Results

Inclusion of Studies

After reviewing the titles and abstracts of 21 articles, a total of 15 articles were selected for full-text review. Fourteen of these papers fulfilled the inclusion criteria and a further 5 articles were identified through the reference list and citations within the identified articles. A total of 19 articles have been included in this systematic review.

Study Characteristics

Nineteen longitudinal studies and one prospective study were identified, with a total of 924 patients (range 6–242 patients, mean 48.6 patients). Seventeen of these papers were single-centre studies with all patients undergoing DWI before the initiation of NACT and either after the completion of the first or second cycle of NACT. Two multi-centre papers were included. Every study included patients with locally advanced breast cancer with the exception of Hu et al. [21] and Theilmann et al. [22], who both included patients with metastatic breast cancer within their patient samples ($n = 164$ and $n = 16$ respectively). The majority of included patients were female, with only 1 male patient included in the study by Theilmann et al. [22]. Four studies compared the accuracy of DWI against other imaging techniques in their ability to determine tumour response.

Patient and Tumour Characteristics

Patient ages ranged from 25 to 75 years; however, patient ages were not published in all articles. Infiltrative ductal carcinoma and infiltrative lobular carcinoma were amongst the most common tumour types. Six of the studies provided information on the staging categories using the TNM Staging Criteria [23]. From these 6 articles, 76% of patients presented with operable disease, as defined by the National Surgical Adjuvant Breast and Bowel Project definition of operability (stages IIa, IIb, IIIa) [24]. Kawamura et al. [25] and Li et al. [26] included a small number of patients with tumour stage IV.

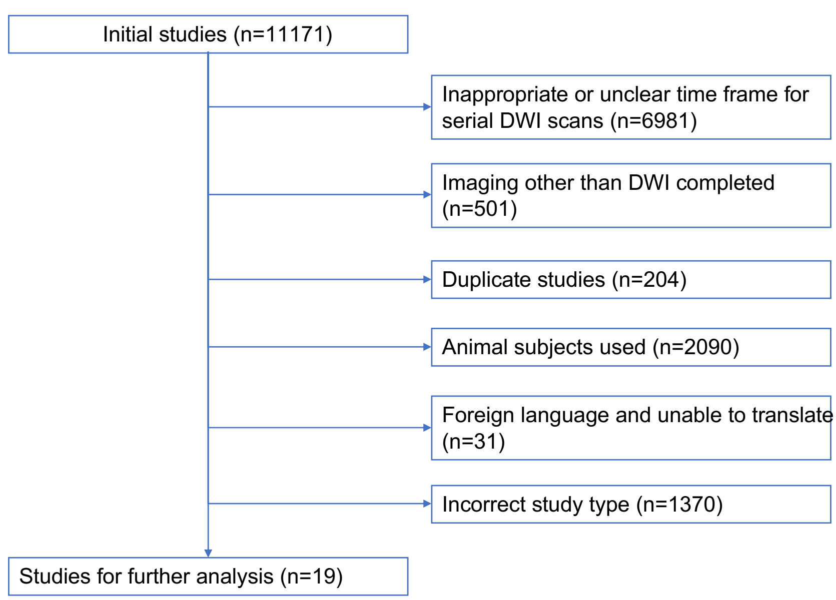

Fig. 1 Breakdown of exclusion criteria and number of studies excluded per criteria

Neoadjuvant Chemotherapy Characteristics

NACT regimens were primarily anthracycline based or a mixture of anthracycline and taxane based. The total number of planned cycles each patient received varied from 1 cycle to 12 cycles. Patients underwent a wide variety of NACT regimens with the most commonly used agents being 5-fluorouracil, epirubicin and cyclophosphamide.

DWI Characteristics and Timing of Scans

Eight of the included studies utilised a 1.5 T MRI scanner; eight studies utilised a 3.0 T MRI scanner. The studies by Pickles et al. [11], Galbán et al. [27] and Partridge et al. [28••] used a mixture of 3.0 T and 1.5 T systems. All patients were scanned with dedicated bilateral breast coils. All patients received a DWI scan before the initiation of their treatment and at a specified time point early in their treatment phase; scans taken after the third cycle of NACT were not included in the dataset. There was little variability in the index test for DWI. All bar the articles by Atuegwu et al. 2011 [29] and Atuegwu et al. 2013 [30] (89% of articles) used ADC measurements as an index test.

Determination of Pathological Response

A variety of definitions of response were used across the included studies. Eight (42%) used RECIST (response evaluation criteria in solid tumours) [31] and 5 (26%) used tumour diameter or volume measured on MRI post-therapy as their reference standards for response. Atuegwu et al. 2011 [29] calculated tumour cellularity from serial scans with mathematical modelling techniques. Only five studies (26%) used post-operative pathological examination of the breast tumour to determine response. Tables 1 and 2 highlight the important data collected from the studies.

Discussion

Currently, tumour diameter measured via MRI is the most commonly used quantitative measure in determining breast tumour response to NACT [4]. Tumour volumes are measured mid-treatment (usually after 3 cycles) and compared with initial scans to determine size changes; a reduction in tumour diameter is deemed to be a response to treatment. NACT is not an effective treatment for all breast cancer patients and carries serious and debilitating side effects; therefore, it is important to investigate other non-invasive methods to distinguish responders from non-responders early in the treatment pathway. Consequently, this opens up research into novel imaging techniques.

DWI has been examined as a potential imaging technique that will provide accurate and reliable prediction of early treatment response to NACT. This systematic review identified 19 studies assessing the accuracy of DWI in predicting pathological response to NACT early within the treatment pathway. The aim is to answer a key question, is DWI capable of accurately distinguishing between NACT responders and non-responders at an earlier stage? To our knowledge, this is the first systematic review of the diagnostic accuracy of DWI in early breast tumour response.

Variability across the patient selection, DWI acquisition parameters and the methods to distinguish treatment responders from non-responders precluded formal pooled analysis. However, a descriptive summary of the evidence suggested several findings of relevance to future research into DWI as a predictor of clinical outcomes in breast cancer patients. Definitive conclusions from the collected data are limited by the small sample sizes and the lack of significance testing in some studies; however, cross-study comparisons can be made to answer the proposed research question.

Apparent Diffusion Coefficient

The overwhelming majority of papers measured absolute ADC values as their chosen reference standard (17 out of 19 articles). Fifteen of these articles (88%) demonstrated a statistically significant increase in ADC for responders compared with non-responders ($p < 0.05$). Kawamura et al. [25] were able to demonstrate noticeable increases in ADC for responders; however, statistical analysis did not demonstrate a significant difference ($n = 11$). El bakoury et al. [32] were also unable to demonstrate significant differences in ADC between responders and non-responders; however, they were able to demonstrate a significant correlation between the percentage increase of ADC value between initial measurement and after the 1st cycle of NACT. These differences in conclusions are possibly due to the timings of DWI scans. The serial DWI scans for these patients in the study by El bakoury et al. [32] were taken up to 55 days after their first cycle of chemotherapy, where Theilmann et al. [22] and Galbán et al. [27] were able to demonstrate significant changes to ADC values as early as 3 days post-treatment initiation.

Pickles et al. [11] were the first authors to demonstrate absolute changes in mean ADC prior to changes in tumour size; an increase of mean ADC from 1.08×10^{-3} mm^2/s pre-treatment to 1.25×10^{-3} mm^2/s after the first cycle of NACT was demonstrated across patients who responded to the treatment. These results are further supported by the largest multicentre trial included in this systematic review. The ACRIN 6698 Trial [28••] ($n = 242$) demonstrated that, regardless of response status, a generally increasing trend

Table 1 Study characteristics and data analysis of the included studies

Study, year	Study characteristics					Data analysis	
	MRI timing after NACT initiation		Initial sample size	Final sample size	Age range	Index tests	Reference standard
	Cycles	(Weeks)					
Atuegwu et al. 2011	1	(1)	6	6	?	Simulated tumour proliferation rate	Tumour cellularity
Atuegwu et al. 2013	1	(1–3)	28	22	28–67	Tumour cellularity	Pathological examination of tumour
Che et al. 2016	2	(2)	58	36	?	ΔADC_{mean}	RECIST
El bakoury et al. 2017	1	(4, 5)	20	19	24–68	ΔADC_{mean}, $\%\Delta ADC_{mean}$, Δtumour volume	Pathological examination of tumour
Galbán et al. 2015	1–2	(0–5)	39	39	24–69	ΔADC_{mean}, $\%\Delta ADC_{mean}$	ΔTumour volume post-NACT
Hu et al. 2017	2	(6)	164	164	35–57	ΔADC_{mean}, Δlongest tumour diameter	RECIST
Iwasa et al. 2014	1	(1)	24	24	32–69	$\%\Delta ADC_{mean}$, greatest tumour diameter on ultrasonography	RECIST
Jensen et al. 2011	1	(3)	15	12	62–72	ΔADC_{mean}, tumour diameter	ΔTumour diameter post-NACT
Kawamura et al. 2011	1	(3)	11	8	38–64	ΔADC_{mean}, $\%\Delta ADC_{mean}$	RECIST
Li et al. 2011	1	(2, 3)	32	32	25–63	ΔADC_{mean}, Δtumour volume	RECIST
Manton et al. 2005	2	(6)	46	22	?	ΔADC_{mean}, MRS and T_1-weighted parameters[c]	Pathological examination of tumour
Partridge et al. 2018	1	(3)	272	242	38–58	$\%\Delta ADC_{mean}$	Pathological examination of tumour
Pickles et al. 2005	1, 2	(3, 6)	10	8	?	ΔADC_{mean}, Δlongest tumour diameter, Δtumour volume	RECIST
Sharma et al. 2009	1, 2	(?, ?)	81	56	30–75	$\%\Delta ADC_{mean}$	ΔTumour volume post-NACT
Theilmann et al. 2004	1–2	(0–5)	16	13	38–73	ΔADC_{mean}, $\%\Delta ADC_{mean}$, tumour volume	ΔTumour volume post-NACT
Tozaki et al. 2009	1	(5)	9	7	27–61	ΔADC_{mean}, Cho[a]	Grade A to D[b]
Wilmes et al. 2013	2	(3)	9	9	24–66	ΔADC_{mean}	ΔTumour volume post-NACT
Wu et al. 2015	1	(1)	31	31	33–62	ΔADC_{mean}, $\%\Delta ADC_{mean}$	RECIST
Xu and Zhang, 2017	1	(4)	174	174	37–53	ΔADC_{mean}	RECIST

? = data unavailable from article

[a] Values of Cho (choline signals) were extracted from ^{1}H MR spectroscopy imaging. [b] Tumour response scale as determined by Sataloff et al. 1995.
[c] MRS and T1-weighted parameters include K^{trans}, K_{ep}, v_e and MEF

of ADC throughout treatment was seen. However, change in ADC only became predictive of treatment response after the 3rd cycle (95% CI, $p = 0.017$).

Only one article [33] demonstrated MRI tumour diameter as a more accurate predictor of clinical response after 1 cycle of NACT compared with changes in the tumour ADC mean ($p = 0.005$ and $p = 0.008$ respectively), with a mean increase in ADC values of 0.12 mm^2/s for NACT responders. The differences in these results are possibly due to the difference in reference standard used across

Table 2 DWI sequence, b values, magnet strength, slice thickness and pixel size of the included studies

Study, year	DWI sequence	b values (s/mm^2)		Magnet strength (T)	Slice thickness (mm)	Pixel size (mm)
		Min.	Max.			
Atuegwu et al. 2011	Single-shot spin echo	50	600	3.0	5.0	2.00 × 2.00
Atuegwu et al. 2013	Single-shot echo planar	0 or 5-0[c]	500 or 60-0[c]	3.0	5.0	2.00 × 2.00
Che et al. 2016	Single-shot spin echo	0	1000	3.0	5.0 (1-mm gap)	2.50 × 2.00
El bakoury et al. 2017	Single-shot echo planar	0	800	1.5	4.0	1.41 × 1.41
Galbán et al. 2015	Single-shot spin echo (UM) Single-shot dual spin echo (UH)	0	800	1.5 and 3.0[b]	4.0 (UM) 5.0 (1-mm gap) (UH)	1.32 × 1.32 (UM) 2.66 × 2.66 (UH)
Hu et al. 2017	Single-shot echo planar	0	800	1.5	6.0 (0.2-mm gap)	1.01 × 1.40
Iwasa et al. 2014	Single-shot echo planar	0	1500	3.0	4.5	3.13 × 3.13
Jensen et al. 2011	Twice-refocused spin echo	50	800	3.0	3–3.5	1.77 × 1.76
Kawamura et al. 2011	Single-shot echo planar	50	1500	3.0	3.0(0.6-mm gap)	3.01 × 3.01
Li et al. 2011	Single-shot echo planar	0	1000	1.5	4.0 (1-mm gap)	1.00 × 1.25
Manton et al. 2006	Single-shot echo planar	0	680	1.5	4.0–9.0 (2 mm gap)	1.17 × 2.34
Partridge et al. 2018	Single-shot echo planar	0	800	1.5 and 3.0	4.0–5.0	1.70 × 2.80
Pickles et al. 2006	Single-shot dual spin echo	0	700	1.5 and 3.0[a]	5.0 (1-mm gap)	2.66 × 2.66
Sharma et al. 2009	Single-shot echo planar	0	1000	1.5	5.0	1.95 × 1.95
Theilmann et al. 2004	Single-shot echo planar	0	450	1.5	6.0	2.81 × 3.00
Tozaki et al. 2009	Single-shot echo planar	500	3000	1.5	3.0	3.00 × 3.00
Wilmes et al. 2013	Single-shot echo planar	0	600	1.5	3.0 (STD) and 4.0 (HR)[a]	3.13 × 3.13 (STD) and 1.10 × 1.01 (HR)
Wu et al. 2015	Single-shot echo planar	0	1000	3.0	5.0 (1 mm gap)	2.50 × 2.00
Xu and Zhang, 2016	Single-shot echo planar	0	800	3.0	4.0	?

? = missing data

[a] Wilmes et al. (2013) collected data from standard DWI (STD) and high-resolution DWI (HR). [b] The University of Michigan (UM) utilised a 3.0 T system, the University of Hull (UH) utilised 1.5 T and 3.0 T scanners. [c] The study by Atuegwu et al. 2013 used a variety of b values in their scanning parameters

the studies. Treatment response defined by Jensen et al. [33] was comparatively strict, measuring tumour diameter of less than 20 mm at the end of chemotherapy as a positive response, regardless of initial tumour diameter. Other authors used the RECIST criteria or tumour volume changes as predictors of treatment response which take into account the percentage change of overall tumour size. Other reasons for differences in outcomes of these studies include the differences in NACT regimes, timing of serial DWI scans and choice of DWI acquisition parameters.

Instead of measuring the raw ADC values, four studies examined percentage changes in ADC values between the initial and early DWI measurements. El bakoury et al. [32] demonstrated an increase of 20% or more in ADC measurements taken before and after the first cycle of NACT as an accurate predictor of clinical response ($p = 0.011$). These changes were seen before morphological changes could be demonstrated on MRI. Iwasa et al. [34] similarly explored percentage changes of ADC as a discriminator with a significant correlation between percentage change in ADC and the response rate ($r = 0.597$, $p = 0.016$).

Mathematical Modelling

Mathematical modelling was identified as index tests in two of the included studies. Mathematical models are reproducible, which is important for radiologists, where operator error can occur when measuring tumour volumes and outlining regions of interest. Atuegwu et al. [29] presented an equation for the estimation of tumour proliferation rates. The estimation of proliferation rates was calculated using the ADC data from two time points (pre-NACT and after one cycle) and then used with a logistic model of tumour growth to predict cellularity after therapy. This logistic model included some simplifying assumptions; however, the authors were able to demonstrate very strongly significant ($p < 0.0001$, $n = 6$) predictions of tumour cellularity, and therefore NACT response at the end of the treatment cycle.

In a subsequent paper by Atuegwu et al. 2013 [30], the authors were able to further improve the mathematical model by including data regarding cellular variations and volume fractions. The sensitivity and specificity in correctly predicting tumour response from this study of 28 patients were 82.4% and 72.7% respectively ($n = 26$). For comparison, the sensitivity and specificity in the article with the second largest sample size included in this systematic review ($n = 174$) solely measuring the mean ADC after 1 course of NACT are 87.2% and 40.0% respectively. The specificity is much improved when using a mathematical model, which is important in determining false negatives.

Both of the studies discussed here provide better sensitivities to distinguishing tumour responders when compared with a meta-analysis conducted by Yuan et al. [35] ($n = 1212$) in the diagnostic accuracy of MRI on predicting pathological response (63%). The study sizes are smaller; however, mathematical modelling provides intriguing evidence into the integration of quantitative information gained from DWI in the search for a non-invasive method for accurately and reliably predicting tumour response.

Diffusion-Weighted Imaging vs. Other Imaging Techniques

Five studies compared DWI against other imaging techniques in their ability to accurately predict tumour response in this setting. Manton et al. [18] compared three imaging techniques—DWI, dynamic contrast-enhanced (DCE) MRI and proton magnetic resonance spectroscopy (MRS). A range of predictive parameters were gathered, and ADC mapping after the second course of chemotherapy was not found to significantly distinguish between responders and non-responders. This was a relatively early study that was conducted before the introduction of parallel imaging. The later studies utilised parallel imaging techniques which help to reduce distortion on DWI and, in turn, provide better specificity of ADC values [36].

Xu and Zhang [37•] also compared DCE-MRI against DWI ($n = 174$). They were able to demonstrate that parameters gained from DCE-MRI scans were significant in predicting tumour response; however, the most accurate predictor remained ADC (sensitivity 80%, specificity 94.9%).

Jensen et al. [33] compared MRI tumour diameter, DCE-MRI and DWI against one another. Kinetic parameters (K^{trans} and v_e) were obtained from DCE-MRI. DWI was found to be a more accurate quantitative measurement in distinguishing responders from non-responders when compared with DCE-MRI in this study. These results are in keeping with the results found by Xu and Zhang [37•] and are in agreement with other studies that have challenged DCE-MRI in this setting [38, 39]. DCE-MRI has been argued to be a suboptimal imaging technique in this setting due to its difficulty in distinguishing viable tumour from scarred, necrosed or fibrosed tissues, which can lead to inaccuracies in residual tumour size measurements and false positive results.

Tozaki et al. [40] compared DWI against MRS. Levels of choline (Cho) from MRS were compared with values of ADC from DWI after the first cycle of NACT ($n = 9$). The authors demonstrated that Cho is a significant predictor of treatment response ($p = 0.01$) compared with DWI ($p = 0.32$). This study compared two non-contrast approaches to demonstrate features of breast cancer previously hidden to conventional MRI techniques. Although available in the research setting, implementing MRS in the clinical setting is challenging. Longer acquisition times, difficult standardisation and better availability of DWI make DWI a more desirable option [41].

Iwasa et al. [34] compared DWI against grey-scale ultrasonography. Tumour response by ultrasonography was demonstrated by changes in tumour size after the first cycle of NACT. In this study, percentage change in ADC was the only variable that correlated with the response rate. The authors of this article were able to demonstrate the strongest correlation for the use of DWI in breast tumour response across all the articles included in this systematic review.

Limitations

At present, this is the largest systematic review on this topic; however, there are numerous limitations to the conclusion derived from these pooled studies. The subjects were investigated with the use of different MRI equipment and with a variety of acquisition parameters such as field strength, scan sequence and b values. This can influence the range of ADC values and additional quantitative measurements obtained. Further variations between study characteristics to be taken into consideration include the treatment regimens of NACT, timing of response evaluation and the response criteria. The majority of included articles contained small sample populations which can weaken the overall statistical power of the study. Quality assessment checks were completed for each individual study; however, the impact of the range of included sample sizes on the final descriptive analysis could not be neglected. The diversity of reference tests and statistical analysis used in each paper made pooled analysis difficult.

This review did not include analysis between DWI and other clinically relevant biological features such as hormonal receptor status and genetic expression (e.g. HER2 and BRCA1). This is an interesting aspect of breast tumour response and a goal for further studies.

Conclusion

MRI technology is rapidly evolving, and the data gained from quantitative measurements is forever expanding. Improvements to scanning techniques and accuracy of ADC measurements hold the potential for developing DWI into a highly reliable and easily employed method in the assessment of breast tumour response early in the NACT treatment pathway. ADC and mathematical modelling have been studied as potential predictors of chemotherapy response. Sixteen out of the 19 papers (84%) were able to demonstrate DWI as an accurate imaging technique for distinguishing responders from non-responders. There is a distinct lack of standardisation across DWI scan techniques with small sample sizes and paucity of statistical comparators that limit pooled analysis in this systematic review.

With increasing data being gained from MRI scans, the ability to use multiple parameters to determine response to therapy may provide the most accurate and reliable method. This research project was able to demonstrate some substantiation into the use of DWI; however, further studies with homogenous study methods, formal pathological reference standards and statistical analysis are required to provide sufficient evidence for the use of DWI as an accurate predictor of treatment response.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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