Radiological and Pathological Predictors of Response to Neoadjuvant Chemotherapy in Breast Cancer: A Brief Literature Review

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Key Words

Gene expression · Hormone receptors · Magnetic resonance imaging · Neoadjuvant chemotherapy · Pathological complete response · Predictive marker

Abstract

Background: Early clinical response to neoadjuvant chemotherapy (NACT) in breast cancer correlates with pathological response at surgery. A tailored approach using biomarkers to predict response to NACT has become a research priority. Predictors of response can be divided into pathological and radiological biomarkers. Advances in gene expression profiling and diffusion-weighted MRI techniques are used to predict tumour response, and combinations thereof are the future of predicting response to NACT in early-stage breast cancer. **Methods:** We searched Medline, CINAHL and Embase databases for studies on NACT. Key words used were NACT, breast cancer, pathological* complete response, primary chemotherapy, radiological*, predictor*, gene expression and biomarkers limited to the English language. Pathological markers such as tumour subtypes, topoisomerase II α expression, Ki67, apoptosis-related markers and gene expression profiling were included. **Results:** From 119 articles, 42 studies were reviewed; the majority of studies identified used pathological clinical response as an end point to NACT,

whilst others used complete clinical response. Despite extensive studies, results regarding long-term survival following NACT and potential predictors are inconclusive. **Conclusion:** Future development of a predictive model combining key pathological and radiological biomarkers could provide personalised treatment regimens that improve pathological complete response rates and longer-term outcomes.

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Introduction

Response to systemic treatment can be monitored prior to surgery. Neoadjuvant chemotherapy (NACT) enables pre-surgical reduction in tumour burden, early treatment of micrometastatic disease and provides a better chance of breast conservation surgery by reducing the total amount of tissue resected in cancers more than 20 mm in size [1]. Since its introduction in the late 1970s, a large number of studies have assessed the use of NACT in invasive breast cancer, with emerging interest in its potential role in ductal carcinoma in situ in recent years. Standard NACT regimens include anthracycline combinations with or without addition of taxanes and anti-human epidermal receptor type 2 (HER2) therapy in HER2-positive cases. Theoretically, multiple combinations of

NACT regimens favour a tailored approach to treat breast cancer, although an optimal regimen is yet to be identified. Multiple drug combinations, genetic variability of tumours and variability in outcome measures of available studies make identifying reliable predictive markers a significant challenge.

Pathological complete response (pCR) is a surrogate marker for evaluating response to NACT and a prognostic marker for survival in many studies, but pCR is not achieved in all patients. It would be useful to identify predictive markers to distinguish subgroups of patients with a high or a low probability of response to therapy so that an individualised treatment plan can be implemented [2]. However, the definition of pCR varies in the literature: pCR can be defined as the absence of any residual invasive cancer of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of NACT; this is adopted by many studies including the NSABP B-27 trial [3–5]. Although pCR is a universally accepted end point, there are various pathological classification systems for grading response and there is no evidence that one pathological system is superior to another. Although there is extensive research on assessing response to NACT in early-stage breast cancer, comparing response between studies is challenging as response to therapy is dependent upon the subset of cancer, type of regimen, grading criteria for tumour classification and the end point used within each study.

Multiple studies have investigated the use of pathological biomarkers and imaging modalities to predict response or resistance to NACT within their data to identify a tailored treatment regimen. Current techniques include clinical assessment, imaging modalities (ultrasound, mammography and MRI) and molecular and histological analysis of tumours. However, neoadjuvant approaches have failed to demonstrate consistent longer-term advantages over post-operative chemotherapy, and thus a potential survival advantage with pre-operative chemotherapy remains controversial. In this paper, we will discuss the existing literature on the use of NACT and the potential roles of molecular pathology and radiology as potential predictors of response.

Selection of Studies

A search of Medline, CINAHL and Embase databases of studies on NACT was performed. Key words used were neoadjuvant chemotherapy, breast cancer*, pathological* complete response, primary chemotherapy, radio-

logical*, predictor*, gene expression and biomarkers. The search strategy was limited to the English language and years 2000–2015, where studies with surgery as the primary modality for local control of disease after chemotherapy were included. Despite broad search criteria, only a small number of existing randomised controlled trials were relevant to this study.

Pathological Predictive Markers

To date, several markers have been investigated as predictors of response to NACT; these include hormone receptor (HR) status [oestrogen (ER) and progesterone (PR) negative/positive], tumour type and differentiation, HER2/cerbB-2, apoptosis-related genes, tumour proliferation and more recently gene expression profiling [6].

Tumour Characteristics

Evidence suggests invasive lobular carcinoma (ILC) responds poorly to NACT compared to patients with invasive ductal cancer (IDC). A retrospective analysis of patients receiving anthracycline-based NACT demonstrated a pCR rate of 3% in ILC patients compared to 15% in IDC patients. It was found that more patients with ILC were ER positive (92 vs. 62% in IDC) and had a lower tumour grade. This difference in pCR remained significant following adjusting for ER status, suggesting ILC as an independent predictor [7]. Similarly, when analysing chemosensitivity of ILC and IDC treated with NACT, Mathieu et al. [8] reported that ILC was an independent predictor of poor clinical response. Other pathological characteristics such as poor differentiation of tumour and high grade are also more NACT sensitive compared to tumours that are of low grade and well differentiated. Supporting this, poor tumour differentiation, negative ER and topoisomerase II (TopoII) expression and positive nm23-H1 status are also established as markers predicting pCR [9].

Evidently, histological and biological factors have also been shown to predict response to NACT [10]. Connexins contribute to carcinogenesis and tumour progression through the loss of cell cycle control. Teleki et al. [11] investigated connexin expression and cell differentiation prior to and after NACT to assess disease survival and pathological response in a cohort dominated by HR-positive and HER2-negative cases. Connexin 46 and 26 expression statistically correlated with better survival after chemotherapy, and thus may improve the assessment of

pathological response after NACT compared with current classification systems. These studies suggest HR status and tumour grade as useful predictors of pathological response to NACT. Similarly, Huober et al. [12] determined the effect of NACT on mid-course response and pCR at surgery in different breast cancer subtypes within the GeparTrio trial (n = 2,072). Overall pCR (defined as no invasive residuals in breast and axilla) was 20.5%. The highest pCR was observed in triple-negative or grade 3 tumours (57%). Grading, clinical staging and age were independent predictive factors for pCR in luminal tumours, HER2 tumours and triple-negative breast cancer subtypes, respectively. Furthermore, a recent meta-analysis by Cortazar et al. [13] found that the association between pCR and long-term outcomes was strongest in patients with triple-, HER2- and HR-negative tumours. Thus, the prognostic value is greatest in patients with aggressive tumour subtypes.

Molecular Markers

HR Status

Oestrogen and progesterone are known to modulate expression of growth factor receptor pathways and downstream cell cycle regulatory genes known as nuclear proto-oncogenes [14, 15]. In a large retrospective study by Guarneri et al. [16], 24% of patients with ER-negative tumours achieved pCR compared to 8% of patients with ER-positive tumours, irrespective of the NACT treatment regimen ($p < 0.001$). Supporting this, there have been a number of prospective clinical trials demonstrating high pCR in HR-negative tumours [4, 15–18]. When analysing functional germline polymorphisms to predict response to NACT, Szkandera et al. [19] noted that pCR was significantly more frequent in ER-negative cancers than ER-positive cancers, and pCR was also associated with a higher grade ($p = 0.006$). However, Ring et al. [15] found that in 435 patients receiving NACT, although ER-negative tumours were more likely to achieve a pCR rate (21.6% in ER-negative vs. 8.1% in ER-positive tumours), HR status and grade did not appear to be independent predictors.

Alternatively, von Minckwitz et al. [20] investigated response-guided NACT in early-stage breast cancer in a prospective phase III trial involving 2,072 patients with early-stage breast cancer who underwent conventional chemotherapy with TAC (Taxotere, Adriamycin and cyclophosphamide) and response-guided chemotherapy. Disease-free survival was significantly longer in patients

who had received more cycles of TAC, particularly in case of response-guided chemotherapy, compared to patients who had conventional chemotherapy in all HR-positive tumours. This trial demonstrates that patients with luminal cancers have a greater benefit with response-guided chemotherapy.

HER2 Expression

Approximately 15% of breast cancers demonstrate protein expression/amplification of the HER2 gene, the expression of which is associated with a poor prognosis, independent of other clinical and pathological variables [21, 22]. Multiple studies have assessed HER2 overexpression as a biomarker predicting response to NACT, for instance anthracycline versus non-anthracycline regimens (such as doxorubicin). However, the predictive value of HER2 overexpression to improve the efficacy of anthracycline-based adjuvant therapy is inconclusive [23].

A meta-analysis demonstrated a greater benefit for anthracycline-based therapy in women with HER2 overexpression for disease-free and overall survival [24]. Petit et al. [25] also reported a correlation of response between anthracycline-based NACT and HER2 status. A high-dose anthracycline regimen and HER2 overexpression predicted an overall greater response rate compared to low- or high-dose anthracycline and normal HER2 expression. Dhesy-Thind et al. [26] support this, although the mechanism underlying the interaction between HER2 and anthracycline therapy is not fully understood. These reports suggest that breast cancer with HER2 overexpression may be a predictor of overall effective response to NACT.

The use of trastuzumab, a humanised monoclonal antibody, in combination with NACT in HER2-positive breast cancer has resulted in pCR rates ranging from 18 to 65%, and improvements in disease-free and overall survival [27, 28]. The NOAH (Neoadjuvant Herceptin) trial assessed the efficacy of adding trastuzumab to NACT regimens in patients with newly diagnosed locally advanced breast cancer. Patients with HER2-positive disease treated with trastuzumab combined with NACT had a significantly improved overall response rate (87 vs. 74%) and pCR in breast tissue (43 vs. 22%) compared with those who received NACT alone [29]. In addition to this, the GeparQuattro (German Breast Group/Gynaecologic Oncology Study Group) trial also found that 32.9% of patients who received trastuzumab in addition to chemotherapy regimens achieved pCR, compared with 15.7% for patients who received chemotherapy alone [30].

More recently, the addition of newer anti-HER2 drugs such as pertuzumab and lapatinib enabling dual HER2

blockage has improved pCR rates and overall survival rates. The Neo-ALTTO trial assessed HER2-positive patients' response to NACT given with lapatinib, trastuzumab or the combination of both. pCR with the combination was 51.3% compared with 29.5% for trastuzumab alone. Alternatively, the NeoSphere trial assessed the combination of trastuzumab and pertuzumab versus trastuzumab alone. In this study, women with HER-positive breast cancer were randomly assigned to four groups: trastuzumab + docetaxel (group A), pertuzumab + trastuzumab + docetaxel (group B), trastuzumab + pertuzumab (group C) and pertuzumab + docetaxel (group D). Findings demonstrated 45.8% pCR in group B, compared to 29 and 24% in groups A and D, respectively. Furthermore, 16.8% of patients that received anti-HER2 therapy alone (group C) achieved pCR, thus questioning whether a subgroup of breast cancer patients can be treated with monoclonal agents alone, avoiding chemotherapy [31]. Results such as these encourage further investigation into using molecularly targeted approaches in the neoadjuvant setting.

TopoII α Expression

TopoII works to reduce DNA recoiling, allowing selected regions of DNA to untangle and engage in transcription, replication and repair. The roles of TopoII as a marker for anthracycline response and microtubule-associated protein tau (MAPT) for taxane sensitivity are evident in the recent literature. HER2 has also been described as a marker of both anthracycline and taxane sensitivity [32]. This may be a result of the close location of HER2 and TopoII genes on chromosome 17. Due to their location, TopoII gene aberrations are mainly associated with HER2 amplification; based upon this, it can be argued that HER2 is only a surrogate marker and TopoII overexpression could be the underlying predictive marker of response to anthracycline-based chemotherapy [33]. Previous studies have also revealed that TopoII gene amplification apparently does not always lead to protein overexpression [32]. In addition, MacGrogan et al. [34] reported that high expression in TopoII protein was associated with tumour regression (50%) after six cycles of NACT. On the contrary, the GeparTrio phase III trial did not find a correlation for both TopoII and MAPT with pCR in a sample population.

Ki67 Expression

Ki67, a proliferation marker, has been widely investigated as a marker to allow decision making in breast cancer patients. Many studies have investigated the signifi-

cance of Ki67 in the context of NACT; however, there is limited evidence on its predictive and prognostic value. One particular study examined the progression of cancer during NACT and found that patients in whom progression occurred had had a higher Ki67 proliferation rate than those who responded to chemotherapy [35]. In a study by Fasching et al. [36] in core biopsies of 552 patients, Ki67 was positive in 23.4% of cancer cells in patients with pCR. Patients with triple-negative or HR-positive, HER2-negative breast cancer also appeared to have a favourable prognosis when pCR was achieved, despite having a high Ki67 proliferation rate in these subgroups, thus suggesting Ki67 also has independent predictive and prognostic value for NACT treatment response. Inwald et al. [37] evaluated the routine use of Ki67 as a prognostic marker by analysing histological parameters of this marker in a routine clinical setting. A total of 3,658 patients with invasive breast cancer were included in the study, and a strong correlation was disclosed between tumour grading and Ki67 ($p < 0.001$). In addition, disease-free survival was associated with low Ki67 expression, adding greater value to prognosis than grading systems alone, as suggested by previous studies [36–38]. Equally, it can be argued that Ki67 expression, which is used in standard practice, may also have a strong value in predicting response to NACT.

Apoptosis-Related Markers

Many chemotherapeutic agents destroy cancer cells by inducing apoptosis [39]. Therefore, studies have evaluated the role of proteins such as p53 and Bcl-2, which are involved in the apoptotic pathway, in predicting response to chemotherapy.

p53 is a tumour suppressor gene that is the most frequently mutated gene in human cancer occurring in at least 50% of all cancers. p53 is involved in the apoptotic pathway by inducing cell cycle arrest itself and initiating apoptosis. In theory, the use of p53 as a marker to predict response to NACT is promising; however, in many studies p53 expression is evaluated by immunohistochemistry. As such, high p53 staining can be presented as abnormal but can miss clinically relevant mutations and thus is poorly represented [40–42]. However, TP53 mutation response in taxane versus anthracycline therapy was investigated using a functional yeast assay [43]. The trial demonstrated that TP53 was prognostic for overall survival but not predictive for sensitivity to taxane treatment. However, again, the tumour subtype is a strong predictor of pathological response and is a confounding factor.

The Bcl-2 gene encodes a 26-kDa protein, which is involved in inhibiting apoptosis. Alternatively, BAX, another protein, functions closely with Bcl-2, but as a pro-apoptotic agent. Thus, studies have suggested either elevation of Bcl-2 or reduction in BAX may predict pathological response to NACT. Ogston et al. [44] and Buchholz et al. [45] reported that the absence of detectable Bcl-2 predicted a better chance of pCR. Again, it is noteworthy that Bcl-2 expression is also higher in ER-positive tumours, as it is an oestrogen-regulated gene (also dependent upon the tumour subtype; luminal A and B). One would question whether Bcl-2 expression is an independent predictor of lower pathological response when ER expression is taken into account. Similarly, tumours with high ER expression that have lower pathological response may have higher Bcl-2 expression. Given this, although Bcl-2 may have prognostic significance, its role as a predictive marker is not well defined.

Gene Expression Profiling

Gene expression profiling is the focus of much research activity for the identification of prognostic and predictive marker genes in response to NACT. However, there are limited data available concerning clinical utility, particularly as many studies are limited by small patient numbers and gene expression is dependent upon the tumour subtype [46, 47]. A recent study of 113 patients with stage II–III cancer showed that the use of a 30-gene molecular predictor of pCR identified all but 1 patient who had achieved pCR. When compared with clinical predictors such as age, tumour grade and ER status, the use of gene expression profiling showed significantly higher sensitivity [48]. However, to what extent this genomic predictor of sensitivity is specific to the therapy received (paclitaxel, 5-fluorouracil, doxorubicin and cyclophosphamide) rather than being a genetic marker of chemotherapy sensitivity is unclear. Another study by Gianni et al. [46], in which RNA was extracted from formalin-fixed paraffin-embedded core biopsies before treatment, correlated the expression of 384 genes with pCR following paclitaxel- and doxorubicin-based NACT. Findings revealed 86 genes correlating with pCR (unadjusted $p < 0.05$). pCR was more closely correlated with higher expression of proliferation- and immune-related genes and with lower expression of ER-related genes.

In addition to this, Oncotype Dx has shown potential utility in predicting a chemotherapy benefit. Data from exploratory neoadjuvant trials revealed pCR or complete

clinical response only in patients with a recurrence score of 25 or higher [46, 49]. Rody et al. [32] performed gene expression profiling of 50 patients within the GEPTRIO study, an anthracycline- and taxane-based trial, to investigate the predictive value of TopoII α , MAPT and HER2 mRNA expression for pCR. HER2 gene expression was strongly predictive of pCR ($p = 0.017$) as well as overall response ($p = 0.037$) and clinical complete response, whereas no correlation with pCR was observed in TopoII α and MAPT. This study also provides greater insight into the predictive value of various tumour subsets.

Gene expression profiling has also led to recognition of new predictors in solid cancers. Poly(adenosine diphosphate-ribose) polymerase (PARP) is a key biomarker in DNA repair and cellular stress response, and some studies have suggested that inhibitors of PARP demonstrate promising clinical activity in metastatic, triple-negative or BRCA-mutated breast cancer. Von Minckwitz et al. [50] evaluated the predictive and prognostic value of cytoplasmic PARP (cPARP) after neoadjuvant anthracycline/taxane-based therapy. High cPARP expression significantly correlated with non-lobular histology ($p < 0.001$), undifferentiated grade, positive nodal status and negative HR status, but, interestingly, it did not correlate with HER2 status. pCR was 26.5% with high expression, compared to 8% with low expression ($p < 0.001$). High cPARP expression correlated with aggressive tumour patterns and sensitivity to anthracycline-specific therapy; it may be that cPARP-positive breast cancers may become a new clinically relevant entity. The potential role of PARP inhibitors as new anticancer agents is an ongoing research area in several clinical studies [51, 52].

Imaging Modalities as Predictive Markers

MRI-based evaluation of tumour size is the current gold standard in monitoring breast cancers. It relies upon contrast-enhanced imaging using paramagnetic contrast agents. With regard to assessing response and residual tumour burden following treatment, MRI has been found to be superior to conventional ultrasound scan (USS).

Abraham et al. [53] found MRI accurately predicted the pathological determination of residual disease in 30 of 31 patients with stage II, III and IV breast cancer following NACT. In a study by Londero et al. [54], assessment of tumour response was more accurate when using USS after MRI for uncertain foci of multifocal or multicentric disease such as ductal carcinoma in situ or ILC (increase in diagnostic accuracy from 73 to 84.5%), whilst others have

argued MRI solely being an ineffective predictor due to size overestimation. McGuire et al. [55] studied the discrepancy between post-neo-adjuvant breast tumour size on MRI and residual tumour size by assessing patients that had post-NACT MRI staging prior to surgery. The average tumour size by MRI was 1.2 cm after chemotherapy, whilst the average pathological tumour size was 1.7 cm. However, these ranges differ between tumour subtypes (i.e. the greatest difference was in luminal tumours and the least in triple-negative and HER2-positive tumours). Although MRI is an effective tool in measuring tumour size after NACT, tumour subtypes affect accuracy. These conventional modalities rely largely upon sizing of the tumour and can underestimate anti-tumour effects of newer cytostatic agents whereby tumour shrinkage may be minimal or delayed. Furthermore, the assessment of infiltrative breast cancers with irregular or multifocal growth can also prevent reproducible size measurements. Kim et al. [56] studied the utility of MRI and PET/CT after NACT evaluating the correlation with pathological grading based upon tumour cellularity rather than RECIST. In some tumours, chemotherapy can reduce cellularity dramatically with minimal overall impact upon tumour size, thus objective criteria based upon tumour size such as UICC or RECIST guidelines lack in credibility [57].

Many studies have investigated the use of PET imaging via visualisation of metabolic activity of cancer tissue. Wahl et al. [58] reported that in patients with locally advanced breast cancer with partial or complete pathological response, ^{18}F -FDG uptake decreased promptly with treatment. Similarly, Schelling et al. [6] found a significant difference ($p < 0.05$) when comparing ^{18}F -FDG uptake with pathological response using distinct histopathological criteria, namely minimal residual disease and gross residual disease. The accuracy of predicting histopathological response was 88 and 91% after the first and second cycles of therapy, respectively. However, current studies are limited with small sample sizes and, therefore, cannot be generalised. Arguably, PET imaging, which also exposes patients to high doses of radiation, is a poor detector of small breast lesions and thus may not be an ideal predictor of response to NACT in comparison with MRI.

Emerging response assessment techniques include quantitative methods of measuring tumour blood flow, magnetisation transfer MRI, diffusion-weighted MRI, hyperpolarised MR, MR elastography and chemical exchange saturation transfer MRI, which aim to provide a more accurate means of quantifying tumour response with reducing impact of interobserver reliability, are not yet incorporated into standardised practice.

MRI can assess both functional activity and morphology of the cancer, and additional lesions can be biopsied under MRI guidance if conventional imaging is normal. In current practice, the role of MRI to assess response to chemotherapy is widening. The functional aspect such as diffusion-weighted imaging will improve the sensitivity and specificity of MRI to assess response. A meta-analysis by Marinovich et al. [59] demonstrated the accuracy of MRI over imaging modalities such as USS and mammography. However, despite notable differences between various imaging modalities, it was established that when assessing pCR, MRI accuracy in determining response to NACT was compromised. Therefore, the evidence highlights the importance of developing a predictive model based upon pathological biomarkers.

Combining Pathological and Radiological Predictors

The I-SPY trial (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis) is a multicentric study integrating clinical, imaging and genomic data to identify biomarkers predictive of response to NACT for women with stage III breast cancer. The aims of this study were to correlate contrast-enhanced MRI results with molecular markers to identify the right surrogate marker for early response, thus assisting physicians to provide a better prognosis for breast cancer patients and to select tailored treatments. At all points of treatment, MRI size measurements were superior to clinical examination, with tumour volume changes demonstrating greatest relative benefit at the second MR examination. In the trial, Ki67 immunohistochemical staining was performed where tumour proliferation was categorised into low, intermediate or high. pCR was significantly higher with high Ki67 (34%), and Ki67 was also significantly associated with increased responsiveness in HER2-negative subsets. These findings highlight the potential for adding Ki67 to standard receptor subtyping, which may improve further prediction of pCR in future trials [60, 61]. Randomised controlled trials are an effective means of integrating diverse data types across the research spectrum to achieve a more reliable outcome. The study also provides additional insight into previous NACT trials such as NSABP B-27, where although pCR improved significantly when taxane (paclitaxel) was added to anthracycline-based chemotherapy, the improvement was not of same magnitude as that for recurrence-free or overall survival [4]. Given that all these trials have contained a mix of receptor subsets, where

Table 1. A comparison of imaging modalities in predicting pCR following NACT

Study	Study type/ time period	Patients, n	Mean age, years	Type of cancer	Predicted response to pCR
Shin et al., 2011 [62]	Prospective/4 years	43	42.7	Invasive ductal carcinoma Micropapillary carcinoma	ICC 0.65 – clinical examination 0.69 – MMG 0.78 – USS 0.97 – MRI
Croshaw et al., 2011 [63]	Retrospective review, Jan 2005 to Sep 2010	61	56	IDC (50) ILC (10) Other (2)	Accuracy to pCR 54% – clinical examination (28/52) 71% – MMG (31/49) 80% – USS (41/54) 70% – MRI (28/40)
Peintinger et al., 2006 [64]	Phase 3 randomised controlled trial	162	51.6	IDC (84%) ILC (8%) Mixed ductal and lobular (4.3%) Other (6%)	53% – clinical examination 67% – MMG + USS 63% – clinical examination + USS + MMG
Kwong et al., 2006 [65]	Prospective	17 (only 6 achieved pathological response)	–	Locally advanced breast cancer	66.6% discordance between MRI- predicted response and pCR
Yeh et al., 2005 [66]	Cohort, Jun 2000 to Mar 2003	31	45	Stage IIb–III breast cancer IDC (n = 23) ILC (n = 2) Mixed ductal and lobular (n = 1) Other invasive cancer (n = 5)	19% – clinical examination 26% – MMG 35% – USS 71% – MRI
Londero et al., 2004 [54]	Prospective study	15	–	Ductal carcinoma in situ and ILC	MMG 6.7% – clinical CR 53.3% – PR USS/MRI 13.3% – clinical CR 60% – PR
Abraham et al., 1996 [53]	Prospective study	39	–	Stage II, III and IV breast cancer	52% – cases of MMG correlated with MRI 97% cases MRI predicted residual disease accurately

CR = Complete response; MMG = mammography; PR = partial response.

tumour biology is different, comparisons in future trials should be anchored within molecular subsets rather than across whole trial populations (table 1).

Conclusion

NACT is an approach that offers the advantages of down-staging disease, potentially reducing the extent of surgery and, in an era of individualisation of therapy, testing the efficacy of therapy administered to patients. Despite exploring prognostic values of existing pathological and radiological biomarkers, there is a lack of robust evidence regarding the optimum method for predicting re-

sponse to therapy and the value of present systems available. It is conceivable that a combination of latest advances in radiological and pathological biomarkers would provide the novel predictive surrogate marker for response to NACT. However, further research is required to discover this method. Currently, gene profiling and a combination of pathological markers hold the most promising role in predicting early response to NACT and present an area of intensive research to develop personalised NACT. Further clinical trials are warranted to focus upon the identification of molecular profiles and predictive markers associated with pCR in the early stages of breast cancer preferably using a standardised grading system.

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