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Overview

Neoadjuvant Therapy in Early Breast Cancer: Treatment Considerations and Common Debates in Practice

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Abstract

Neoadjuvant treatment offers a number of benefits for patients with early breast cancer, and is an important option for consideration by multidisciplinary teams. Despite literature showing its efficacy, the use of neoadjuvant therapy varies widely. Here we discuss the clinical evidence supporting the use of neoadjuvant therapy in early stage breast cancer, including patient selection, monitoring response, surgery and radiotherapy considerations, with the aim of assisting multidisciplinary teams to determine patient suitability for neoadjuvant treatment.

Key words: Breast cancer; chemotherapy; endocrine therapy; multidisciplinary; neoadjuvant treatment; patient management

Introduction

Originally a means to downstage patients with inoperable locally advanced breast cancer, neoadjuvant therapy is now integral to the treatment of patients with early stage disease. Large clinical trials such as EORTC 10902 and NSABP B-18 have shown no differences between the same systemic therapy given pre- or post-surgery on disease-free (DFS) and overall survival [1–3]. Other benefits (i.e. the conversion of patients requiring mastectomy to breast-conserving surgery [BCS]) and some potential concerns have been investigated and are well recognised (Table 1). It is therefore important for the multidisciplinary team (MDT) to consider the benefits and risks when selecting patients who may benefit from neoadjuvant therapy.

Anthracycline plus taxane-based chemotherapy is the most widely used neoadjuvant chemotherapy (NAC) regimen for all early breast cancer subtypes and is associated with high rates of clinical response (up to 90% in NSABP B-27) [15]. Progression during NAC is infrequent, with a rate of 3% in one meta-analysis of 1928 patients [16]. In patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer, trastuzumab with or without pertuzumab should be administered concomitantly with a taxane [17–19]. For patients with triple negative breast cancer (TNBC), the addition of carboplatin in the GeparSixto [9] and CALGB 40603 [20] studies have shown an increased pathological complete response (pCR) rate, although with increased toxicity and without a significant increase in BCS rate. Ongoing studies such as NRG-BR003 (NCT02488967) [21] and M14-011 BRIGHTNESS (NCT02032277) [22] will provide additional data on the effects of platinum agents as neoadjuvant or adjuvant treatment, respectively, on survival outcomes.

To date, neoadjuvant endocrine therapy has been used less frequently than chemotherapy. Aromatase inhibitors

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Table 1
Clinical benefits and potential concerns associated with neoadjuvant treatment for early breast cancer

	Benefits	Potential concerns
Impact on surgery	• Downstage tumours to permit breast-conserving surgery rather than mastectomy [4–6], improving cosmetic outcomes. • De-escalate surgical treatment of the axilla [7]. • Provide time for germline mutation test results (i.e. *BRCA1/2*) that may influence surgical plan.	• Cancer may progress and become inoperable (a rare event with appropriate monitoring of response). • Reduced window of opportunity for fertility preservation [8]. • Increasing tumour response may not achieve a reduction in mastectomy rates, regardless of downstaging and effectiveness of therapy regimen [9,10]. • Increased locoregional recurrence rates in patients who do not undergo surgery after neoadjuvant treatment [11].
Disease information and monitoring	• Provide individualised post-treatment prognostic information (e.g. pathological complete response, residual cancer burden) for management decisions. • Permits clinicians to monitor response to therapy at an early stage; potentially allowing time and flexibility to switch therapies if patients do not respond [12,13].	• Potential loss of staging information. • Potential for over-treatment, if decision is based on incomplete information (e.g. size of lesion is overestimated because of associated ductal carcinoma *in situ* seen radiologically). • Potential for under-treatment if therapy is stopped or changed mid-course [14]. • Limited evidence base to guide adjuvant radiotherapy decisions or management of patients with residual disease.

are used in selected patient subgroups (i.e. postmenopausal women with larger, hormone receptor-rich breast cancers), usually when systemic chemotherapy is not indicated either due to tumour biology or patient characteristics [17,18,23]. This may include node-positive or node-negative patients [23,24]. With appropriate patient selection, the risk of disease progression is low, although treatment duration is longer than for NAC [25]. A trial of 182 patients treated with neoadjuvant letrozole showed a 69.8% BCS rate at 3 months, rising to 83.5% after 2 years of treatment [26]. Llombart-Cussac *et al.* [27] reported a median time to maximum response with letrozole of 4.2 months. However, over a third of responding patients required more than 6 months of treatment. A recent meta-analysis of 20 studies indicated that neoadjuvant endocrine therapy may be as effective as NAC, but with lower toxicity [28]. Therefore, neoadjuvant endocrine treatment should be considered in selected patients.

Initiating Neoadjuvant Treatment

Factors to Consider when Selecting Patients for Neoadjuvant Therapy

Although there is consensus on the patient subgroups most likely to benefit from neoadjuvant treatment [17,18], its utilisation in clinical practice remains highly variable [29–31]. All early stage breast cancer patients identified as likely to require adjuvant chemotherapy should be considered for NAC, as they may potentially benefit from treatment before surgery. Factors favouring NAC in patients with operable breast cancer include:

- high tumour volume-to-breast ratio;
- lymph node-positive disease;
- biological features of primary cancer (high grade, hormone receptor-negative, HER2-positive, TNBC);
- younger age.

The efficacy of neoadjuvant treatment is assessed by evaluating the clinical and radiological response during and after therapy, and the pathological response after surgery. The likelihood of achieving a significant response is predicted by cancer phenotype; patients with HER2-positive and TNBC have the highest probability of achieving pCR after NAC (up to 50.3% for hormone receptor-negative/HER2-positive patients receiving HER2-targeted therapy, and 33.6% for TNBC) [32], making them good candidates for NAC consideration [32,33]. By contrast, pCR rates are lower for hormone receptor-positive/HER2-negative cancers; however, patients in this group may still achieve a meaningful clinical and radiological response from NAC, particularly younger patients with grade 3 cancers and low hormone receptor levels. Careful selection within these subgroups is required.

Histological subtype is also important. Invasive lobular cancers (ILCs) represent 10–15% of breast cancers and are typically hormone receptor-positive and histological grade 2. NAC is less beneficial in this group: fewer patients are downstaged to permit successful BCS, re-excision rates after BCS are higher and the likelihood of pCR is significantly lower than invasive cancers of no special type (NST) [34].

Just considering patients with pCR, significantly lower BCS rates were observed in ILC than invasive NST [35]. The number needed-to-treat to achieve significant downstaging was higher in ILC (11.5 and 15.4 for cT2 and cT3, respectively) than in invasive NST (8.5 and 7.2, respectively) [36]. The greatest likelihood of response is in ILCs with more aggressive biological features (i.e. grade 3, hormone receptor-negative/HER2-positive) [35,36]. Lower response rates have also been reported in mucinous, metaplastic and apocrine carcinomas [37].

As discussed, DFS and overall survival seem to be equivalent in studies where identical chemotherapy was given pre- versus postoperatively [1–3], contradicting the original hypothesis that early treatment of micrometastatic disease would improve survival. Nevertheless, given the current appreciation of the importance of intrinsic subtype in almost every aspect of breast cancer behaviour, it is important to ask whether there may be specific patients to whom neoadjuvant therapy should be administered to improve long-term outcomes. A trend for improved overall survival was noted in the NSABP B-18 study in women aged younger than 50 years treated with NAC compared with adjuvant chemotherapy, and this might reflect the increased frequency of hormone receptor-negative disease in younger patients [6]. A prospective registry study also reported a trend towards improved DFS in TNBC patients who received NAC, although there were significant imbalances in the treatment arms [38]. Therefore, there is currently insufficient data to recommend neoadjuvant over identical adjuvant chemotherapy on the basis of improved survival in any subgroup.

Breast cancer treatment has evolved into a truly multidisciplinary endeavour, requiring a team that includes surgeons, clinical and medical oncologists, radiologists, pathologists and nurses in patient care. When discussing neoadjuvant treatment, it is crucial that provisional histological grade (i.e. derived from the core biopsy specimen), hormone receptor and HER2 results, and radiological results are available at the MDT meeting [39]. MDT discussions should include the proposed surgical plan after treatment, which will be determined by the tumour response to NAC.

Figure 1 provides a suggestion for the information that should be available and discussed to aid decision-making by the MDT. Once a patient has been identified for neoadjuvant therapy, radiological marker clips should be placed in the breast, and any positive nodes should also be marked pretreatment [40].

Treatment recommendations should be consistent with local and national guidelines [41]. Once the neoadjuvant treatment recommendation has been made, the benefits and risks should be discussed with the patient to help them make an informed choice.

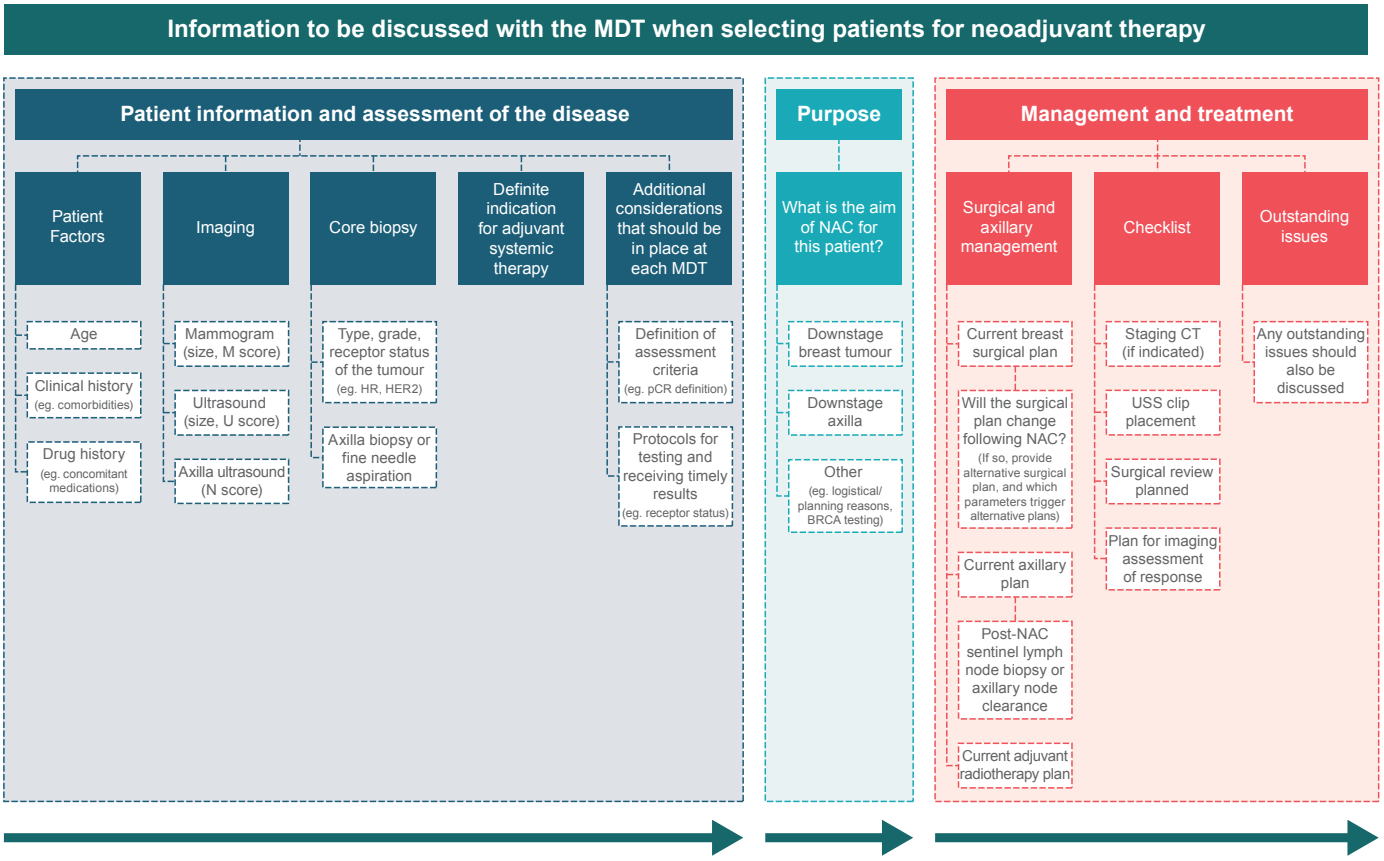

Fig 1. Topics and information for discussion at multidisciplinary team (MDT) meetings. HER2, human epidermal growth factor 2; HR, hormone receptor; NAC, neoadjuvant chemotherapy; USS, ultrasound.

Monitoring Response to Neoadjuvant Treatment

Monitoring during Neoadjuvant Treatment

Clinical assessments and imaging are the mainstay when monitoring treatment response and aid the early identification of potential disease progression. Imaging should include a bilateral mammogram and/or breast ultrasound, both before and after NAC, and repeated during the treatment course if there are any clinical concerns regarding progression. For neoadjuvant endocrine therapy, 3-monthly assessments can be completed. Studies have suggested a potential correlation between early radiological response and pCR [42].

Not all patients require magnetic resonance imaging (MRI) during NAC treatment [18,43,44], but it is the most accurate and sensitive modality for identifying residual disease after treatment [18,44,45]. MRI accurately predicts pathological findings in TNBC, HER2-positive and hormone receptor-negative tumours [46], with significant correlations between MRI and tumour changes during NAC [47]. MRI can be helpful for the purposes of surgical planning [13,44] and is indicated in cases where there are discrepancies between mammography and ultrasound, as it may influence subsequent surgical decision-making.

The full course of NAC should be completed unless there is evidence of disease progression. Although the concept of 'response-guided' therapy is attractive, it is still evolving as clinical data regarding its effectiveness are as yet inconclusive [48]. It is crucial for MDTs to review the small number of patients who experience cancer progression during NAC; the appropriate action for most of these patients is to cease treatment and proceed immediately to surgery and/or radiotherapy.

Surgical Management of Patients after Neoadjuvant Therapy

Advantages of Breast-conserving Surgery

BCS improves psychosocial and cosmetic outcomes after breast cancer surgery over mastectomy [49,50]. Hence, a key benefit of neoadjuvant treatment is enabling BCS for patients in whom mastectomy would otherwise be indicated. Indeed, studies have shown that NAC increases BCS rates [2,51], although patients eligible for BCS may still opt for mastectomy [52]. As cosmetic outcome is influenced by the volume of tissue excised [53], it is logical to assume that an NAC-mediated reduction in resection volume will improve cosmetic outcome, but not all studies have shown a reduced excised volume at BCS after NAC [54]. When the tumour lies in a cosmetically sensitive area (i.e. the upper inner quadrant) it is acceptable to use NAC to reduce the volume of excised tissue necessary in patients suitable for BCS.

There are circumstances where mastectomy may be indicated despite a good response to NAC. These include the presence of widespread malignant microcalcifications (confirmed histologically to represent ductal carcinoma *in situ*), *BRCA1/2* gene mutation carriers considering a bilateral risk reduction, or patient choice.

Previous concerns of increased locoregional recurrence (LRR) risk following NAC to downstage and permit BCS [55] have not been borne out. Studies have suggested that BCS combined with whole breast radiotherapy is no different to or has a higher survival rate than mastectomy [56–59] with similar LRR rates. A recent meta-analysis of TNBC suggests that LRR rates for BCS plus radiotherapy are lower than for mastectomy [60]. Furthermore, a meta-analysis of eight studies has shown that as long as surgery remained a component of the treatment pathway, there was no increase in LRR rates after BCS [11]. The concerns surrounding operative complications after NAC are similarly unfounded, as the rate is low, even for patients undergoing immediate breast reconstruction [11,61].

Patterns of tumour response may influence surgical planning. There are two general patterns of response after NAC: concentric shrinkage or a scattergun/honeycomb response (Figure 2), where the residual carcinoma presents as multiple, scattered foci over an ill-defined tumour bed [62,63]. This latter pattern of response is particularly problematic when planning surgical procedures, as obtaining clear margins is more difficult [63].

Recent improvements of systemic therapy efficacy in specific subtypes such as hormone receptor-negative/HER2-positive disease, where pCR rates exceed 60%, raise the question of whether surgery could be omitted in patients who achieve a radiological complete response after NAC [64,65]. At present, this remains a research question and is being explored in the UK and Europe by the NOSTRA and MICRA [66] trials, respectively, although surgery should not be omitted without evidence from such clinical trials [64,65].

Defining the Surgical Margin

Local margin guidelines accepted for primary BCS should also be adopted for BCS post-NAC. The most appropriate margin width after NAC has not been defined separately, but even for patients with adverse biology, the available evidence does not suggest a need to increase surgical margin width [67,68].

Managing the Axilla: Timing Sentinel Lymph Node Biopsy

Local guidelines on management of the axilla should be followed as per MDT discussion before initiating NAC; the final decision on sentinel lymph node biopsy (SLNB) should be taken after full clinical and radiological axillary assessment after neoadjuvant treatment. In the UK, post-NAC SLNB is now accepted practice in patients with pre-treatment negative nodes (ultrasound scan with or without fine needle aspiration/core biopsy), although this is not uniformly applied even though lymph node staging

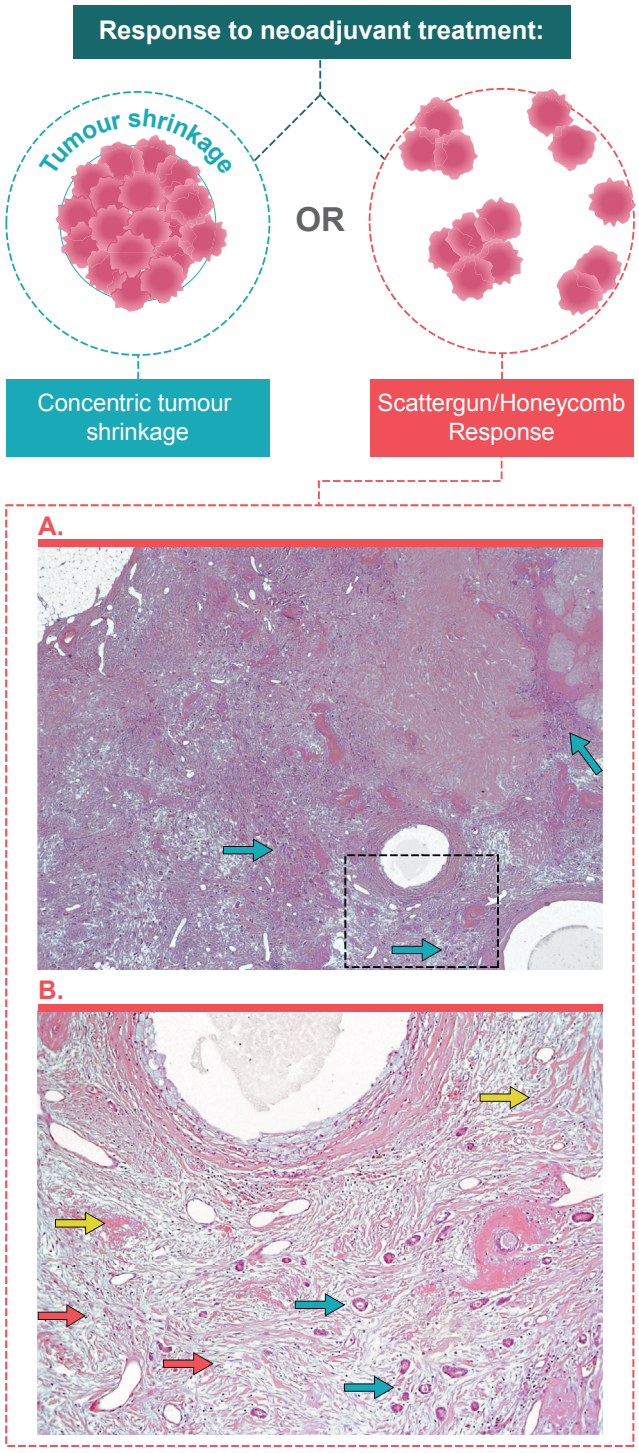

Fig 2. Patterns of response following neoadjuvant treatment. Haematoxylin and eosin (H&E) stained section of tumour bed with fibrosis and elastosis indicating response to neoadjuvant chemotherapy. (A) Low power view; scanty scattered islands of residual invasive carcinoma are present (blue arrows), box represents view of (B). (B) High power view, showing oedema (red arrows), fibrosis (yellow arrows) and residual small islands of invasive carcinoma (blue arrows).

after NAC has greater prognostic significance than axillary node status at the outset [69], and SLNB accurately stages the axilla in patients who are clinically node negative at diagnosis [7]. The management of pre-NAC node-positive patients is more controversial, with many patients condemned to axillary clearance. There is now increasing evidence that this represents over-treatment, particularly in patients with HER2-positive and TNBC tumours, since they achieve a high nodal pCR rate, as shown by post-NAC SLNB [69]. Axillary clearance carried out on patients with nodal pCR may be regarded, at least in retrospect, as a failure of current decision-making algorithms, and efforts must continue to be applied to reduce the exposure of patients to the morbidity of an axillary clearance. Crucially, this depends on the accuracy of post-NAC SLNB. Based on results from the Z-1071 study, post-NAC SLNB should retrieve more than two nodes to reduce the false negative rate to 9.1%; the accuracy of SLNB after NAC is directly related to the number of nodes retrieved [70]. If adequate numbers cannot be retrieved, then axillary lymph node dissection should be considered [69]. This practice is being prospectively evaluated in the UK by the ROSCO trial (EudraCT 2013-004307-39) [71]. A targeted axillary dissection using a combination of removing the clipped node and SLNB provides a high degree of accuracy in assessing the post-NAC axilla [72]. Implementing these recommendations can reduce false negative rates to as low as 2.0% [40].

Patient Management after Neoadjuvant Treatment and Surgery

The Basis for Radiotherapy Planning and Management

It is generally recommended that patients who have BCS undergo radiotherapy [41], but there is more uncertainty regarding post-mastectomy chest wall radiotherapy. In the absence of clear guidelines, there is concern about whether to base radiotherapy decisions on the tumour parameters before or after NAC. Most evidence guiding radiotherapy originates from adjuvant clinical trials, but this evidence can also support decision-making with neoadjuvant treatment. The recent EBCTCG meta-analysis of post-mastectomy patients showed that chest wall radiotherapy reduced both the recurrence and mortality rates of node-positive patients even after systemic adjuvant chemotherapy [73], suggesting that chest wall radiotherapy is appropriate in post-NAC patients who remain node positive. For patients who achieve pCR after NAC, the results from the NSABP B-18 and B-27 studies showed very low rates of LRR post-mastectomy in the absence of radiotherapy [74], suggesting that omission of radiotherapy may be possible in this subset. However, these data arise from a relatively small number of patients, and the omission of chest wall and regional nodal radiotherapy after pCR remains an area of controversy that is being addressed by the ongoing NSABP B-51/RTOG 1304 study [75].

If patients have not achieved pCR after NAC, other parameters may assist radiotherapy decisions, such as tumour size, skin (e.g. T4 stage) or nodal involvement. In the latter case, supraclavicular fossa (SCF) radiotherapy should be considered if four or more axillary lymph nodes are involved after NAC, as would be the case in patients who

had not received NAC. In those with one to three positive nodes after NAC, the decision around SCF radiotherapy is less clear, as these patients would not receive SCF radiotherapy in the adjuvant setting. However, in the neoadjuvant setting, there is a concern that the patient may have had a heavier lymph node burden at baseline, despite the downstaging achieved with NAC. If there is histopathological evidence of scarring and treatment response in other nodes, it is reasonable to consider SCF radiotherapy on this basis, although there is no direct evidence from clinical trials that confirms or refutes this at present. Axillary radiotherapy should be considered if the patient is sentinel node positive and has not had axillary clearance [41].

At the moment, there is no specific evidence relating to the use of a tumour bed boost following neoadjuvant radiotherapy. Therefore, patients should be treated per standard protocols for the adjuvant setting. While the relative benefits of a boost seem to apply broadly, absolute benefits are greater in women 50 years of age and younger [76]. Recent consensus statements issued by the Royal College of Radiologists in the UK recommend a boost for all patients who have undergone BCS and are younger than 50 years old, with consideration in those over 50 years with higher risk pathological features (especially grade 3 and/or extensive intraductal component) [77].

It is clear that balancing potential risks of over-treatment with the risks of under-treatment (e.g. increased LRR rates and decreased survival) in the absence of definitive data is not straightforward [78]. In practice, most MDTs continue to adopt a conservative approach in line with the guidelines issued by the American National Comprehensive Cancer Network, which state that the indications for radiotherapy should be based on the maximum/worst stage from the pre- or post-treatment pathological stage and tumour characteristics [19].

Pathological Complete Response as a Measure of Efficacy of Neoadjuvant Chemotherapy

Using pCR as a prognostic marker of long-term outcome for the individual patient is well established [79]; achieving pCR is associated with improved survival outcomes [32,33]. The probability of achieving pCR depends on cancer subtype and is seen most frequently in TNBC and HER2-positive tumours. The association between pCR and survival outcomes is not as evident in slowly proliferating, hormone receptor-positive [80], luminal A cancers [81]. The predictive validity of pCR is therefore variable and dependent on the tumour biology.

pCR is also recognised by regulatory authorities such as the European Medicines Agency and the Food and Drug Administration as a standard efficacy endpoint to evaluate drugs given as NAC in early breast cancer clinical trials, pending confirmatory results from large adjuvant studies [32,82,83]. These bodies have provided standardised pCR definitions in their guidance [82,83]. However, definitions used in practice vary, which has implications when evaluating the outcomes of clinical trials [84].

In addition to pCR, the residual cancer burden provides another method to assess NAC response by incorporating bidimensional measurements of the residual tumour, histological assessment of the tumour cellularity and nodal disease burden (number of nodes involved and size of largest metastasis) to estimate the volume of residual disease [85]. Patients are placed in three risk groups, which are associated with distant relapse-free survival [63,85,86] (Table 2).

Table 2
Residual cancer burden definitions and estimated relapse-free survival rates

Residual cancer burden risk class	Definition	Cut-off	Estimated percentage of relapse-free survival of patients treated with T/FAC, % (95% confidence interval)*	
			5-year	10-year
RCB-0	No traces of residual disease (complete pathologic response)	RCB = 0	Overall: 92 (86, 96) TNBC: 94 (84, 98); HR+/HER2−: 88 (72, 95); HER2+: 94 (80, 99)	Overall: 86 (78, 91) TNBC: 86 (73, 93); HR+/HER2−: 83 (63, 93); HER2+: 88 (72, 96)
RCB-I	Minimal residual disease	≤1.36	Overall: 94 (88, 97) TNBC: 89 (73, 96); HR+/HER2−: 100; HER2+: 89 (61, 97)	Overall: 85 (75, 91) TNBC: 81 (63, 93); HR+/HER2−: 97 (81, 100); HER2+: 63 (35, 82)
RCB-II	Moderate residual disease	>1.36	Overall: 80 (76, 84) TNBC: 62 (50, 72); HR+/HER2−: 87 (82, 90); HER2+: 62 (42, 76)	Overall: 68 (62, 73) TNBC: 55 (43, 66) HR+/HER2−: 74 (67, 80); HER2+: 44 (26, 61)
RCB-III	Extensive residual disease	>3.28	Overall: 58 (50, 65) TNBC: 26 (14, 41); HR+/HER2−: 70 (60, 77); HER2+: 47 (23, 68)	Overall: 46 (37, 54) TNBC: 23 (12, 37); HR+/HER2−: 52 (40, 63); HER2+: 47 (23, 68)

HER2, human epidermal growth factor 2; HR, hormone receptor; RCB, residual cancer burden; TNBC, triple negative breast cancer.
* Data from Symmans *et al.* [87] for patients treated with paclitaxel followed by fluorouracil, doxorubicin and cyclophosphamide (T/FAC).

Management of Early Stage Breast Cancer Patients who do not Achieve a Pathological Complete Response

Recent advances in adjuvant chemotherapy may offer additional options for patients who have not achieved pCR. The CREATE-X study randomised patients with HER2-negative cancer and residual disease post-NAC to receive eight cycles of capecitabine versus placebo and reported improved 5-year DFS and overall survival in favour of capecitabine [88]. A similar approach in the ongoing KATHERINE study (NCT01772472) [89] evaluates trastuzumab emtansine as adjuvant therapy in HER2-positive patients without pCR following NAC. Trials such as PENELOPE-B (NCT01864746) [90] are evaluating the cyclin-dependent kinase 4/6 inhibitor, palbociclib, in hormone receptor-positive patients.

We anticipate that clinical trials will increasingly recruit from the subgroup of patients without pCR. It is therefore important for the MDT to be aware of national study portfolios, as these trials may only be open at a subset of sites, necessitating referral to the nearest centre. Recruitment to these studies may offer patients with a high predicted subsequent event rate access to therapies beyond standard practice.

Communicating Treatment Response to Patients

It is essential to communicate to patients that achieving pCR is not the only positive outcome measure of NAC, as downstaging from mastectomy to BCS, irrespective of pCR, is itself a positive outcome.

Data on patient perception and psychological morbidity in relation to NAC response are limited. One study's patients with locally advanced breast cancer reported increased levels of anxiety and depression in patients whose tumour size did not decrease by more than 50% after treatment [91].

As pCR is less frequent and less strongly associated with recurrence in hormone receptor-positive/HER2-negative cancers, the failure to achieve pCR here does not inevitably reflect a poor outcome. It is important for patients to understand that adjuvant endocrine therapy will be offered to reduce the risk of disease recurrence, so setting patients' expectations of treatment goals is crucial.

Conclusion

When evaluating outcomes such as DFS and overall survival, NAC is at least equivalent to adjuvant treatment. However, NAC may bring other potential benefits. Therefore, we strongly urge the MDT to consider whether an early breast cancer patient may benefit from treatment before surgery. Clinical trials for new drugs and novel combinations increasingly exploit neoadjuvant use and will be key to improving treatment of patient subgroups. Particularly, the opportunity for individualised molecular assessment during neoadjuvant therapy will further enhance scientific understanding of breast cancer biology and behaviour.

Although current guidelines have now specified recommendations for neoadjuvant treatment in early stage breast cancer [17,19,41], consensus needs to be reached to ensure that all patients who could potentially benefit are discussed by the MDT before any surgical intervention, in order to provide the optimum care for each early breast cancer patient.

Conflicts of Interest

H. Cain: Roche Products Ltd (speaker's fees, honoraria and advisory board); I.R. Macpherson: Amgen (advisory board), Celldex (advisory board), Chugai (advisory board), Eisai (advisory board and speaker's fees), Genomic Health (travel), Novartis (speaker's fees), Pierre Fabre (advisory board), Pfizer (advisory board), Roche Products Ltd (advisory board and speaker's fees); M. Beresford: Amgen (travel), Bayer (speaker's fees and honoraria), Celgene (speaker's fees and honoraria), Eisai (honoraria), MSD (travel), Pfizer (advisory board); S.E. Pinder: Roche Products Ltd (advisory board, honoraria and travel), Genomic Health (advisory board); J. Pong: Roche Products Ltd (employee); J.M. Dixon: Roche Products Ltd (advisory board).

Statement of Search Strategies Used and Sources of Information

This paper reflects expert opinion and current literature accessed by the authors; no formal search strategy has been defined.

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