REVIEW ARTICLE

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Utility of neoadjuvant chemotherapy in the treatment of operable breast cancer

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Abstract

Neoadjuvant chemotherapy (NAC) is a legitimate alternative to first-line surgical therapy for the treatment of breast cancer patients, as level one evidence shows the effect on overall survival is equivalent to that of adjuvant chemotherapy. In the treatment of women with operable breast cancer, NAC provides a number of potential advantages including: improving the chance of achieving breast-conserving surgery, improving cosmesis after breast-conserving surgery, downstaging the breast and axilla, allowing time to fully consider surgical options, time for genetic testing and facilitating breast reconstruction in otherwise high-risk patients. However, in Australia, NAC is poorly utilized with less than 3% of women with operable breast cancer receiving NAC. This review discusses the potential harms and benefits of NAC, discusses areas of controversy in the use of NAC and describes how we have used NAC in our own practice. We conclude that if it is obviously necessary for the newly presenting breast cancer patient to have chemotherapy as part of the treatment, it is worth considering NAC. In many patients, the potential benefits of NAC outweigh the harms. However, maximizing these benefits is closely aligned with appropriate patient selection and timely multidisciplinary team communication.

Introduction

Neoadjuvant chemotherapy (NAC) has traditionally been used in the treatment of inoperable breast cancer. More recently, the role of NAC in the treatment of operable breast cancer has been acknowledged to the extent that a 2012 International Consensus Conference recommended that NAC be considered in all breast cancer patients who will require chemotherapy.[1] Yet, NAC is used in only 3.8% of cases in the United States[2] and in 2.75% of operable breast cancer cases in Australia and New Zealand according to BreastSurgANZ Quality Audit data (BreastSurgANZ Quality Audit, unpublished results).

When it was first introduced, the main hypothesis for the use of NAC in breast cancer was to increase overall survival. However, early randomized controlled trials comparing NAC with adjuvant chemotherapy (AC) in breast cancer patients, including the National Surgical Adjuvant Breast and Bowel Project B-18 and B-27 trials[3–6] and the European Organization for Research and Treatment of Cancer 10902 trial,[7] did not demonstrate the posited survival advantage expected from early treatment of micrometastatic disease. Instead, AC and NAC were shown to have equal efficacy in improving overall survival.

The survival analysis from these older trials may now be less clinically relevant because of advances in chemotherapy regimens and increased knowledge regarding the molecular subtypes of breast cancer. NAC may be more likely to benefit patients with rapidly growing and early spreading subtypes of breast cancer, but a survival advantage for patients with selected subtypes is, as yet, unproven. Given the increasing interest in NAC as a model for testing new drug therapies, it is timely to revisit the overall benefit-to-harm trade-off of NAC.

Before doing so, it is important to note that surgery retains a fundamental role in the treatment of breast cancer patients who have received NAC. Initial concerns that NAC patients had higher rates of local recurrence in early trials were likely to be due to subsequent treatment with radiotherapy without surgery in some series.[8] All

NAC patients require surgery for removal of the primary site, for axillary staging or treatment and for accurate histological assessment of pathological response (which can vary between the breast and axilla).[1,9,10]

This article begins by defining the terminology used in appraising NAC outcomes. It then provides an overview of the most relevant literature and reports on the only published Australian clinical data from the authors' case series to argue for an expanded role for NAC in the treatment of operable breast cancer.

Defining tumour response

NAC facilitates the investigation of tumour biology and allows an assessment of the individual tumour response to chemotherapy. Consequently, defining response, both clinical and pathological, is of utmost importance. In previous NAC trials, clinical response based on examination findings has been simply defined: a clinical complete response occurs when the tumour can no longer be palpated after NAC, a clinical partial response occurs when there is a reduction in tumour size of 50% or more, clinical stable disease is no change or up to a 50% reduction in size and clinically progressive disease is progression on treatment.[6]

Various definitions of pathological response have been used. The most clear-cut definitions, used in our own audit, are those proposed in a 2012 review and meta-analysis: a pathological complete response (pCR) was defined as no residual invasive or *in situ* disease in the breast or assessed lymph nodes, a pathological partial response was characterized by the presence of individual or small clusters of tumour cells in a desmoplastic or hyaline stroma and breast cancers not exhibiting either of these changes were classified as having no pathological response.[11] The utility of these definitions is that in a meta-analysis of 6377 patients, they discriminated most robustly between patients with favourable and unfavourable outcomes.

In addition, this analysis validated pCR as a surrogate endpoint for survival in some breast cancer subtypes (luminal B/Her2-negative, non-luminal Her2-positive and triple-negative disease). However, an earlier and smaller study found no association between residual *in situ* disease and outcome[12] and the Seventh Edition American Joint Committee on Cancer staging system for Breast Cancer defines a pCR as no invasive breast cancer in the breast or lymph nodes.[13] Accurate pathological evaluation is essential and while not routinely reported by our pathology services, the Residual Cancer Burden (RCB) index ranks response to NAC into four categories (RCB 0, I, II, III) that represent no residual disease through to extensive residual disease with no obvious treatment response and has utility both in clinical research and in prognostication. In all patients, those with a RCB of 0 or I have a good prognosis, RCB II is intermediate and RCB III have significantly worse prognosis. In hormone receptor-positive patients, the RCB index stratifies RCB 0, I and II patients into a group with good prognosis while only those classified RCB III have worse prognosis.[14]

Evaluating harms and benefits

In light of the 2012 International Consensus Conference recommendation that NAC be considered in all women who will require chemotherapy as part of their breast cancer treatment,[1] we sought to review the most relevant literature and audit our own practice to highlight the potential harms and benefits of NAC. Patients who clearly require chemotherapy are those with large, high-grade breast cancers, triple-negative breast cancer (TNBC) and Her2-positive breast cancer. From January 2007 to December 2012, our practice managed 51 operable breast cancer patients using NAC. All patients were evaluated with bilateral mammograms and breast and axillary ultrasound to define the extent of the primary tumour and to assess the regional lymph nodes. Computed tomography and bone scans excluded distant metastases. Breast magnetic resonance imaging was used in 15 of the 51 women and was performed for several reasons: when there was discordance between clinical examination and the mammographic/ultrasound assessment, to confirm unifocal disease in some patients hoping for breast-conserving surgery (BCS), to exclude multiple breast cancers in patients of high genetic risk and in one case to identify an occult primary breast cancer that presented with palpable axillary node metastases. The median tumour size was 50 mm, 37% were Her2 positive and 29% were TNBC (details of NAC patient management, the audit methodology and raw data are provided in the Supporting Information Appendix S1). Table 1 summarizes the factors that should be considered in selecting women for NAC and these are discussed in the succeeding paragraphs.

Potential harms

The literature review and practice audit identified four potential disadvantages of NAC.

(1) NAC has the potential to delay surgery in patients who do not respond to chemotherapy

Published data demonstrate clinical tumour shrinkage in 70–80% of patients[11] and this could potentially be improved with more stringent patient selection. In one large series, there were 1762 patients (91%) that had some response, 107 (6%) with stable disease and only 59 (3%) that had clinically progressive disease.[15] Patients with low-grade and lobular breast cancers are less likely to respond to or benefit from NAC.[11,16] Importantly, there was no progression of the primary cancer in any of our 51 patients during NAC indicating that none of these women were oncologically disadvantaged in choosing this treatment path. Regular clinical and ultrasound assessment during treatment (initially after two cycles) is essential in order to identify patients who do not respond to NAC and require a change in treatment strategy. This is particularly important in patients who are borderline resectable at presentation because the opportunity for surgical intervention may be lost if progression occurs.

(2) Loss of detailed pathology that traditionally guides multidisciplinary management

Early multidisciplinary discussion is essential and the decision to undertake NAC can only be reliably made if the diagnostic core biopsy has oestrogen receptor (ER), progesterone receptor (PR) and Her2 immunohistochemistry. In addition, Her2 *in situ* hybridization is required when NAC is being seriously considered. These biomarkers guide the application of chemotherapy. Further detail regarding chemotherapy regimens is contained in the Supporting

Table 1 Factors for consideration in the utilization of NAC

NAC	Greater benefit	Less benefit
Tumour type	High grade High Ki67 Luminal B Her2 positive, hormone-negative TNBC	Low grade Low Ki67 Luminal A Lobular subtype
Surgical advantage	Enable/improve BCS Enable IBR Reduce ALND	BCS appropriate at diagnosis IBR appropriate at diagnosis
Decision making	Genetic testing Surgical options Reconstruction options	Uncomplicated Radiotherapy plan uncertain IBR + PMRT?
Research	Access to clinical trials Tumour response to drug allowing biomarker discovery Individualized therapy	–
Other	Pregnancy	–

ALND, axillary lymph node dissection; BCS, breast-conserving surgery; IBR, immediate breast reconstruction; NAC, neoadjuvant chemotherapy; PMRT, post-mastectomy radiotherapy; TNBC, triple-negative breast cancer.

Information Appendix S1. In the adjuvant setting decisions around the application of axillary, supraclavicular and post-mastectomy radiotherapy (PMRT) are based on tumour size, margins and the number of involved lymph nodes.[17,18] The loss of this detail and hence the decision regarding radiotherapy must often be made up front in early multidisciplinary discussion. Ongoing clinical trials are evaluating the role of PMRT after a pCR.[19]

(3) Reduced time between surgery and PMRT

In women undergoing two-stage implant-based breast reconstruction, the shortened time between surgery and PMRT must be considered. In the adjuvant setting, gradual filling of the tissue expander can take 3 months after surgery and can occur during AC. In the setting of NAC, either rapid expansion or a delay in PMRT is required. This disadvantage is confined to women undergoing mastectomy and two-stage implant-based immediate breast reconstruction (IBR) after NAC who require PMRT. In our own series, BCS was achieved in 21 NAC patients (41%) and 30 underwent mastectomy (59%). IBR was performed in eight of the mastectomy patients (27%) and seven required PMRT. There is limited data addressing the role of PMRT after NAC in patients who have a pCR[20] and further prospective trials are ongoing (see earlier text) to assess whether PMRT is beneficial in this patient group.

(4) The current lack of evidence-based resources for women considering NAC

This article aims to contribute to the assessment of the relative benefits and harms of NAC so that consumer-oriented information can be made available. This may be particularly important in preparing women for the potential psychological distress that could be associated with the failure of their tumour to respond to NAC.[21] The Australia and New Zealand Breast Cancer Trials Group is evaluating a decision aid to assist women with the difficult process of weighing up the potential harms and benefits of NAC for them personally.[22]

Potential benefits

In contrast, we believe the benefits of NAC are greater for appropriately selected women. Seven potential benefits of NAC are outlined in the succeeding paragraphs:

(1) Prediction of oncological outcome

NAC allows assessment of the individual's biological response to chemotherapy. Overall clinical tumour shrinkage has been reported in 70–80% of NAC breast cancer patients and 15–35% achieved a pCR.[11] In our own audit, tumour shrinkage occurred in 79% and the overall pCR rate was 28% with a range from 6% in ER/PR positive/Her2 negative breast cancers to 47% in TNBCs.

The NeoALTTO Trial more recently assessed the use of dual anti-Her2 agents in patients with Her2-positive primary breast cancers >2 cm in diameter and a pCR was achieved in 51.3% of patients in the combination therapy arm.[23] The use of NAC in TNBC, which has a poorer overall prognosis, has been supported by high pCR rates. New trials, such as the Australia and New Zealand Breast Cancer Trials Group Eliminate Study, will assess the combination of neoadjuvant endocrine therapy and NAC in larger ER positive breast cancers. Invasive lobular cancers are known to respond poorly to NAC with respect to both pCR and BCS rates[16,24] because of variation in the molecular characteristics of the tumour.[25]

(2) The ability of NAC to facilitate increased rates of BCS has been well documented[6,8,26]

NAC reduces the amount of breast tissue removed in breast-conserving procedures[27] and this correlates with better cosmetic outcomes.[28] This is particularly important in patients who are marginal for BCS prior to NAC. While pCR is desirable, our own data demonstrates that it is not necessary in order to avoid mastectomy. As noted, NAC-induced tumour shrinkage was achieved in 79% of our patients. In 16 of 51 patients, NAC was used with the specific aim of enabling BCS. Eleven subsequently had successful BCS (69%) but only four of these women had a pCR.

(3) NAC can also facilitate IBR

BCS provides better aesthetic outcomes than mastectomy alone, but avoiding mastectomy is not the only aesthetic benefit of NAC. Thirty of our patients still required mastectomy but eight were able to undergo IBR. All were two-stage implant-based reconstructions. A recent review of post-mastectomy reconstruction highlights significant international variation in IBR rates (4.9–81.2%) and

demonstrates clinicians' preference for IBR in patients with small tumours who are less likely to require adjuvant treatments.[29] We have found that NAC facilitates IBR but the same oncological rules of clear margins and thorough surgery have to be followed as sometimes the residual tumour is unexpectedly extensive despite an apparent good clinical and radiological response.

(4) NAC enables more timely treatment

The optimal time from diagnosis to the initiation of chemotherapy is unclear but in some studies long delays have been associated with poor outcomes.[30–32] NAC removes the possibility that surgical complications, or complex surgery that prolongs recovery, might delay initiation of AC. This is especially relevant for patients undergoing IBR. Data from the National Comprehensive Cancer Network Outcomes Database has identified IBR as causing the greatest increase in the time from diagnosis to initiation of chemotherapy (from 12.0 to 14.7 weeks, $P < 0.001$) and these IBR patients were also more likely to initiate chemotherapy more than 120 days after diagnosis.[33]

NAC also provides a greater window for genetic counselling and testing, the results of which may affect decisions about the extent of surgery. Even when genetic testing is not indicated, surgical choices can be difficult for the patient to process and fully evaluate at the time of diagnosis. If it is clear that the patient requires chemotherapy then NAC can give women more time to evaluate their increasingly complex surgical options. NAC is also useful in pregnancy-associated breast cancer where the pending delivery of the baby can influence the timing of surgery and chemotherapy.[34]

(5) NAC has the potential to downstage the axilla

The degree of involvement of the axillary nodes post-NAC is a predictor of subsequent relapse.[35] Currently, management of the axilla after NAC is controversial. Before commencing NAC, the axilla is either negative or positive, based on clinical/ultrasound/fine-needle aspiration or core biopsy examination. In the negative axilla patients, sentinel node biopsy (SNB) can be performed before or after NAC but most now agree that SNB after NAC is more appropriate.[1] However, patients undergoing NAC often have large, high-grade tumours where rates of axillary node metastases exceed 50% and with 40–80% also having non-sentinel node (SN) involvement.[36] Thus, the risk of false-negative results in terms of regional control is potentially higher and the utilization of SNB has been controversial.

SNB after NAC has two main benefits. Firstly, prognostic information is available and some patients may benefit from the downstaging effect of NAC by avoiding further axillary surgery. In our practice, SNB is used after NAC in patients who have a clinically and radiologically negative axilla at presentation. Only two of the 21 patients undergoing SNB had viable tumour identified in the SNs and both underwent axillary dissection. Ideally, larger studies are needed to confirm the oncological safety of a negative SNB in this group of patients but it is unlikely that this will ever be addressed in an randomized controlled trial. It is therefore important for large databases, such as the BreastSurgANZ Quality Audit, to continue to record outcomes data.

The second group of patients who may benefit is those with cytologically proven axillary node metastases before NAC. There is currently no high-level evidence to suggest that these patients can safely avoid axillary dissection. However, it is possible that NAC may facilitate this in selected patients.

Recent studies have evaluated the accuracy of SNB after NAC in clinical complete response patients. In two meta-analyses, the SN identification rates were 90% and 94.3%. The pathologic SN status accurately predicted that of the completion axillary dissection in both studies with false-negative rates of 12% and 7.4%, respectively.[37,38] The prospective observational studies ACOSOG Z1071 and SENTINA demonstrate that SNB can be accurately used after NAC has downstaged the axilla, although failure of detection and false-negative rates were slightly higher.[39,40]

Further prospective trials are underway to determine the role of axillary surgery in patients who have clinical and biopsy-proven nodal disease prior to NAC and subsequently have a negative SNB.[1,41] However, until oncological outcomes are determined in a clinical trial setting, axillary dissection is appropriate, especially because high rates of local recurrence in the breast have been documented in patients who had breast surgery omitted after NAC.[8] In our own series, 30 of the 51 patients had axillary metastases identified before NAC. All of these patients underwent axillary dissection with their definitive breast surgery. Nine had substantial downstaging of the axilla after NAC with no residual axillary disease.

(6) Clinical trials evaluating new therapeutic agents are moving to the neoadjuvant setting

Surrogate endpoints, specifically pCR, are being utilized to facilitate timely assessment of efficacy of new drug combinations with the expectation being that the results of smaller neoadjuvant trials would mirror much larger adjuvant therapy trials of the same combinations of drugs. This theory was expected to be reinforced by the results of the NeoALTTO trial that demonstrated improved rates of pCR in patients treated with dual Her2 blocking agents compared with trastuzumab alone.[23] However, the recent presentation of matching adjuvant ALTTO data failed to substantiate the improved pCR rate achieved by dual Her2 blocking agents. These contrasting findings raise doubts about the modelling efficacy of smaller NAC trials.[42]

Despite this, post-NAC tissue assessment will assist in the development of new biomarkers and therapeutic targets. Experience with managing NAC patients will be essential for participation in these trials so clinicians who use NAC will have an advantage from a research perspective and their patients will have the potential to benefit from involvement in clinical trials.

(7) NAC will facilitate individualized treatment

Optimal selection of women for NAC and the management of patients with residual disease post-NAC require ongoing research. Trials such as I-SPY 1 and 2 represent the beginnings of a treatment model in which molecular assessment allows personalized treatment. Results from the I-SPY 1 trial are already defining the molecular (Her2 positive, TNBC) and magnetic resonance imaging characteristics (solid) that are more likely to benefit from NAC.[43,44] This therapeutic approach has produced promising results in these high-risk patients, with low local recurrence rates and 50% of patients undergoing BCS rather than mastectomy.[45]

Conclusions

The benefits of NAC outweigh its potential harms in many patients. However, not all women are equally likely to benefit. Tumour subtype gives a reasonable indication but we do not have a definitive way of knowing *a priori*. The challenge in utilizing NAC is in selecting women who are most likely to benefit. Results from our series and our review of the literature support the assertion that consideration of NAC is warranted in all women who require chemotherapy as part of their breast cancer treatment.

In determining the likely benefit-to-harm trade-off for each of these women, multidisciplinary team discussion is essential and ideally this formal discussion would take place prior to surgery. In Australia, traditional referral patterns dictate that a patient's first contact is usually with a breast surgeon and formal multidisciplinary team discussion of the patient usually occurs post-operatively. While both of these factors may make NAC less likely, this does not have to be the case. Our practice offers NAC to appropriate patients because the surgeons always consider this possibility and work closely with their multidisciplinary team colleagues between formal meetings to arrange additional consultations and testing as needed prior to surgery.

Table 1 outlines items to be considered in determining the likely benefit-to-harm trade-off for each woman. While a pCR is desirable and an indicator of favourable prognosis, it is not necessary to attain many of the other benefits of NAC including increased chance of BCS, higher rates of IBR, more time for individualized treatment and a better-informed patient. Breast surgery techniques continue to evolve, facilitating safer oncological procedures and improved aesthetic outcomes. NAC can enable a greater number of patients to benefit from these surgical advances. Surgeons and their breast cancer patients need to be informed of the benefits-to-harms trade-off of NAC so that they can make evidence-based decisions about its use.

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References

1. Kaufmann M, von Minckwitz G, Mamounas EP *et al*. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. *Ann. Surg. Oncol.* 2012; **19**: 1508–16.
2. Onitilo AA, Onesti JK, Single RM *et al*. Utilization of neoadjuvant chemotherapy varies in the treatment of women with invasive breast cancer. *PLoS ONE* 2013; **20**: e84535.
3. Fisher B, Brown A, Mamounas E *et al*. Effect of preoperative chemotherapy on loco-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J. Clin. Oncol.* 1997; **15**: 2483–93.
4. Bear HD, Anderson S, Brown A *et al*. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from national surgical adjuvant breast and bowel project protocol B-27. *J. Clin. Oncol.* 2003; **21**: 4165–74.
5. Bear HD, Anderson S, Smith RE *et al*. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: national surgical adjuvant breast and bowel project protocol B-27. *J. Clin. Oncol.* 2006; **24**: 2019–27.
6. Rastogi P, Anderson SJ, Bear HD *et al*. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *J. Clin. Oncol.* 2008; **26**: 778–85.
7. van der Hage JA, van de Velde CJ, Julien JP, Tubianna-Hulin M, Vandervelden C, Duchateau L. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. *J. Clin. Oncol.* 2001; **19**: 4224–37.
8. Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. *J. Natl Cancer Inst.* 2005; **97**: 188–94.
9. Kaufmann M, Morrow M, von Minckwitz G, Harris JR, Biedenkopf Expert Panel Members. Locoregional treatment of primary breast cancer: consensus recommendations from an international expert panel. *Cancer* 2010; **116**: 1184–91.
10. DeMichele A, Berry DA, Zujewski J *et al*. Developing safety criteria for introducing new agents in neoadjuvant trials. *Clin. Cancer Res.* 2013; **19**: 2817–23.
11. von Minckwitz G, Untch M, Blohmer JU *et al*. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J. Clin. Oncol.* 2012; **30**: 1796–804.
12. Mazouni C, Peintinger F, Wan-Kau S *et al*. Residual ductal carcinoma in situ in patients with complete eradication of invasive breast cancer after neoadjuvant chemotherapy does not adversely affect patient outcome. *J. Clin. Oncol.* 2007; **25**: 2650–5.
13. Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (eds). *AJCC Cancer Staging Manual*, 7th edn. New York, NY: Springer, 2010.
14. Symmans WF, Peintinger F, Hatzis C *et al*. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J. Clin. Oncol.* 2007; **25**: 4414–22.
15. Caudle AS, Gonzalez-Angulo AM, Hunt KK *et al*. Predictors of tumour progression during neoadjuvant chemotherapy in breast cancer. *J. Clin. Oncol.* 2010; **28**: 1821–8.
16. Petrelli F, Barni S. Response to neoadjuvant chemotherapy in ductal compared to lobular carcinoma of the breast: a meta-analysis of published trials including 1,764 lobular breast cancer. *Breast Cancer Res. Treat.* 2013; **142**: 227–35.
17. Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and on 15-year survival: an overview of the randomised trials. *Lancet* 2005; **366**: 2087–106.
18. Early Breast Cancer Trialists' Collaborative Group. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014; **383**: 2127–35.
19. Mamounas EP, White JR, Bandos H *et al*. NSABP B-51/RTOG 1304: randomised phase III clinical trial evaluating the role of postmastectomy chest wall and regional node XRT (CWRNRT) and postlumpectomy RNRT in patients (pts) with documented positive axillary (Ax) nodes before neoadjuvant chemotherapy (NC) who convert to pathologically negative Ax nodes after NC. *J. Clin. Oncol.* 2014; **32**: 5s (Suppl.; abstr TPS1141).
20. Shim SJ, Park W, Huh SJ *et al*. The role of postmastectomy radiation therapy after neoadjuvant chemotherapy in clinical stage II-III breast cancer patients with pN0: a multicenter, retrospective study (KROG 12-05). *Int. J. Radiat. Oncol. Biol. Phys.* 2014; **88**: 65–72.

21. Chintamani, Gogne A, Khandelwal R *et al*. The correlation of anxiety and depression levels with response to neoadjuvant chemotherapy in patients with breast cancer. *JRSM Short Rep.* 2011; **2**: 15.
22. Zdenkowski N, Butow PN, Fewster S *et al*. Exploring decision making about neoadjuvant chemotherapy for early breast cancer. *J. Clin. Oncol.* 2014; **32** (Suppl.; abstr e20578).
23. Baselga J, Bradbury I, Eidtmann H *et al*. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. *Lancet* 2012; **379**: 633–40.
24. Huober J, von Minckwitz G, Denkert C *et al*. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. *Breast Cancer Res. Treat.* 2010; **124**: 133–40.
25. Lips EH, Mukhtar RA, Yau C *et al*. (I-SPY TRIAL Investigators). Lobular histology and response to neoadjuvant chemotherapy in invasive breast cancer. *Breast Cancer Res. Treat.* 2012; **136**: 35–43.
26. Boughey JC, Peintinger F, Meric-Bernstam F *et al*. Impact of preoperative versus postoperative chemotherapy on the extent and number of surgical procedures in patients treated in randomized clinical trials for breast cancer. *Ann. Surg.* 2006; **244**: 464–70.
27. Cochrane RA, Valasiadou P, Wilson ARM, Al-Ghazal SK, MacMillan RD. Cosmesis and satisfaction after breast-conserving surgery correlates with the percentage of breast volume excised. *Br. J. Surg.* 2003; **90**: 1505–9.
28. Fisher ER, Wang J, Bryant J, Fisher B, Mamounas E, Wolmark N. Pathobiology of preoperative chemotherapy. *Cancer* 2002; **95**: 681–95.
29. Brennan ME, Spillane AJ. Uptake and predictors of post-mastectomy reconstruction in women with breast malignancy – systematic review. *Eur. J. Surg. Oncol.* 2013; **39**: 527–41.
30. Colleoni M, Bonetti M, Coates AS *et al*. Early start of adjuvant chemotherapy may improve treatment outcome for premenopausal breast cancer patients with tumors not expressing estrogen receptors. The International Breast Cancer Study Group. *J. Clin. Oncol.* 2000; **18**: 584–90.
31. Lohrisch C, Paltiel C, Gelmon K *et al*. Impact on survival of time from definitive surgery to initiation of adjuvant chemotherapy for early-stage breast cancer. *J. Clin. Oncol.* 2006; **24**: 4888–94.
32. Gagliato Dde M, Gonzalez-Angulo AM, Lei X *et al*. Clinical impact of delaying initiation of adjuvant chemotherapy in patients with breast cancer. *J. Clin. Oncol.* 2014; **32**: 735–44.
33. Vandergrift JL, Niland JC, Theriault RL *et al*. Time to adjuvant chemotherapy for breast cancer in National Comprehensive Cancer Network Institutions. *J. Natl Cancer Inst.* 2013; **105**: 104–12.
34. Loibl S, von Minckwitz G, Gwyn K *et al*. Breast carcinoma during pregnancy. International recommendations from an expert meeting. *Cancer* 2006; **106**: 237–46.
35. Escobar PF, Patrick RJ, Rybicki LA, Hicks D, Weng DE, Crowe JP. Prognostic significance of residual breast disease and axillary node involvement for patients who had primary induction chemotherapy for advanced breast cancer. *Ann. Surg. Oncol.* 2006; **13**: 783–7.
36. Spillane AJ, Brennan ME. Accuracy of sentinel lymph node biopsy in large and multifocal/multicentric breast carcinoma: a systematic review. *Eur. J. Surg. Oncol.* 2011; **37**: 371–85.
37. Xing Y, Foy M, Cox DD, Kuerer HM, Hunt KK, Cormier JN. Meta-analysis of sentinel lymph node biopsy after preoperative chemotherapy in patients with breast cancer. *Br. J. Surg.* 2006; **93**: 539–46.
38. Tan VKM, Goh BKP, Fook-Chong S, Khin LW, Wong WK, Yong WS. The feasibility and accuracy of sentinel lymph node biopsy in clinically node-negative patients after neoadjuvant chemotherapy for breast cancer – a systematic review and meta-analysis. *J. Surg. Oncol.* 2011; **104**: 97–103.
39. Kuehn T, Bauerfeind I, Fehm T *et al*. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. *Lancet Oncol.* 2013; **14**: 609–18.
40. Boughey JC, Suman VJ, Mittendorf EA *et al*. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer. The ACOSOG Z1071 (Alliance) Clinical Trial. *JAMA* 2013; **310**: 1455–61.
41. Mittendorf EA, Caudle AS, Yang W *et al*. Implementation of the american college of surgeons oncology group z1071 trial data in clinical practice: is there a way forward for sentinel lymph node dissection in clinically node-positive breast cancer patients treated with neoadjuvant chemotherapy? *Ann. Surg. Oncol.* 2014; **21**: 2468–73.
42. Piccart-Gebhart MJ, Holmes AP, Baselga J *et al*. First results from the phase III ALTTO trial (BIG 2–06; NCCTG [Alliance] N063D) comparing one year of anti-HER2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T→L), or their combination (T + L) in the adjuvant treatment of HER2-positive early breast cancer. (EBC). *J. Clin. Oncol.* 2014; **32**: 5s (Suppl.; abstr LBA4).
43. Mukhtar RA, Yau C, Rosen M *et al*. Clinically meaningful tumor reduction rates vary by prechemotherapy MRI phenotype and tumor subtype in the I-SPY 1 TRIAL (CALGB 150007/150012; ACRIN 6657). *Ann. Surg. Oncol.* 2013; **20**: 3823–30.
44. Essermann LJ, Berry DA, DeMichele A *et al*. Pathologic complete response predicts recurrence-free survival more effectively by cancer subset: results from the I-SPY 1 Trial – CALGB 150007/150012, ACRIN 6657. *J. Clin. Oncol.* 2012; **30**: 3242–9.
45. Cureton EL, Yau C, Alvarado MD *et al*. Local recurrence rates are low in high-risk neoadjuvant breast cancer in the I-SPY 1 Trial (CALGB 150007/150012; ACRIN 6657). *Ann. Surg. Oncol.* 2014; **21**: 2889–96.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Author's case series of neoadjuvant chemotherapy in patients with operable breast cancer.