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Neoadjuvant therapy for breast cancer, including surgical considerations

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Introduction

Over the past half century, breast cancer management has evolved from primarily surgical therapy to a multidisciplinary approach including surgery, radiation therapy and systemic therapy. This shift is based on an increased understanding of invasive breast malignancy as a systemic disease and is based on the improved outcomes with the addition of systemic therapy to local regional therapy.

In this regard, observations of micrometastatic disease in early stage breast cancer led to the initial rationale for prospective randomised clinical trials evaluating the survival outcome of neoadjuvant or preoperative chemotherapy as compared to adjuvant chemotherapy in this population. While these trials were unable to demonstrate a survival benefit to preoperative chemotherapy several advantages were realised, including the prognostic impact of response to therapy and facilitation of breast-conserving therapy (BCT) for increased numbers of women.

Rapid advances in care and improved understanding of tumour biology have continued to guide treatment recommendations and allow for limited surgery in certain populations with downstaging of disease in the breast and axilla. Furthermore, the neoadjuvant platform and assessment of response has allowed for an improved understanding of tumour biology and drug development. In the setting of hormone receptor-positive disease, neoadjuvant endocrine therapy is gaining favour in postmenopausal women. Future studies may be able to further personalise therapy by avoiding surgery completely in exceptional responders to neoadjuvant therapy.[1,2]

In contemporary practice, a neoadjuvant chemotherapy approach is utilised in patients with inflammatory breast carcinoma, locally inoperable breast cancer, locally advanced disease and selected patients with early stage operable breast cancer, particularly when the use of neoadjuvant therapy will allow for more cosmetically acceptable breast-conserving therapy and increasingly for those who will be recommended adjuvant chemotherapy as determined by tumour molecular subtype.

The evidence base for neoadjuvant systemic therapy in breast cancer is reviewed, as is the evolving landscape and implications for clinical practice.

Landmark clinical trials evaluating neoadjuvant chemotherapy in operable breast cancer

Several randomised clinical trials have been performed world-wide comparing neoadjuvant chemotherapy with adjuvant chemotherapy in women with operable breast cancer (see Table 16.1). In the USA, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 was a landmark trial comparing adjuvant and neoadjuvant chemotherapy with four cycles of adriamycin cyclophosphamide (AC) in stage I–IIIA (T1–3 N0–1) operable breast cancer.[3] This randomised trial of over 1500 women showed no difference in overall survival and disease-free survival if chemotherapy was delivered in the neoadjuvant or adjuvant setting; a finding that has persisted after 16 years of follow-up.[4] Thirteen per cent of patients

Table 16.1 • Landmark prospective randomised clinical trials of neoadjuvant chemotherapy compared to adjuvant chemotherapy in operable breast cancer

Trial	Neoadjuvant regimen		Overall survival			Disease-free survival			BCS		pCR
			Neoadj.	Adj.		Neoadj.	Adj.		Neoadj.	Adj.	
NSABP B-18[3,4]	AC	5 yr	80%	81%		67%	67%		68%	60%	13%
		8 yr	72%	72%		55%	55%				
		16 yr	55%	55%	HR = 0.99; 95% CI 0.85–1.16, *P* = 0.90	39%	39%	HR = 0.93; 95% CI 0.81–1.06, *P* = 0.27			
NSABP B-27*[4]	AC	5 yr	82%	82%		68%	70%				13%
	AC + T		83%			71%					26%
		8 yr	74%	75%	*P* = 0.76	59%	62%				
			75%			62%					
EORTC 10902[5]	FEC	10 yr	64%	66%	HR = 1.09; 95% CI 0.83–1.42, *P* = 0.54	48%	50%	HR = 1.12; 95% CI 0.9–1.39, *P* = 0.30	35%	22%	4%

*NSABP B-27 had three treatment groups all of which received neoadjuvant AC, group 1 did not have additional adjuvant therapy, group 2 also received docetaxel without adjuvant chemotherapy and group 3 received neoadjuvant AC with adjuvant docetaxel.

AC, adriamycin cyclophosphamide; adj., adjuvant; BCS, breast-conserving surgery; FEC, fluorouracil, epirubicin, cyclophosphamide; pCR, pathological complete response; T, taxane (docetaxel).

in the neoadjuvant chemotherapy group were found to have no residual disease on final pathology. Improved survival was associated with pathological complete response (pCR) and pathologically negative axillary nodes in the neoadjuvant chemotherapy group. Furthermore, rates of breast conservation were increased in the neoadjuvant chemotherapy group as compared to the adjuvant chemotherapy group (67.8% vs 59.8%).

The survival equivalence of chemotherapy given in the preoperative or postoperative setting has been confirmed by subsequent prospective randomised trials including the NSABP B-27 trial comparing the addition of preoperative and postoperative docetaxel to the neoadjuvant anthracycline-based regimen and the European Organization for Research and Treatment of Cancer (EORTC) 10902 study comparing preoperative and postoperative fluorouracil, epirubicin, cyclophosphamide (FEC) for four cycles.[5] Furthermore, a meta-analysis of 14 published randomised controlled trials evaluating the optimal timing of chemotherapy in relation to surgery supported this conclusion in the 10 trials describing survival outcome among 4620 women.[6]

These trials determined that in operable breast cancer there is no survival advantage to neoadjuvant chemotherapy over adjuvant chemotherapy. However, several advantages to a neoadjuvant chemotherapy approach emerged from these early randomised trials, including improved survival in patients who achieve pCR and pathologically node-negative disease as well as increased rates of breast conservation in patients initially planned for mastectomy.

Response to neoadjuvant chemotherapy

Perhaps one of the most striking insights from the neoadjuvant trials is the ability to assess tumour response in vivo and the prognostic significance of this response to therapy with respect to outcome. Although varying definitions exist in the literature, pathological complete response (pCR) typically refers to no pathological evidence of residual invasive disease after neoadjuvant chemotherapy in the breast (ypT0 or ypT0/is) and axilla (ypN0). Achieving pCR has been associated with improved survival in virtually every individual trial and has been used as a surrogate endpoint for prognosis in several neoadjuvant clinical trials.

The pCR rate among the randomised trials evaluating neoadjuvant and adjuvant chemotherapy ranged from 4% to 29.2%.[6,7] Factors associated with increased likelihood of pCR include age less than 40, smaller tumour size (<2.0 cm), ductal histology, high grade, high Ki67, oestrogen receptor (ER)-negative, triple-negative and human epidermal growth factor receptor-2 (HER2)-positive disease.[8] A recent pooled analysis of the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) evaluating 12 international neoadjuvant clinical trials including 11 955 patients found patients with pCR in the breast and axilla to have improved survival outcomes as compared to those with pCR in the breast alone. This association was strongest in the more aggressive tumour subtypes, triple-negative and HER2-positive. On a trial level analysis however, improvement in the pCR odds ratio did not correlate with survival outcome.[9] Unfortunately, despite attaining pCR, a small percentage of patients do develop distant disease or local recurrence, particularly those who were clinical stage IIIB or higher at presentation, were premenopausal and had 10 or fewer lymph nodes examined.[10]

Moving beyond pCR to predict outcome, calculation of the residual cancer burden (RCB) can further discriminate response to neoadjuvant therapy by evaluating the primary tumour size, cellularity of the invasive component, size of largest nodal metastasis and number of pathologically positive nodes. The RCB index has been shown to be associated with outcome such that an increased RCB is associated with increased risk of 5-year distant relapse from 2.4% for RCB-I to 53.6% in RCB-III, and RCB-0 or RCB-I is comparable to pCR with respect to prognosis.[11]

Neoadjuvant chemotherapy allows for an in vivo evaluation of tumour chemosensitivity and assessment of response to therapy which has prognostic significance with respect to outcome. pCR and pathologically negative axillary nodes are associated with improved survival outcomes.

Influence of tumour molecular subtype on response to therapy

One of the most striking advances in understanding breast cancer tumour biology came with the classification of molecular subtypes described by Perou and colleagues in 2000.[12] These subtypes of breast malignancy described as luminal A, luminal B, basal-like and HER2-enriched, are associated with differing activity and biological behaviour. Clinically, the oestrogen receptor (ER), progesterone receptor (PR) and HER2 receptor are used as surrogates to approximate these subtypes and guide clinical decision-making.

A differential response to neoadjuvant chemotherapy by subtype has been documented by several studies and clinical trials. A meta-analysis of 30 studies

showed an overall pCR rate (breast) of 19.2% after neoadjuvant chemotherapy. By subtype, estimates of pCR were 8.3% in hormone receptor (HR)-positive HER2-negative disease, 18.7% in HR-positive HER2-positive disease, 31.1% in triple-negative disease and 38.9% in HR-negative HER2-positive disease.[13] Moreover, recent analysis of the ACOSOG Z1071 trial evaluating sentinel lymph node (SLN) dissection following neoadjuvant chemotherapy in biopsy-proven clinically node-positive patients, found pCR rates (breast and axilla) of 11.4% in HR-positive HER2-negative disease, 38.2% in triple-negative disease and 45.4% in HER2-positive disease.[14]

✔✔ Tumour subtype has a profound impact on response to neoadjuvant chemotherapy with HER2-positive HR-negative tumours having the highest rates of pCR followed by triple-negative tumours.

Triple-negative breast cancer

Triple-negative breast cancer (TNBC) is characterised by lack of expression of the oestrogen, progesterone and HER2 receptor. These tumours are typically more aggressive with increased cellular proliferation, high grade and poor prognosis. TNBC, however, can be highly responsive to neoadjuvant chemotherapy with pCR in approximately one-third of patients and furthermore, in the setting of pCR, overall survival is comparable to that of the more favourable HR-positive subtype.[15]

Currently, there is no targeted therapy for TNBC, limiting systemic therapy options to chemotherapy alone. There is an association between TNBC and BRCA mutations. Because of the value of platinum compounds in other malignancy due to such mutations, cisplatin and carboplatin have been investigated in combination with conventional chemotherapy as to their impact on pCR and outcome in TNBC. The CALGB 40603 (Alliance) trial compared carboplatin or bevacizumab concurrent with weekly paclitaxel and dose-dense AC. The investigators found an increase in pCR with the addition of both carboplatin (60% vs 44%, $P=0.0018$) and bevacizumab (59% vs 48% $P=0.0089$). However, increased toxicity was noted with the additional therapy.[16] A meta-analysis of 28 trials, six of which were randomised trials, evaluating the role of platinum-based therapy (cisplatin, carboplatin) in the neoadjuvant setting found an overall pooled pCR of 45% (41.9% with cisplatin and 46.3% with carboplatin). Compared to non-platinum-based therapy the pCR rate increased from 32% to 48% ($P<0.0001$). Furthermore, pCR was twofold higher in TNBC than that of non-TNBC treated with platinum-based chemotherapy (48.4% vs 19.6%).[17]

Furthermore, TNBC does not appear to be one single molecular entity, which may account for heterogeneity in terms of response. Gene expression studies have classified seven molecular subtypes of TNBC – basal-like 1, basal-like 2, mesenchymal-like, mesenchymal stem-like, immunomodulatory, luminal androgen receptor (LAR) and unstable, with differing response to conventional chemotherapy.[18] With respect to pCR, one study found the highest pCR rate in the basal-like 1 group (52%) with the lowest pCR rate in the basal like-2 (0%) and LAR (10%) groups. Further clinical trials are needed to determine the clinical significance of non-responders and to identify opportunities for targeted therapies that may increase the pathological complete response rates.

✔ In contemporary clinical practice, patients with stage II or III triple-negative breast cancer are treated with anthracycline–taxane-based chemotherapy in the neoadjuvant setting, with significant rates of pCR in approximately one-third to one-half of patients. Platinum-based therapy further increases pCR rates in TNBC but may be associated with increased toxicity.

HER2-positive breast cancer

HER2-positive or amplified breast cancers historically have been associated with an unfavourable outcome. However, the addition of anti-HER2-directed targeted therapies to standard chemotherapy regimens has revolutionised clinical care and outcomes within this subtype. Buzdar et al. were the first to describe the response to trastuzumab in the neoadjuvant setting in 2005. This trial conducted at the University of Texas MD Anderson Cancer Center (MDACC) found an increased rate of pCR in stage II and IIIA patients treated with neoadjuvant chemotherapy and trastuzumab as compared to chemotherapy alone (65.2% vs 26.3%, $P=0.016$).[19] This trial was stopped early as there was no longer equipoise given the significant response with the addition of trastuzumab. Furthermore, disease-free survival was improved from 85.3% to 100% with the addition of trastuzumab ($P=0.041$).[20] These findings were described in the larger NOAH trial with a pCR of 19% in the chemotherapy alone arm versus 38% with the addition of trastuzumab. Similarly, improved disease-free survival was demonstrated with the addition of trastuzumab (56% vs 71%, $P=0.013$).[21]

Subsequent studies have demonstrated a similar finding with increased pCR with addition of trastuzumab to neoadjuvant chemotherapy in HER2-positive disease.[22–24] With the development of subsequent HER2-targeted agents, lapatinib and pertuzumab, trials evaluating the response to dual

Table 16.2 • Neoadjuvant clinical trials evaluating dual anti-HER2-targeted therapy in HER2-positive invasive breast cancer

	Neoadjuvant regimen	pCR breast	pCR breast and axilla
NeoALTTO[26]	Lapatinib → lapatinib + paclitaxel	24.7%	20%
	Trastuzumab → trastuzumab + paclitaxel	29.5%*	27.6%*
	Lapatinib + trastuzumab → lapatinib + trastuzumab + paclitaxel	51.3%* *P = 0.0001	46.8%* *P = 0.0007
NeoSphere[25]	Trastuzumab + docetaxel	29%*	21.5%
	Pertuzumab + trastuzumab + docetaxel	45.8%*	39.3%
	Pertuzumab + trastuzumab	16.8%	11.2%
	Pertuzumab + docetaxel	24% *P = 0.0140	17.7%
CHER-LOB[27]	(Paclitaxel → FEC) + trastuzumab		25%
	(Paclitaxel → FEC) + lapatinib		26.3%
	(Paclitaxel → FEC) + trastuzumab + lapatinib		46.7% P = 0.019
TBCRC 006[28]	Lapatinib + traztusumab	27%	
TRYPHAENA[29]	(FEC→ docetaxel) + trastuzumab + pertuzumab	61.6%	50.7%
	FEC→ (docetaxel + trastuzumab + pertuzumab)	57.3%	45.3%
	Carboplatin + trastuzumab + pertuzumab	66.2%	51.9%
NSABP B-41[24]	AC → paclitaxel + trastuzumab	52.5%*	49.4%*
	AC → paclitaxel + lapatinib	53.2%	47.4%
	AC → paclitaxel + trastuzumab + lapatinib	62%* (P = 0.095)*	60.2%* (P = 0.056)*

AC, adriamycin cyclophosphamide; FEC, fluorouracil, epirubicin, cyclophosphamide; pCR, pathological complete response.

anti HER2-targeted therapy in the neoadjuvant setting have been extensively studied[25–29] (Table 16.2). Perhaps the most notable of these trials was the NeoSphere study.[25] This trial evaluated trastuzumab and pertuzumab in the neoadjuvant setting with docetaxel in stage II and III invasive breast cancer. Anthracycline-based chemotherapy was administered in the adjuvant setting. The pCR rate (breast) was highest in the group treated with neoadjvuant trastuzumab, pertuzumab and docetaxel (45.8%) as compared to trastuzumab or pertuzumab with docetaxel alone (29% and 24%, respectively). Interestingly, in the group treated with dual-agent therapy alone without docetaxel, in the preoperative setting the pCR rate (breast) was 16.8%, suggesting a subset of patients benefit from dual anti-HER2 therapy without chemotherapy. Furthermore, within this group the pCR was notably higher in ER-negative disease as compared to ER-positive disease. Toxicities include decreased left ventricular systolic function, diarrhoea, hepatotoxicity, neutropenia and skin-related reactions.

The improved pCR rate (as a proxy for improved survival outcome and reduced local regional recurrence rates) with the addition of pertuzumab to standard therapy led to accelerated drug approval in the neoadjuvant setting by the United States Food and Drug Administration.[30]

Another promising anti-HER2-directed therapy, TDM-1 or ado-trastuzumab emtansine, has been used in advanced HER2-positive breast cancer although is not currently standard first-line therapy. TDM-1 consists of trastuzumab linked to emtansine allowing for targeting to the HER2 receptor with intracellular delivery of toxic chemotherapy. In the neoadjuvant setting, TDM-1 has been studied in the phase II Women's Healthcare Study Group-Adjuvant Dynamic marker-Adjusted Personalized Therapy (WSG-ADAPT) HER2+/HR+ trial. This randomised study of 376 patients found pCR rates of 40.5% for TDM-1 alone, 41.5% for TDM-1 and endocrine therapy and 15.1% for trastuzumab with endocrine therapy (P <0.001).[31] This finding is very interesting considering lower pCR rates for chemotherapy and anti-HER2 therapy in HER2-positive ER-positive disease as compared to ER-negative disease. Furthermore, the KATHERINE trial, which has completed accrual and has not yet reported, evaluates TDM-1 as compared to standard trastuzumab in HER2-positive breast cancer with residual disease after neoadjuvant systemic therapy.[32] The portfolio of HER2 neoadjuvant clinical trials most strongly illustrates the utility of the neoadjuvant platform to identify targeted therapies in particular populations to achieve improved clinical outcomes.

✔✔ In contemporary clinical practice patients with stage II or III HER2 positive breast cancer are likely to be offered chemotherapy and trastuzumab and pertuzumab in the neoadjuvant setting. These tumors demonstrate the highest rates of pCR.

Hormone receptor-positive breast cancer

Hormone receptor (HR)-positive HER2-negative breast cancer has the least impressive response to neoadjuvant chemotherapy despite having a favourable overall outcome which is largely attributed to low proliferative tumour biology and the use of endocrine therapy in the adjuvant setting. Neoadjuvant endocrine therapy in postmenopausal women with HR-positive HER2-negative disease has gained increased favour, despite low rates of pCR, as an approach to downstage disease and to facilitate breast conservation.[33] Several trials have compared tamoxifen to aromatase inhibitors in the neoadjuvant setting, showing improved efficacy of aromatase inhibitors in clinical response and conversion to breast conservation from mastectomy[34–36] (Table 16.3). Furthermore, the ACOSOG Z1031 trial compared neoadjuvant exemestane, letrozole and anastrozole, finding comparable rates of clinical response and BCT.[37]

Semiglazov and colleagues have studied neoadjuvant chemotherapy as compared to neoadjuvant endocrine therapy in postmenopausal women with ER-positive clinical stage IIA to stage IIIB breast cancer. This trial randomised 239 women to therapy with exemestane or anastrozole as compared to chemotherapy (doxorubicin and paclitaxel) for 3 months before surgery and found no difference with respect to response. There was no statistically different response in pCR between the endocrine therapy group and chemotherapy group (3% vs 6%). There was also no difference of BCT or local recurrence at 36 months and higher complications were noted in the chemotherapy group.[38]

A meta-analysis of 20 randomised trials evaluating neoadjuvant endocrine therapy in 3490 patients with ER-positive breast cancer treated with neoadjuvant endocrine therapy was recently published.[39] The authors conclude no difference in response between neoadjuvant endocrine therapy and neoadjuvant chemotherapy in ER-positive breast cancer, with low rates of pCR in the three randomised trials comparing these therapies. Increased toxicity was noted in the neoadjuvant chemotherapy groups. Furthermore, superiority of aromatase inhibitors to tamoxifen or combination therapy was demonstrated with regards to response (clinical and radiographic) and BCS rates.

A German pooled analysis of 6377 patients treated with anthracycline–taxane-based neoadjuvant chemotherapy showed that in low proliferative groups (lobular histology, grade 1 disease and HR-positive) pCR did not predict survival outcome and thus may not be an appropriate endpoint in this subgroup.[40] Similarly, neoadjuvant endocrine trials have demonstrated low rates of pCR, allowing for emergence of other factors to determine biological effect, including change in Ki67 (cellular proliferation) or the Preoperative Endocrine Prognostic Index score.[41] Neoadjuvant endocrine therapy is emerging as a significant approach to locally advanced ER-positive breast cancer over neoadjuvant chemotherapy. Ongoing clinical trials will provide further insights including the ALTERNATE (Alliance) trial randomising patients to anastrazole, fulvestrant or combination and utilising biochemical markers of response to determine if patients should continue on the pathway of neoadjuvant endocrine therapy or proceed with chemotherapy or surgery.[42]

Table 16.3 • Neoadjuvant endocrine therapy randomised clinical trials comparing aromatase inhibitor therapy to tamoxifen

	Duration	Therapy	Clinical response	Response by US	BCT
P024[34]	16 week	Letrozole Tamoxifen	55% 36% (P <0.001)	35% 25% (P=0.042)	45% 35% (P=0.022)
IMPACT[35]	12 week	Anastrozole Tamoxifen Anastrozole + Tamoxifen	37% 36% 39% (P=NS)	24% 20% 28% (P=NS)	46% 22% 26% (P=0.03)
PROACT[36]	12 week	Anastrozole Tamoxifen	48.6% 35.8% P=0.04)	36.6% 24.2% (P=0.03)	43% 30.8% (P=0.04)

BCT, breast-conserving therapy; US, ultrasound.

In postmenopausal women with lower-grade, oestrogen receptor-positive breast cancer, neoadjuvant endocrine therapy with aromatase inhibitors can facilitate breast-conserving surgery (BCS). pCR is infrequently achieved in cases treated with neoadjuvant endocrine therapy or neoadjuvant chemotherapy. In this subtype with favourable tumour biology lack of pCR may not confer a worse survival.

Imaging surveillance during neoadjuvant therapy

There is no standard method for monitoring response to neoadjuvant therapy. Dedicated breast imaging can be used as an adjunct to clinical examination in monitoring the response to therapy during the neoadjuvant course. Local therapy benefits from marker clip placement in the malignancy and any involved node prior to the initiation of therapy to ensure localisation and excision of the malignancy. [43] Unfortunately, neither mammogram nor ultrasound have been shown to be reliable predictors of pCR although the combination has been associated with increased sensitivity and specificity as compared to physical examination alone.[44] Breast MRI has demonstrated the best discrimination in determination of response to neoadjuvant therapy. The American College of Radiology Imaging Network (ACRIN) 6657/I-SPY trial found response by breast MRI to be an important early predictor of response.[45] Furthermore, the Translational Breast Cancer Research Consortium (TBCRC) trial 017 found overall accuracy of 74% for MRI response in predicting pCR. Factors associated with radiographic complete response (rCR) and pCR included triple-negative, HER2-positive and lower T stage.[46]

While radiographic response is not able to predict pathological response it offers an objective assessment of response identifying poor responders and guiding local therapy decision-making.

Implications for local regional therapy following neoadjuvant therapy

Management of the breast primary

A documented benefit of neoadjuvant therapy is downstaging of the disease in the breast allowing for BCS in approximately one-quarter of patients initially planned for mastectomy[6] (**Fig. 16.1**). The oncological safety in this approach is grounded in the observation that there is not an increased risk of local regional recurrence (LRR) within this setting despite resection of the residual tumour volume as opposed to the initial tumour burden. Initial analysis of the NSABP B-18 trial suggested a slight increase in the in-breast tumour recurrence rate (IBTR) after BCT in the neoadjuvant group, but this difference was not statistically significant (7.9% vs 5.8% $P = 0.23$). With 10 years of follow-up, results from the NSABP neoadjuvant trials have been reported showing the cumulative incidence of LRR in B-18 was 14.3% and B-27 12.2%. Collective analysis found the cumulative incidence of LRR of 10.3% after BCS with radiation therapy and 12.3% after mastectomy (no adjuvant radiotherapy). Predictors of increased risk of LRR in both groups were positive clinical nodal status at presentation, positive pathological nodal status and negative pathological node status with no breast pCR. In the BCS group, age <50 was also a significant factor.[47] Factors influencing candidacy for BCS after neoadjuvant chemotherapy include lobular histology, multicentricity and diffuse calcifications on mammography as poor predictors of success.[48]

Findings from the meta-analysis of neoadjuvant clinical trials by Mauri and Mieog demonstrated no difference in LRR among patients treated with BCS followed by radiation therapy in the neoadjuvant as compared to adjuvant treatment groups.[3,33] There was an observed LRR rate of 30% at 10 years when three studies where a significant proportion of patients in the neoadjuvant arm with complete clinical response were treated with radiation alone without definitive surgery were included in the analysis. This underscores the fact that despite complete clinical response operative intervention is indicated given there may be residual disease present and to improve local control.

Investigators at MDACC have developed the MD Anderson prognostic index to assist in selection of appropriate patients for BCS after neoadjuvant chemotherapy. This incorporates four predictors of IBTR and LRR including clinical N2 or N3 disease, residual pathological tumour size >2 cm, multifocal pattern of residual disease and lymphovascular space invasion and assigns each category a score of 1, culminating in an overall score of 0–4. Low risk (0–1), intermediate risk (2) or high risk (3,4) correlates with increasing 5-year IBTR-free survival (97%, 88%, 82%, respectively, $p = 0.0001$) and LRR-free survival (94%, 83%, 58%, respectively, $P = 0.0001$).[49,50]

Tumour subtype also appears to influence rates of BCS and risk of LRR after neoadjuvant chemotherapy. The ACOSOG Z1071 investigators found increased rates of BCS in patients with triple-negative (46.8%) and HER2-positive (43.0%) tumours as compared to HR-positive/HER2-negative disease (34.5%). Furthermore, predictors of successful BCS included

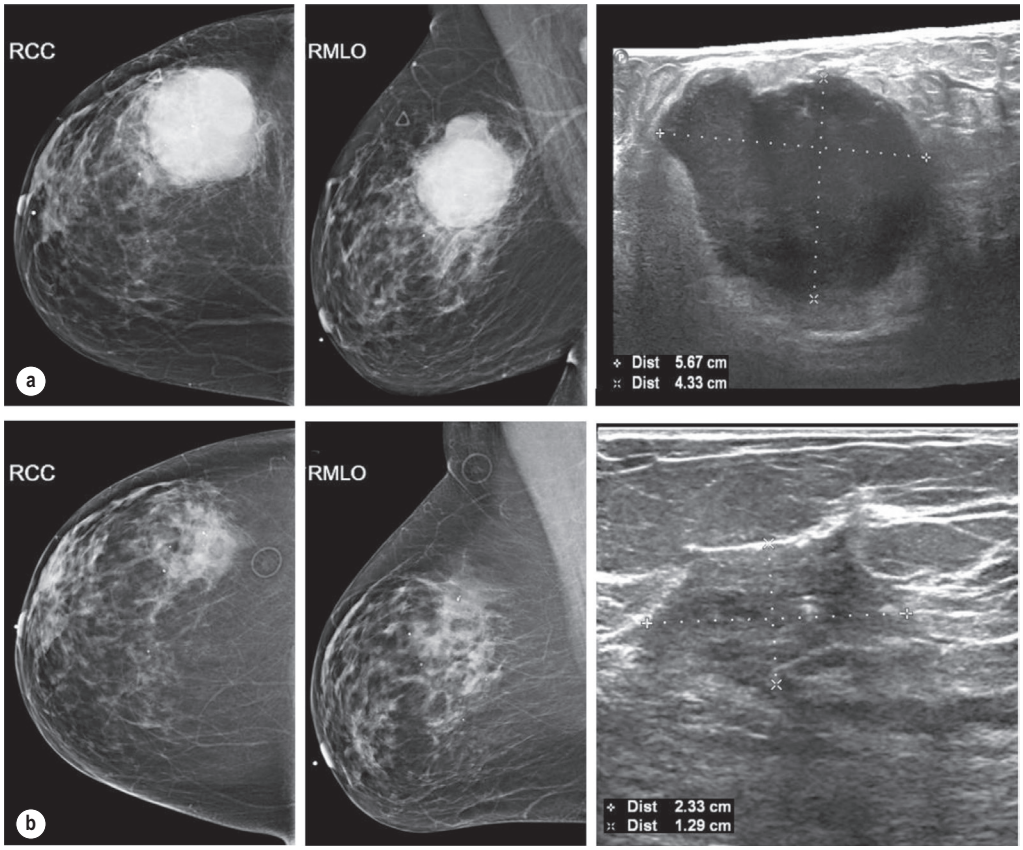

Figure 16.1 • Right mammogram and ultrasound of patient with metaplastic breast cancer clinical T3 N1 M0 invasive ductal carcinoma ER-positive PR-negative HER2-negative treated with neoadjuvant chemotherapy. Panel **(a)** shows pre-chemotherapy mammogram and ultrasound demonstrating T3 malignancy. Panel **(b)** shows significant response following anthracycline–taxane-based chemotherapy with decrease in the size of the breast malignancy. Final pathology showed no residual disease in the breast.

patient age, clinical T stage and tumour subtype.[14] This may be in part secondary to the increased pCR associated with these subtypes. Increased LRR after BCS and mastectomy in locally advanced breast cancer has been associated with the basal subtype as compared with luminal A, luminal B and HER2-enriched subtypes.[51] In comparison, HR-positive disease has been found to be associated with high rates of local control despite low rates of response to neoadjuvant chemotherapy.[52]

✔✔ Neoadjuvant chemotherapy can be utilised to decrease breast tumour burden with increased rates of BCS without compromising local regional control.

Management of the axilla (see also Chapter 10)

In the setting of clinical node-negative invasive breast cancer, sentinel lymph node (SLN) dissection is the standard of care for surgical staging of the axilla. While the timing of SLN dissection prior to or following neoadjuvant chemotherapy previously remained controversial given concern for feasibility and accuracy, this approach has demonstrated oncological safety following chemotherapy.[53] Furthermore, SLN after neoadjuvant chemotherapy shows comparable rates of identification and false-negative rates with a surgery-first approach, meaning axillary lymph node dissection (ALND) can be safely avoided in this population.[53,54]

Patients who present with clinically node-positive disease have been traditionally treated with ALND. However, as approximately 40% of patients with clinically node-positive disease will have pathologically negative nodes following neoadjuvant chemotherapy the role of SLN dissection in this population has been evaluated. Three large prospective clinical trials have evaluated the feasibility and accuracy of SLN in this population – ACOSOG Z1071, SENTinel NeoAdjuvant (SENTINA Arm C) and Sentinel Node biopsy Following Neoadjuvant Chemotherapy (SN FNAC).[55–57] While SLN alone was found to have a

higher than accepted false-negative rate (FNR) threshold of 10% within these trials, several factors influencing the FNR, thereby streamlining the procedure, were described. These include intraoperative lymphatic mapping with dual-agent technique (radioisotope and blue dye), at least 2–3 SLNs evaluated, evaluation with immunohistochemistry (IHC) with consideration of any residual nodal disease as node-positive and targeted excision of the biopsy-proven node (clipped node) (Table 16.4).

From this series of trials, targeted axillary dissection (TAD) emerged whereby patients undergo sentinel node biopsy together with excision of the biopsy-proven involved node at diagnosis. This allows axillary staging after neoadjuvant chemotherapy in patients with an apparent complete axillary response in those with initially N1 disease. At presentation, axillary ultrasound is performed with biopsy of suspicious axillary nodes and clip placement in the biopsy-proven positive node. After neoadjuvant chemotherapy, patients with a complete response by clinical examination and ultrasound undergo SLN dissection with dual mapping technique and excision of the clipped node via wire or I-125 radioactive seed localisation (**Fig. 16.2**). This technique has been documented to be feasible within multidisciplinary clinical practice and has a markedly improved FNR of 2% compared to 10.1% for SLN dissection alone and 4.2% for removal of the clipped node alone.[58,59] Interestingly, it is noted that the clipped node was not a SLN in 23% of cases, supporting preoperative localisation to guide selective excision.

TAD allows for the assessment of residual disease in the axilla after an apparent complete response to neoadjuvant chemotherapy in initially node-positive patients. Currently, in the setting of residual pathological node-positive disease, axillary dissection is the current standard of care outside of a clinical trial. Although long-term outcomes are not yet known, in carefully selected patients with negative TAD and limited initial nodal involvement by axillary ultrasound, consideration may be given to no additional axillary surgery given the high accuracy of this procedure with respect to identifying residual axillary disease.

✔✔ Sentinel lymph node biopsy is indicated after neoadjuvant chemotherapy in initially node-negative patients. Neoadjuvant chemotherapy in initially node-positive patients may downstage disease in the axilla with reasonable rates of pCR which vary by tumour subtype. In this setting, SLNB alone carries a high FNR; however, accuracy for detecting residual nodal disease is increased by using dual tracer lymphatic mapping technique, obtaining 2–3 SLNs, documented excision of the clipped node with prior metastatic disease and definition of SLN positive by IHC to include isolated tumour cells and micrometastatic disease.

Radiation therapy

Adjuvant radiation therapy remains a significant aspect of local regional management in patients treated with BCS. Following mastectomy, radiation therapy has been demonstrated to improve local control in patients treated with neoadjuvant chemotherapy with stage III disease even after achieving pCR.[60] However, the impact of radiation therapy in those with an excellent response to neoadjuvant chemotherapy in patients with clinically node-positive N1 disease is not known and is the subject of ongoing clinical trials.

The Alliance for Clinical Trials in Oncology A11202 trial is evaluating local regional management in women with clinical T1–3 N1 M0 invasive breast cancer and residual pathological axillary disease following neoadjuvant chemotherapy. This trial randomises patients to ALND or radiation alone with both groups planned to receive breast/chest wall radiation and regional nodal irradiation (RNI).[61] The NSABP B-51/RTOG-1304 (NRG 9353) trial is planned to investigate the role of radiation therapy in women with clinical T1–3 N1 M0 invasive breast cancer and found to have pathologically node-negative disease after therapy. In the setting of BCS, patients will be randomised to RNI after whole-breast radiation or whole-breast radiation alone, in those having mastectomy, chest wall and RNI as compared to no radiation.[62] The outcomes of these trials are awaited eagerly to assist further in developing the optimal approach to local regional control following neoadjuvant chemotherapy in patients with clinical node-positive disease dependent on pathological response.

Future directions

Neoadjuvant systemic therapy continues to be a unique platform to investigate and understand tumour biology, response to therapy and prediction of outcome. Identification, refinement and application of targeted therapies, as evidenced in the HER2-positive setting, has been a powerful byproduct of the neoadjuvant approach. Improved understanding of triple-negative breast cancer subtype may provide for additional selected therapy options, particularly in poor responders to standard chemotherapy. Neoadjuvant endocrine therapy has also emerged as having significant effectiveness in women with HR-positive breast cancer comparable to chemotherapy with decreased toxicity. Additionally, sophisticated understanding of endocrine resistance and the addition of growth factor inhibitors such as everolimus (mTOR inhibitor), GDC-0032 (PI3K inhibitor) and palbociclib (CDK 4/6 inhibitor) have

Table 16.4 • Trials evaluating sentinel lymph node (SLN) dissection in the setting of clinical node-positive invasive breast cancer treated with neoadjuvant chemotherapy

	Axillary pCR	SLN identification rate	Overall FNR	FNR by number SLN				FNR by lymphatic mapping technique			Other factors impacting FNR
				1	2	≥3	*P*	Single agent	Dual agent	p	
ACOSOG Z1071[55,65]	41%	92.9%	12.6% (95% CI 9.85–16.05)	31.5%	21%	9.1%	0.007	20.3%	10.8%	0.05	FNR when clipped node identified as SLN 6.8% (95%CI 1.9–16.52%) confirmed in ALND specimen 24.1% excision not confirmed 13.4% no clipped node 14.3% FNR when SLN-positive disease determined by IHC 8.7%
SENTINA (Arm C)[56]	52.3%	80.1%	14.2% (95% CI 9.9–19.4%)	24.3%	18.5%	<10%	0.008	16%	8.6%	0.145	
SN FNAC[57]	34.5%	87.6%	8.4% (95% CI 2.4–14.4%)*	18.2%	4.9%**		0.076	16%	5.2%	0.190	FNR when SLN-positive disease determined by H&E 13.3%

*Overall FNR is determined using IHC to determine residual nodal disease.
**FNR when two or more SLN were identified and examined.
ALND, axillary lymph node dissection; FNR, false-negative rate; H&E, haematoxylin and eosin; IHC, immunohistochemistry; pCR, pathological complete response; SLN, sentinel lymph node.

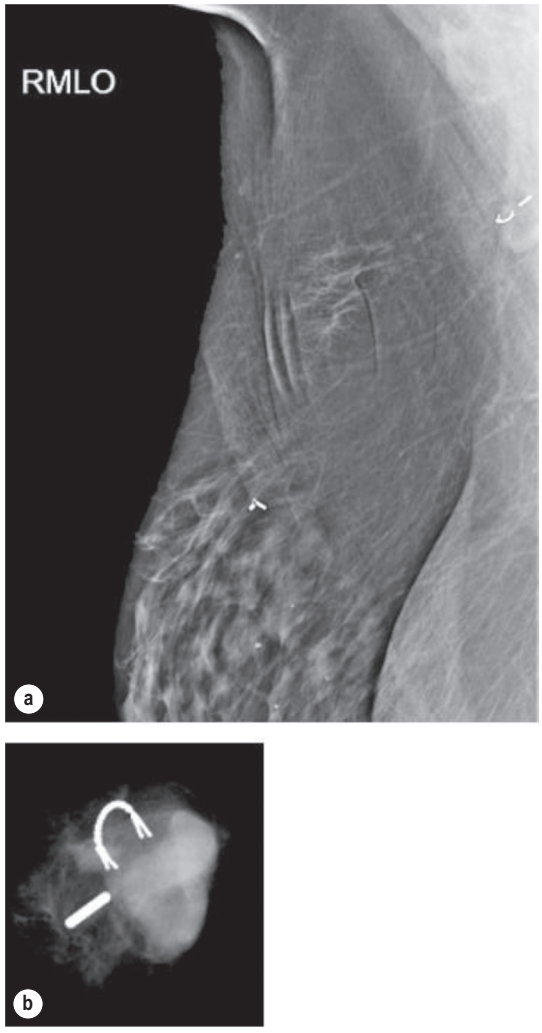

Figure 16.2 • Targeted excision of clipped node via I-125 seed localisation. **(a)** Preoperative mammogram showing clipped axillary lymph node with I-125 radioactive seed. **(b)** Specimen radiograph confirming selective excision of the clipped axillary node with I-125 radioactive seed.

demonstrated improved outcomes compared with endocrine therapy alone, some of which are being studied in the neoadjuvant setting.[63] Significant responses to therapy in the breast and axilla can facilitate downstaging, allowing for limited surgery in selected suitable patients. Furthermore, elimination of surgery in patients with exceptional response to neoadjuvant systemic therapy may be an appropriate strategy, which is under ongoing evaluation in the clinical trial setting.[1,2,64] Certainly, neoadjuvant therapy has asserted its role as a robust mechanism to understand breast cancer biology and tailor systemic and local therapies in selected populations.

Summary

The role of neoadjuvant systemic therapy in breast cancer continues to evolve. Traditionally reserved for locally advanced and inoperable breast cancer, landmark clinical trials have demonstrated equivalence between neoadjuvant and adjuvant systemic therapy in operable breast cancer. Response to therapy has emerged as a significant prognostic indicator, with improved survival in patients demonstrating a pathological complete response. Furthermore, response to therapy is heavily influenced by tumour subtype, with more biologically aggressive subtypes displaying the highest rates of pathological complete response. Neoadjuvant systemic therapy can downstage disease both in the breast and axilla thereby facilitating breast-conserving surgery and limited axillary surgery even in the setting of initially node-positive disease in selected patients. In contemporary practice, the neoadjuvant therapy platform is a robust mechanism for drug development and investigation into the biological impact of therapy while allowing for a personalised approach to therapy with individualised outcomes.

Key points

- There is no survival advantage to neoadjuvant systemic therapy as compared to adjuvant systemic therapy.
- Neoadjuvant systemic therapy allows for assessment of tumour response to therapy and pathological complete response is associated with improved survival outcome.
- There is a varying response to chemotherapy by molecular tumour subtypes; the highest rates of pCR are seen in triple-negative and HER2-positive disease.
- Neoadjuvant endocrine therapy utilising aromatase inhibitors in the preoperative setting allows for downstaging of disease in postmenopausal women with oestrogen receptor-positive breast cancer.
- Rates of eligible patients for breast-conserving surgery are increased after neoadjuvant systemic therapy without compromising local regional control.

- Axillary staging with sentinel node biopsy including excision of the biopsy-proven nodal metastasis at diagnosis after apparent response to neoadjuvant chemotherapy in initially N1 disease is feasible and has a low false-negative rate in selected patients.
- Future directions include identification of exceptional responders to neoadjuvant systemic therapy who may not require surgical intervention and early identification of non-responders in whom novel agents can be trialled.

Full references available at **http://expertconsult.inkling.com**

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