Breast-Conserving Surgery After Neoadjuvant Therapy

28

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28.1 Introduction

Early randomized trials of the addition of neoadjuvant chemotherapy (NACT) to the treatment regimen of patients with breast cancer failed to demonstrate an improvement in overall survival compared with conventional adjuvant therapy; nevertheless, the increased opportunities for breast conservation, owing to downstaging of the primary tumour, and enthusiasm regarding the potential to tailor systemic therapy based on responses observed in the neoadjuvant setting, resulted in the adoption of this approach as a useful clinical tool. That the effectiveness of NACT varies by molecular subtype is becoming increasingly clear, and although the potential of tailoring adjuvant systemic therapy based on treatment response before surgery remains to be realized, the increasing rates of pathological complete response following NACT have had a considerable impact on locoregional treatment considerations. For example, NACT reduces the need for mastectomy and axillary lymph node dissection, thus decreasing the morbidity of surgery, without compromising outcomes. However, selection of the ideal candidates for preoperative chemotherapy remains critical, and personalizing local therapy based on the degree of response is the subject of ongoing clinical trials. The concept of *targeted breast surgery* is a systematic model of surgical techniques for breast conservation after NACT with optimized local outcome and aesthetic results for the patients.

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28.1.1 Neoadjuvant Chemotherapy (NACT)

Preoperative or neoadjuvant chemotherapy (NACT) was initially used in the treatment of patients with locally advanced breast cancer (T4a–T4d disease), after historical series of patients with inflammatory breast carcinoma (T4d disease) and other T4 breast tumours who were treated with initial surgery demonstrated high rates of local recurrence and poor survival [1, 2]. The demonstration in the 1970s that adjuvant chemotherapy improved both disease-free survival and overall survival of women with lymph node-positive breast cancer [3, 4] led to a number of studies examining the role of NACT in locally advanced breast cancer. The results of early studies of NACT indicated a prolongation of disease-free survival and overall survival compared with historical controls [5, 6], coupled with the observation that major reductions in tumour volume occurred in 60–80% of patients treated [7], providing the rationale for clinical trials of this approach in earlier-stage operable breast cancer. The primary aim of these studies was to determine if NACT, through prompt treatment of micrometastases, improved survival compared to chemotherapy given postoperatively. However, a meta-analysis of nine randomized studies, comprising a total of 3946 patients, found no significant survival difference between patients who received NACT and those who received adjuvant therapy, with a summary risk ratio of 1.0 (95% CI 0.90–1.12) [8]. Although this lack of survival difference has persisted in more recent studies [9], a number of benefits of NACT have nevertheless emerged, including increased opportunity to perform breast-conserving surgery (BCS) and a reduced need for axillary lymph node dissection (ALND) [10]. Additionally, the achievement of pathological complete response (pCR) to NACT has emerged as a powerful prognostic factor [11]. The acceptance by the FDA of pCR rate as a criterion supporting the approval of new drugs [12], together with the other benefits discussed, suggests that the use of NACT will continue to increase. This paradigm shift raises a number of important questions regarding appropriate approaches to local therapy for breast cancer, as the

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guiding principles for surgery and postoperative radiotherapy in use today were developed based on the findings of trials in which surgery was the initial treatment modality.

28.1.2 NACT and Breast-Conserving Surgery (BCS)

A meta-analysis of 14 prospective randomized trials of neoadjuvant versus adjuvant chemotherapy in a total of 5500 patients with breast cancer demonstrated that NACT was associated with an absolute decrease in the mastectomy rate of 16.6% (95% CI 15.1–18.1%) [9]. In fact, this 16.6% reduction in the mastectomy rate was an underestimation of the potential benefit of NACT, as many of the patients were candidates for BCS at presentation and, with regard to the surgical approach, could not benefit from NACT. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial [10] and the European Organisation for Research and Treatment of Cancer (EORTC) 10901 trial [13], the rates of BCS after four cycles of anthracycline-based NACT in patients deemed to have required mastectomy if surgery had been the initial treatment were 27% and 23%, respectively. Paradoxically, although rates of pCR to NACT have increased markedly with the use of newer therapeutic agents and targeted therapies, rates of BCS have not risen. For example, in the NSABP B-27 trial [14], the addition of docetaxel to doxorubicin and cyclophosphamide NACT increased the pCR rate from 13.7% to 26.1% ($P < 0.001$), but the rates of BCS were not significantly different between the patients who received docetaxel and those who did not (61.6% vs. 63.7%; $P = 0.33$). More recently, in the Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimization (NeoALTTO) trial in patients with HER2-overexpressing tumours [15], which compared chemotherapy plus trastuzumab and lapatinib with chemotherapy plus either lapatinib or trastuzumab, rates of pCR differed considerably: 51.3% with dual HER2 blockade, 29.5% with trastuzumab, and 24.7% with lapatinib. However, in patients who were not candidates for BCS at randomization, rates of BCS after NACT were 26.4% in the trastuzumab–lapatinib combination group, 27.7% in the trastuzumab group, and 26.4% in the lapatinib group [15]. Indeed, failure to translate increased pCR rates into a higher rate of BCS has been observed in multiple studies (Tables 28.1 and 28.2). This trend is somewhat inexplicable, but is probably attributable to the difficulty in evaluating the extent of residual disease after NACT and before surgery and confusion regarding whether resection of the entire volume of breast tissue originally occupied by the tumour is necessary. Additionally, some definitions of pCR include patients with residual ductal carcinoma in situ (DCIS), which can preclude BCS. Furthermore, just as patients who are candidates for primary BCS often opt for mastectomy [16], patient preference after NACT might also contribute to the observed rates of mastectomy in this setting.

28.1.3 Patient Selection for NACT to Enable BCS

Both anatomical and biological factors are useful in selecting patients with breast cancer in whom NACT is likely to result in tumour downstaging that enables BCS. For instance, patients with high-grade breast tumours that are oestrogen receptor (ER)-negative and/or HER2-positive have a higher likelihood of pCR to NACT. In one study, patients with ER-positive, HER2-negative luminal tumours, which are generally low grade, had a 6% pCR rate with paclitaxel, 5-fluorouracil, doxorubicin, and cyclophosphamide NACT, compared with 45% for HER2-positive or basal-like tumours (which are mostly negative for ER, progesterone receptor [PR], and HER2 and triple-negative breast cancer [TNBC]) [17]. In patients with ER-positive tumours, a 21-gene assay for estimation of disease recurrence (Oncotype DX©, Genomic Health, USA) is predictive of the probability of pCR to NACT, just as this assay is predictive of a benefit from chemotherapy added to endocrine therapy in the adjuvant setting [18]. The suitability of patients with infiltrating lobular carcinoma (ILC) for preoperative therapy to downstage tumours to enable BCS is uncertain. A meta-analysis of data from 12,645 patients with infiltrating ductal cancers and 1764 with ILC reported a pooled pCR rate for ductal cancers of 16.7% (95% CI 13.5–20.5) compared with 5.9% (95% CI 3.6–9.4%) for ILCs—a pooled odds ratio (OR) of 3.1 ($P < 0.00001$) [19]. In the 13 studies included in this meta-analysis that reported rates of BCS, a higher rate was observed in patients with ductal versus lobular cancers (54.8% vs. 35.4%; pooled OR 2.1; $P < 0.00001$). Of note, a comparison of patients with lobular cancer ($n = 75$) and those with ductal cancer ($n = 671$) in two prospective NACT trials found that, after adjusting for hormone-receptor status, HER2 status, histological grade, and p53 expression, rates of pCR did not differ between ductal and lobular cancers, indicating that these additional clinicopathological features could potentially be used to select the subset of patients with lobular carcinoma most likely to benefit from NACT [20]. Importantly, pCR is not absolutely necessary for BCS: only sufficient tumour shrinkage to enable resection of the tumour to clear margins with an acceptable cosmetic result is required. Nevertheless, patients who achieve a pCR are by definition candidates for BCS, and rates of pCR provide a minimum estimate of the proportion of patients likely to benefit from the NACT approach. On the basis of the current data, the patients in whom NACT is most likely to result in tumour downstaging to enable BCS are those with unicentric,

Table 28.1 Comparison of neoadjuvant chemotherapy regimens regarding their outcome in terms of pathological complete response and breast-conserving surgery rates: neoadjuvant trials and trials comparing preoperative versus postoperative administration

Trial	Preoperative therapy	*n*	ypT0/Tis ypN0 (%)	BCS (%)
ypT or *N*, pathological tumour or node category after chemotherapy; *BCS* breast-conserving surgery; *dd* dose dense; *A* doxorubicin; *Doc* docetaxel; *Tam* tamoxifen; *C* cyclophosphamide; *TAC* docetaxel–doxorubicin–cyclophosphamide; *n.a.* not available; *N* vinorelbine; *X* capecitabine; *E* epirubicin; *HER* human epidermal growth factor receptor; *CHT* chemotherapy; *H* trastuzumab; *AGO* Arbeitsgemeinschaft für Gynäkologische Onkologie; *Pac* paclitaxel; *PREPARE* Preoperative Epirubicin Paclitaxel Aranesp Study; *CMF* cyclophosphamide–methotrexate–5-fluorouracil; *SWOG* Southwest Oncology Group; *MDACC* MD Anderson Cancer Center; *FAC* 5-fluorouracil–doxorubicin–cyclophosphamide; *CALGB* Cancer and Leukemia Group B; *Bev* bevacizumab; *Cb* carboplatin; *NSABP* National Surgical Adjuvant Breast and Bowel Project; *ABCSG* Austrian Breast and Colorectal Cancer Study Group; *bpCR* breast pathological complete response; *EORTC* European Organization for Research and Treatment of Cancer; *FEC* 5-fluorouracil–epirubicin–cyclophosphamide				
GeparDo	dd A Doc × 4	126	9.5	69
	dd A Doc × 4 + Tam	122	5.7	69
GeparDuo	dd A Doc + Tam	453	10.2	66
	A C × 4 then Doc + Tam	454	19.2	75
GeparTrio pilot	TAC × 6	252	19.0	n. a.
	TAC × 2 then 4 × N X	33	6	n.a.
GeparTrio	TAC × 6	1085	18.7	68
	TAC × 8	686	29.0	69 responders
				57 nonresponders
GeparQuattro	E C × 4 then Doc + H +/– X	445	40	60
HER2 negative	E C × 4 then Doc × 4	343	18.7	68[a]
	E C × 4 then Doc + X × 4	345	16.5	67
	E C × 4 then Doc × 4 then X × 4	362	19.1	64
HER2 positive	CHT + H for HER2 positive	445	41.3	
AGO-1	E Pac × 4	335	6.6	58
	dd E × 3 then dd Pac × 4	333	13.2	
PREPARE	E C × 4 then Pac × 4	370	14.6	67
	dd E × 3 then dd Pac × 3 then CMF × 3	363	20.4	65
SWOG 0012	A C × 5 every 3 weeks then Pac × 12	179	20.7	n.a.
	A × 15 weekly + C daily then Pac × 12	177	24.3	
MDACC	FAC × 4	100	9.0	n.a
	dd FAC × 4	99	13	
CALGB 40603	Pac × 12 then dd A C × 4	108	39.0	n.a.
	+ Bev × 9 every 2 weeks	110	43.0	
	+ Cb × 6 every 3 weeks	113	49.0	
	+ Cb + Bev	112	60 0	
Older trials comparing pre-op				
and post-op administration				
NSABP B-18	A C × 4	747		67
	Primary surgery	759		60
ABCSG-07	CMF × 3	203	5.9 bpCR	66
	Primary surgery	195		60
EORTC 10902	FEC × 4	350	4.0	35
	Primary surgery	348		22

high-grade, ER-negative, and/or HER2-positive breast cancer [21, 22].

Multiple studies have evaluated the accuracy of MRI compared with physical examination, mammography, and ultrasonography in determining the presence and extent of viable tumour within the breast after NACT [23–27]. In a multi-institutional study of 41 women with palpable breast cancers, Yeh et al. [27] demonstrated that preoperative MRI had the best correlation with surgical specimen pathology when compared with physical examination, mammography, and ultrasonography. Furthermore, in 216 women who participated in the prospective, multi-institutional I-SPY trial [23], MRI was shown to be a better predictor of pathological response to NACT than clinical examination. A meta-analysis of 44 studies including a total of 2050 patients who received NACT found that the median sensitivity of MRI for the detection of residual cancer across studies was 0.92 and the median specificity was 0.60 [24]; however, accuracy differed

Table 28.2 Comparison of neoadjuvant chemotherapy regimens regarding their outcome in terms of pathological complete response and breast-conserving surgery rates: targeted therapy trials

Trial	Preoperative therapy	*n*	ypT0/Tis ypN0 (%)	BCS (%)
ypT or *N* pathological tumour or node category after chemotherapy; *BCS* breast-conserving surgery; *Pac* paclitaxel; *FEC* 5-fluorouracil–epirubicin–cyclophosphamide; *H* trastuzumab; *NSABP* National Surgical Adjuvant Breast and Bowel Project; *A* doxorubicin; *C* cyclophosphamide; *n.a.* not available; *L* lapatinib; *CHER-LOB* Chemotherapy, Herceptin, and Lapatinib in Operable Breast cancer; *NOAH* NeOAdjuvant Herceptin; *CMF* cyclophosphamide–methotrexate–5-fluorouracil; *HER* human epidermal growth factor receptor; *NeoALTTO* Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimization; *P* pertuzumab; *Doc* docetaxel; *Cb* carboplatin, *TECHNO* Taxol Epirubicin Cyclophosphamide Herceptin Neoadjuvant; *E* epirubicin; *Bev* bevacizumab; *X* capecitabine; *Gem* gemcitabine				
Buzdar et al.	Pac × 4 then FEC × 4	19	26	53
	Pac × 4 then FEC × 4 + H × 24 weekly	23	65	57
		(164 planned)		
NSABP B-41	A C × 4 then Pac × 12			
	+ H weekly	177	49.4	n.a.
	+ L	171	47.4	n.a.
	+ H weekly + L	171	60.2	n.a.
CHER-LOB	Pac × 12 then FEC × 4			
	+ H weekly	36	25	67
	+ L	39	26	58
	+ H + L	46	47	69
NOAH	A + Pac × 3 then Pac × 4 then CMF × 3			
	HER2 negative	99	16	n.a.
	HER2 positive	118	19.0	13
	HER2 positive + H × 11 every 3 weeks	117	38.0	23
NeoALTTO	6 weeks L then 12 × Pac + L	154	24.7	43
	6 weeks H then 12 × Pac + H	149	29.5	39
	6 weeks L + H then 12 × P + H + L	152	51.3	41
TRYPHAENA	FEC + H + P × 3 then Doc + H + P × 3	73	56	n.a.
	FEC × 3 then Doc + H + P × 3	75	55	n.a.
	Doc + Cb + H + P × 6	77	64	n.a.
NeoSphere	Doc × 4 + H every 3 weeks	107	21.5	n.a.
	Doc × 4 + H + P every 3 weeks	107	39.3	n.a.
	H + P every 3 weeks	107	11.2	n.a.
	Doc + P every 3 weeks	96	18	n.a.
TECHNO	E C × 4 then Pac + H × 4	217	39.0	64
GeparQuinto				
HER2 positive	E C × 4 then Doc × 4 + H	309	44 6	64
	E C × 4 then Doc × 4 + L	311	30 2	59
HER2 negative	E C × 4 then Doc × 4 + Bev	956	21.7	62
	E C × 4 then Doc × 4	969	18.3	62
NSABP B-40	Doc × 4 then A C × 4	392	25.8	46
	Doc × 4 + X then A C × 4	393	23.2	43
	Doc × 4 + Gem then AC × 4	390	26.9	50
	Bev × 6 for half of all patients		23.0 with Bev	n.a.
			27.6 no Bev	

depending on the definition of pCR used and was lower in studies that permitted residual DCIS in the definition of pCR [24]. This meta-analysis also provided evidence that mammography had lower accuracy for detection of residual disease than MRI (relative diagnostic OR 0.27; 95% CI 0.07–1.02; $P = 0.02$), but differences in accuracy between MRI and ultrasonography and MRI and physical examination were not statistically significant [24]. All of these methods of evaluation are limited in their ability to detect scattered microscopic foci of viable carcinoma, which might have an impact on the success of BCS [26]. Current evidence indicates that the accuracy of MRI after NACT varies with ER, PR, and HER2 status and is greatest in patients with HER2-positive disease or TNBC, probably owing to the higher rates of pCR in these patients than those with other tumour types [28, 29]. Studies addressing the ability of MRI to identify patients who are appropriate candidates for BCS, as opposed to those aimed at identifying pCR or correlating tumour size

based on MRI assessment with pathological tumour size post NACT, are more limited. Straver et al. [30] examined pre-NACT and post-NACT MRI exams in 208 patients; in 35 patients (17%), MRI underestimated tumour size by more than 2 cm, which would have led to inappropriate attempts at BCS in 27 patients (13%). Conversely, MRI overestimated the extent of disease in nine patients (4%), leading to unnecessary mastectomy. Thus, the overall accuracy of MRI for the selection of surgical therapy was 83% [30]. In a study that investigated the relationship between MRI estimation of tumour size after NACT and positive surgical margins in 182 patients with breast cancer, one-third of patients (33%) in whom tumour size was underestimated by more than 2 cm had positive margins compared with 12% of those with lesser degrees of underestimation or overestimation of tumour size (P = 0.005); however, underestimation of tumour size by greater than 2 cm occurred in only 10% of patients [31]. In aggregate, the literature indicates that MRI is useful for selecting patients who are candidates for BCS after NACT. In patients with malignant calcifications, a post-NACT mammogram is also useful for planning the extent of the resection: although calcifications do not always indicate residual malignancy [32], the presence of residual disease cannot be reliably excluded unless all radiographic abnormalities are removed.

28.1.4 Surgical Issues

In patients undergoing NACT with the potential for breast tumour downstaging to enable BCS, the tumour site should be marked with a clip before initiating NACT. Resection of the entire volume of breast tissue originally occupied by tumour is not necessary [33]; however, no consensus has been reached on what constitutes an adequate surgical margin in this setting. The NSABP B-18 trial [34] used the standard NSABP margin definition of no ink on tumour and, after controlling for age and tumour size, found no statistically significant differences in local recurrence between patients who required NACT for downstaging to BCS candidacy, those who were candidates for BCS before NACT, and those who underwent BCS and received adjuvant therapy. Similarly, the meta-analysis by Mieog et al. [9] reported no significant differences in local recurrence for patients with breast cancer who received NACT versus those who received adjuvant therapy, including the subset of patients requiring NACT to downstage the primary tumour to enable BCS. Thus, BCS after NACT can clearly be safe, although the 'Swiss cheese' pattern of response, characterized by scattered microscopic foci of residual viable tumour, has been shown to predict an increased risk of local recurrence in a large population of patients with breast cancer treated with NACT at the University of Texas MD Anderson Cancer Center (MDACC) [35]. In our opinion, the presence of multiple scattered tumour foci in close proximity to the surgical margin warrants consideration of re-excision when less than the original pretreatment tumour volume has been resected after NACT. In the absence of this pattern of tumour response, a margin of no ink on tumour is probably adequate.

28.1.4.1 Targeted Breast Surgery

Breast-conserving therapy (BCT) consisting of surgical removal of the primary tumour followed by whole breast irradiation is an alternative to mastectomy which results in equivalent long-term survival [36]. Although rates of BCT have increased over time worldwide, there remains remarkably little consensus about what amount of normal breast tissue should be removed as a margin to minimize the risk of local recurrence. The conclusion of the SSO (Society of Surgical Oncology)–ASTRO (American Society for Radiation Oncology) Consensus Panel reinforced the importance of obtaining negative margins defined as no ink on tumour (invasive cancer or DCIS) to optimize local control [37]. The most important and potentially practice-changing conclusion was based on the finding in the meta-analysis of Houssami et al. that margins of 1, 2, or 5 mm were not associated with significantly different risks of local recurrences [38]. This meta-analysis could not be used to demonstrate whether a margin of no ink on tumour is adequate for patients with invasive lobular cancer, an EIC in association with invasive cancer, and tumours of unfavourable biological subtype (i.e., triple-negative breast cancer) and in young patients.

Oncoplastic principles were introduced into breast-conserving surgery 20 years ago to allow oncologically safe breast conservation, by performing a wide excision for larger or poorly located tumours, while limiting the risk of postoperative deformities [39]. Numerous surgical techniques with tissue displacement and tissue replacement have been published with different indications, incision lines, and suggested rotation techniques, missing a systematic and structured approach for oncoplastic breast surgery [40]. During the last years, we have defined five reconstruction principles introducing a new concept of breast-conserving surgery, termed *targeted* (*oncoplastic) breast surgery* [40–43].

We prospectively defined six major reconstruction principles in oncoplastic breast-conserving surgery (BCS) based on the localization, size of the segmental resection defect, size of the breast, and the necessity for skin resection during breast-conserving therapy. These major principles were BCS glandular rotation, BCS dermoglandular rotation, BCS thoracic wall advancement, BCS tumour-adapted reduction mammoplasty, BCS thoracoepigastric flap, and BCS latissimus dorsi flap (Figs. 28.1, 28.2, 28.3, 28.4, 28.5, 28.6, and 28.7). Partial mastectomy defects could be reconstructed

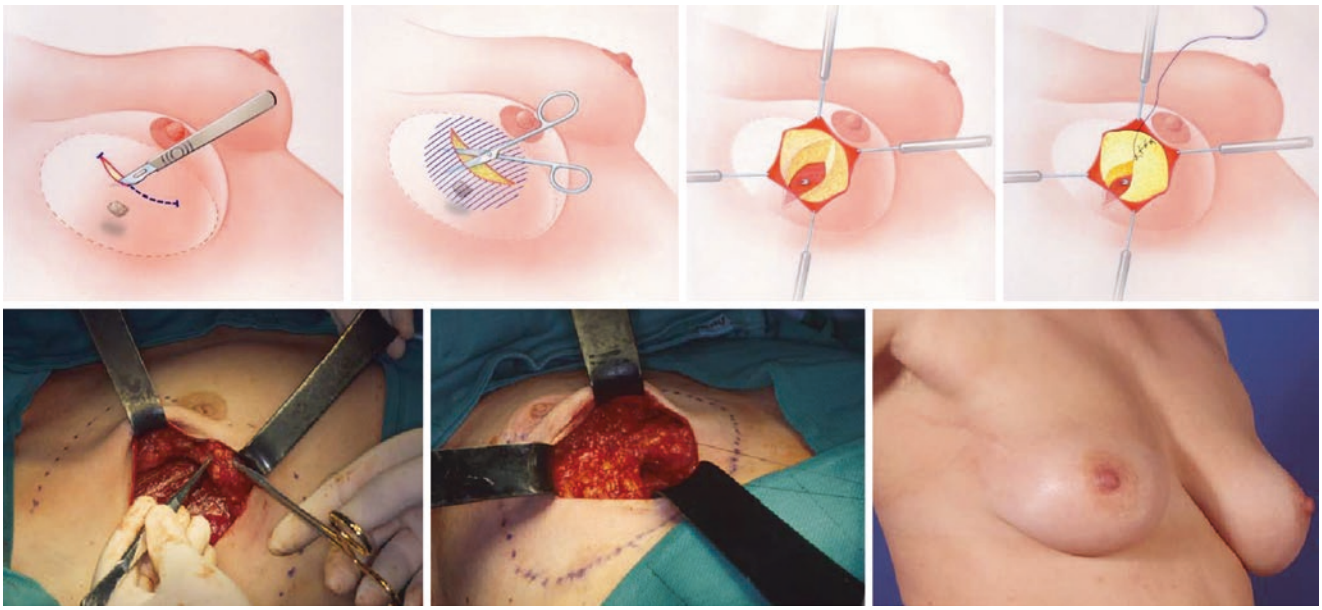

Fig. 28.1 Principles in targeted oncoplastic breast-conserving surgery: BCS glandular rotation. *BCS* breast-conserving surgery

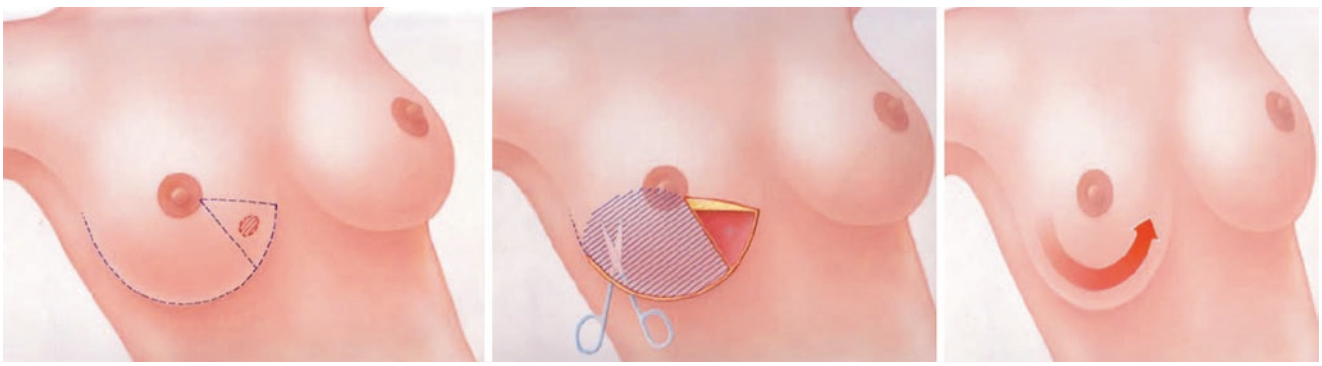

Fig. 28.2 Principles in targeted oncoplastic breast-conserving surgery: BCS dermoglandular rotation. *BCS* breast-conserving surgery

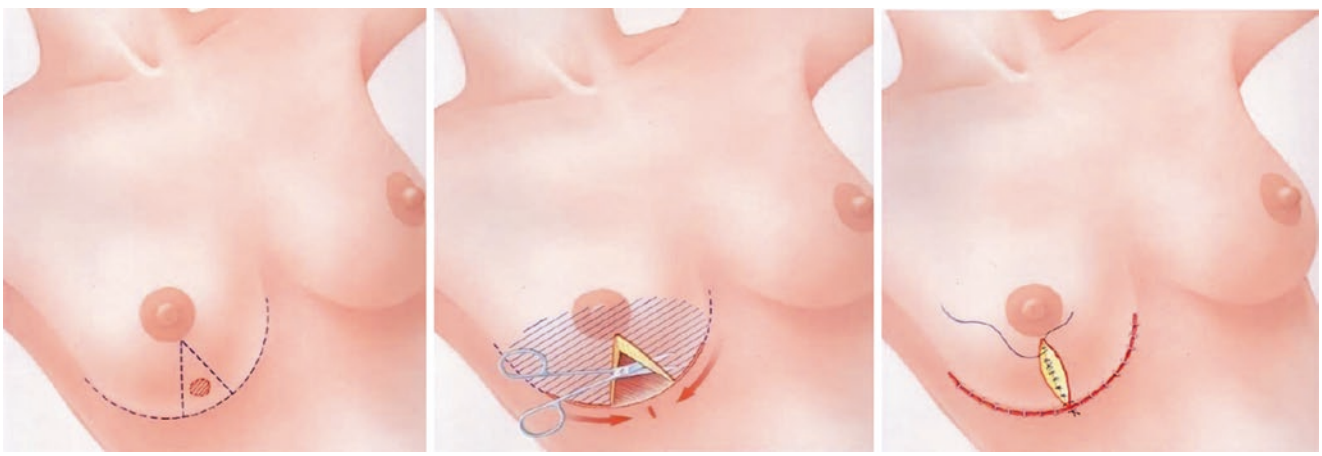

Fig. 28.3 Principles in targeted oncoplastic breast-conserving surgery: BCS dermoglandular rotation (tumour-adapted mastopexy). *BCS* breast-conserving surgery

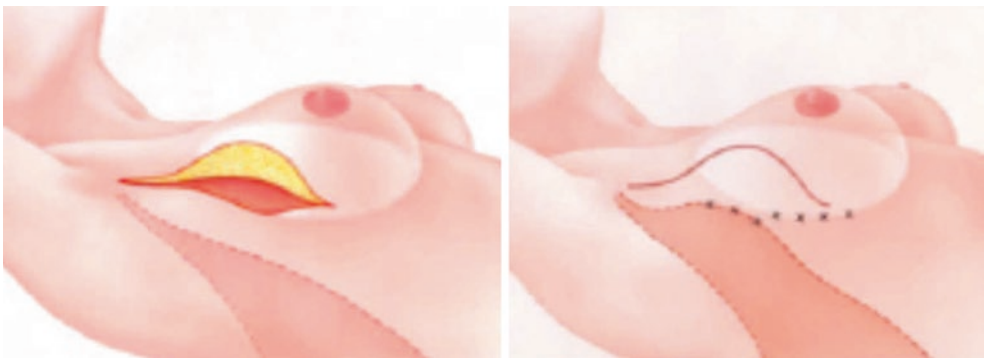

Fig. 28.4 Principles in targeted oncoplastic breast-conserving surgery: BCS thoracic wall advancement according to Rezai. *BCS* breast-conserving surgery

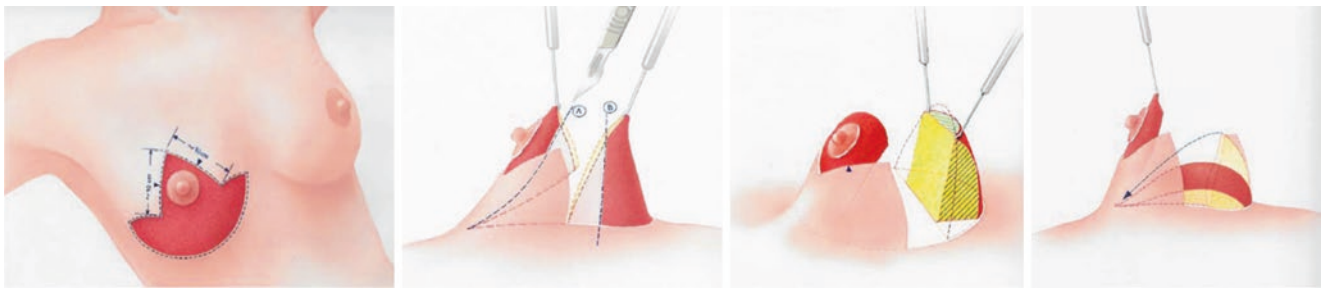

Fig. 28.5 Principles in targeted oncoplastic breast-conserving surgery: BCS tumour-adapted reduction mammoplasty according to Rezai. *BCS* breast-conserving surgery

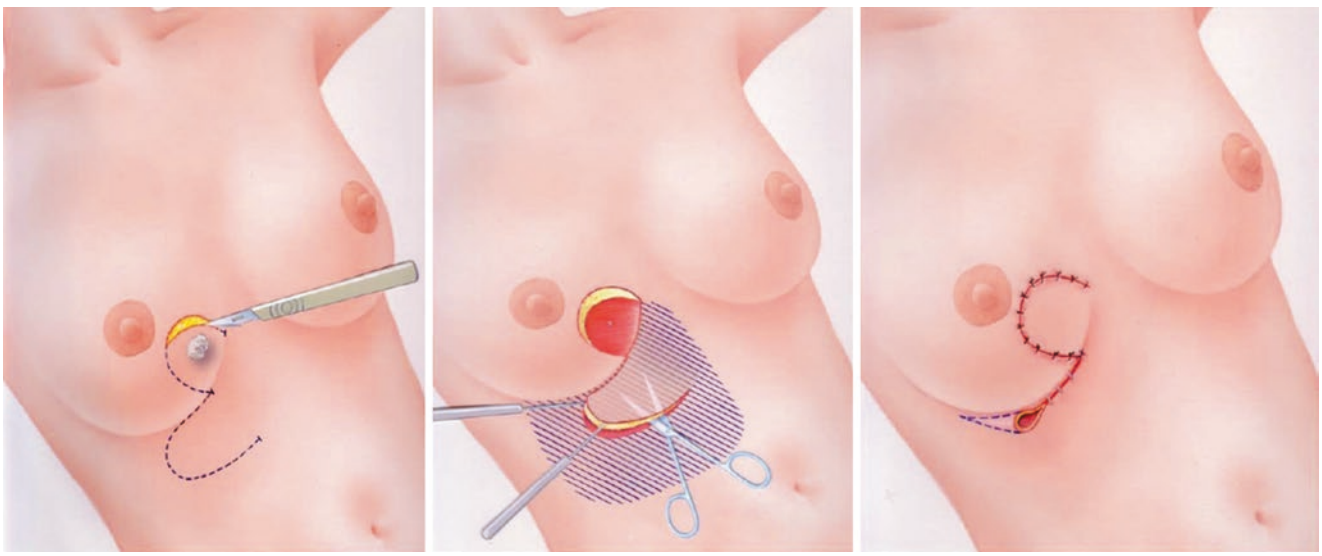

Fig. 28.6 Principles in targeted oncoplastic breast-conserving surgery: BCS thoracoepigastric flap. *BCS* breast-conserving surgery

during BCS with these five oncoplastic principles in 97%. The cosmetic results were good or excellent in 95%. A tumour-free resection margin of 1 mm was mandatory (according to German guidelines) and achieved in 91% during first surgery, while in 5% secondary mastectomy was required. Local recurrences were diagnosed in 1.9% with a median follow-up of 4.2 years.

Our understanding of breast cancer biology has advanced considerably since the initial trials comparing BCT and mastectomy more than 30 years ago. It is apparent that factors such as tumour biology and the availability of effective systemic treatment are at least as important as microscopic residual disease burden in determining local control of breast cancer. Adoption of no ink on tumour as

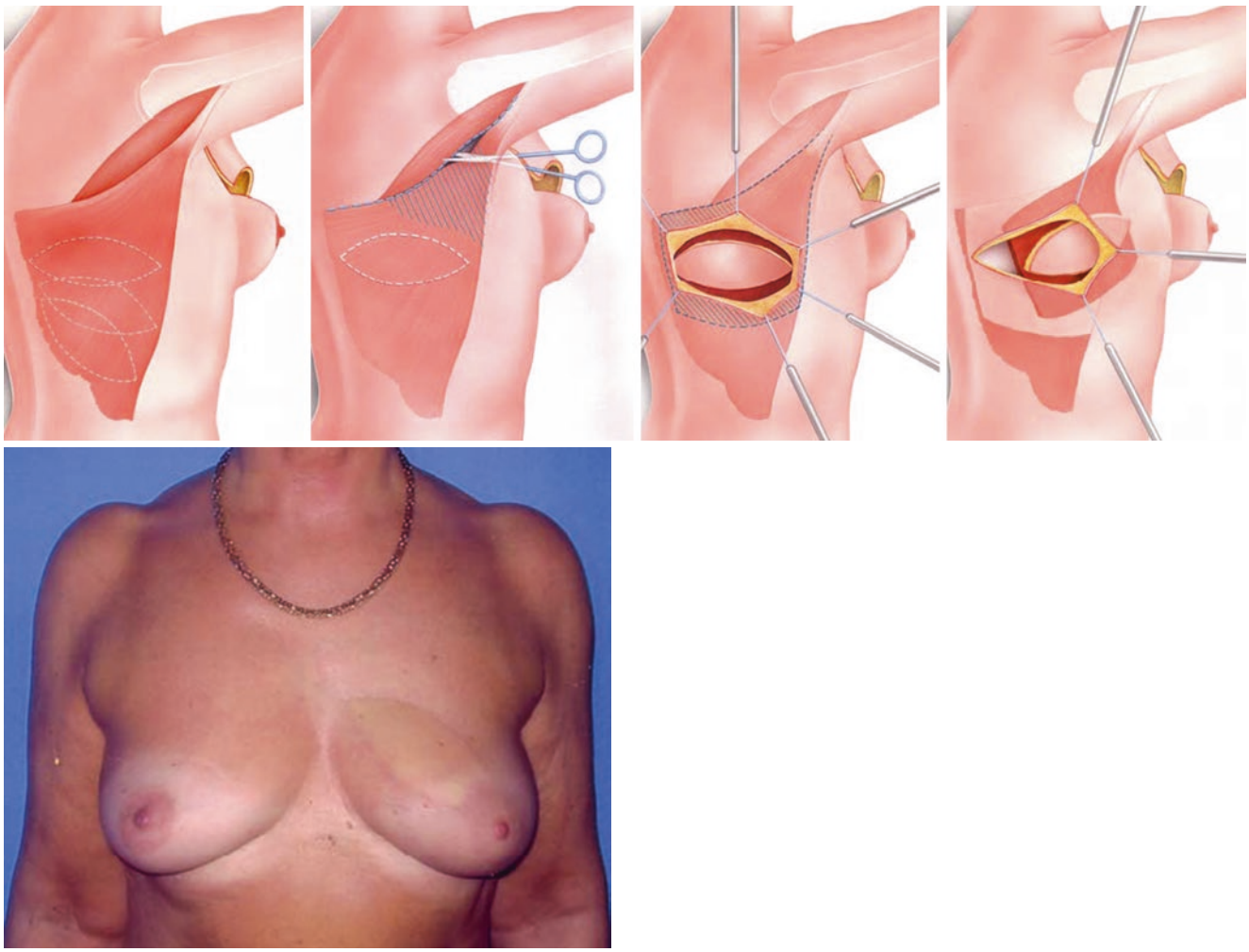

Fig. 28.7 Principles in targeted oncoplastic breast-conserving surgery: BCS latissimus dorsi flap. *BCS* breast-conserving surgery

the standard negative margin definition has clear potential to decrease the use of re-excision and large quadrantectomy-type resections. Adoption of a minimal margin definition removes the rational for the *old* concept of oncoplastic breast surgery—introduced 20 years ago. Further development of the traditional concept of oncoplastic breast surgery to a concept of *targeted* (*oncoplastic*) *breast surgery* with five defined oncoplastic principles allows the reconstruction of segmental resection defects during breast-conserving therapy with highest clinical applicability and results in favourable oncological and aesthetic outcomes. This approach might be useful in extending the indications for breast-conserving therapy. The adoption of a minimal margin definition does not remove the rational for a *new* concept of targeted oncoplastic breast surgery. Targeted oncoplastic breast surgery depends on the anatomical, pathological, and reconstructive aspects of breast cancer to achieve favourable local outcomes for the patients—combining oncological and aesthetic prerequisites [44].

28.1.4.2 Surgical Complications Following NACT

An aspect of NACT that has not yet been investigated thoroughly is the effect of preoperative treatment on surgical complications. The influence of new agents such as biologicals and dose-dense therapies on postoperative wound healing, wound infection, haematoma formation and the need for reoperation has still scarcely been studied. In a recent retrospective analysis [45], data were collected from 44,533 patients after breast surgery. A multivariable regression analysis was performed to identify predictors of postoperative wound complications; 2006 patients received NACT before surgery. Wound complication rates were generally low and comparable in the neoadjuvant treatment and primary surgery groups (3.4 vs. 3.1%). It was concluded that NACT does not influence postoperative wound healing, although there was a trend towards a higher rate of wound complications (4.0%) among patients who had mastectomy and immediate reconstruction after NACT. However, these rates may be an underestimate as postoperative complications

requiring reoperation were excluded. It is understandable that mastectomies with immediate or delayed reconstruction have higher postoperative complication rates than BCS [46]. In smaller series [47–49] of immediate breast reconstruction following NACT, complication rates after mastectomy and immediate autologous or expander/implant reconstruction with or without preceding NACT were compared and reported to be similar. Bearing in mind the small sample sizes, NACT did not, however, seem to affect postoperative complication rates.

Some reports have raised doubt about whether the use of preoperative bevacizumab is safe [50]. Bevacizumab in addition to chemotherapy increases the pCR rate. The GeparQuinto study [51] reported a non-significant increase in overall surgical complications after preoperative addition of bevacizumab (11.0 vs. 15.3%; $P = 0.12$), but revealed an increased risk for patients who required two or more operations to achieve clear margins for BCS [52]. Golshan et al. [53] reported an increased complication rate when performing immediate breast reconstruction using expanders. In a single-arm study, with only 51 patients enrolled, which evaluated neoadjuvant cisplatinum plus bevacizumab, no significant increases in wound healing complications following BCS were observed compared with the results of a previous study in which cisplatinum was given without bevacizumab. Nevertheless, loss of the reconstruction (implant or expander) was reported in four of eight patients. A further study [54] reported no difference in overall surgical complication rate among patients treated with neoadjuvant doxorubicin–cyclophosphamide–paclitaxel with or without bevacizumab. Patients in the two cohorts undergoing mastectomy with or without reconstruction (autologous tissue or implant/expander) were compared. Again, the rate of complications was higher when implants/expanders were used for immediate reconstruction following administration of bevacizumab in a cohort of 119 patients.

28.1.5 Locoregional Recurrence After NACT

In a meta-analysis [55] of nine randomized clinical trials, the clinical outcome of 3861 patients receiving the same systemic therapy either before or after surgery was compared. No significant difference in cancer-related death, disease progression, or distant disease recurrence was reported. A significant increase in LRR rate was observed in the neoadjuvant treatment arm (relative risk 1.22; $P = 0.015$). Four of the nine studies included in this meta-analysis allowed RT alone, without any breast surgery, when a complete clinical response was achieved. The NACT regimens administered in those studies are not comparable with those of the current standard of care, and clinical response was assessed by palpation and X-ray mammography. In addition, complete response was not proven histologically by biopsy before the decision to omit surgery was taken. Thus, an increase in LRR in the neoadjuvant arm is understandable.

Long-term follow-up results of the NSABP B-18 and B-27 trials have been published. These two studies included a total of 3088 patients undergoing NACT or adjuvant chemotherapy. All underwent surgery in the course of treatment. RT was limited to WBI following BCS. Chest wall RT following mastectomy or RT of regional lymph nodes was not allowed in the trial protocols, so an influence of unstandardized RT on locoregional control was avoided. The 10-year cumulative LRR rate after NACT was 12.3% for patients who had a mastectomy and 10.3% for those treated with BCS and consecutive WBI. Clinical tumour size greater than 5 cm in patients who had a mastectomy and age below 50 years in the BCS group had a significant impact on the risk of LRR by 10 years. Clinically node-positive (cN+) disease before NACT and pathological nodal involvement after NACT were independent predictors of LRR, irrespective of type of surgical therapy. Patients who failed to achieve downstaging of the axilla (cN + to ypN0) and breast pCR were at higher risk of LRR. Unfortunately, data concerning hormone receptor and HER2 status were not available, and it could not therefore be determined whether certain subgroups may benefit more or may be at increased risk of LRR after NACT. Moreover, the direct comparison of LRR rates between the two groups in NSABP B-18, which received the same type of chemotherapy (one group before and one after surgery), was not reported.

If subgroups at increased risk of LRR could be identified, this knowledge could be included when deciding on surgical treatment. In a recent meta-analysis [55] of 12,592 patients with breast cancer treated with initial surgery (BCS or mastectomy), it was stated that the risk of LRR may vary between tumour subtypes. Patients with triple-negative breast cancer or a HER2-positive phenotype have a higher risk of LRR than patients with luminal tumours. Lowery et al. [56] reported a LRR rate of 7.1% for BCS and 9.0% for mastectomy at a median follow-up of 57 months for patients with HER2-positive breast cancer, these patients showing the highest risk of LRR. Keeping in mind that these data were collected before the era of trastuzumab and that all NACT was excluded, these rates may not apply to modern NACT regimens. All patients who had BCS underwent adjuvant RT, and 44% of those having a mastectomy received chest wall RT. Adjuvant chemotherapy was administered to 48% of all patients.

Young age is also a risk factor for increased risk of local recurrence. However, it seems that this is especially true for young patients without a pCR. In one study [57], of women who did not achieve a pCR, the LRR rate among those aged 35 years or less was significantly higher than that among women aged 36–50 years ($P = 0.024$). However, there was no age-related difference among women who achieved a pCR.

Is it possible that microscopic residual tumour is left behind when BCS is performed within new margins? It could be speculated that such resistant residual tumour could increase the overall risk of LRR. The main target of NACT is shifting from merely downstaging to monitoring tumour response and tailoring therapy and predicting clinical outcome. At the San Antonio Breast Cancer Symposium 2011, the German Breast Group presented data from a meta-analysis of seven prospective neoadjuvant trials with a total of 6377 patients. LRR rates were analysed according to initial tumour stage, intrinsic tumour subtype, type of surgery, pCR rate, and nodal status. At a median follow-up of 46.2 months, 485 patients had experienced LRR. LRR rates for BCS were significantly lower than those for mastectomy. Not surprisingly, the percentage of women undergoing BCS declined with increasing initial clinical tumour (cT) category (ranging from 77.7% for cT1 to 19.1% for cT4d), and LRR rate rose with increasing tumour size after NACT (from 4.7% for ypT0 to 31.2% for ypT4d). The LRR rate was higher among patients with non-invasive residual disease (9.9 vs. 3.7%). Comparing tumour subtypes, despite achieving a pCR, luminal B/HER2-positive tumours had a higher LRR rate (8.1%) than all other subtypes. Among patients who did not achieve a pCR, triple-negative and non-luminal-like HER2-positive tumours both displayed an extraordinary LRR rate of about 18%.

Weksberg et al. [58] investigated the prognostic outcome of salvage therapy in patients with local recurrence after NACT and BCS. Data were analysed retrospectively for 1589 patients, of whom 448 had undergone surgery after NACT. Among these, 2.6% of patients initially treated with BCS and 5.8% treated with NACT and subsequent BCS experienced LRR at a median follow-up of 91 months. Higher nuclear grade, higher tumour stage, and larger number of involved lymph nodes in the NACT group may account for the difference in LRR rate itself. No significant differences in DFS, OS, and locoregional control were detected in the two groups following salvage treatment for isolated LRR.

Therefore, resection within new margins after NACT is safe and should be offered to more patients, enabling translation of the increasing pCR rates into higher BCS rates and avoidance of unnecessary mastectomies.

28.1.6 Management of the Axilla After NACT

The use and timing of sentinel lymph node biopsy (SLNB) in patients who have undergone NACT has been the subject of considerable debate. Initial concerns regarding the feasibility and accuracy of SLNB following chemotherapy were centred on the potential for altered lymphatic drainage as a result of lymphatic tissue fibrosis or vessel blockage by tumour emboli, as well as the possibility that the effects of chemotherapy might not be uniform throughout the nodal basin. Opponents of SLNB after NACT also argued that knowledge of the axillary node status before NACT was necessary to identify optimal candidates for adjuvant radiotherapy. For women presenting with clinically node-negative disease, these concerns have largely been addressed, and SLNB after NACT is now accepted as standard care [59]. More recent controversy has surrounded the use of SLNB after chemotherapy in patients who present with clinically positive needle biopsy-proven nodal metastases.

28.1.6.1 Clinically Node-Negative Disease

Numerous studies, including the NSABP B-27 trial [60], a large single-institution series from the MDACC [61], and several meta-analyses [62, 63] have established that sentinel lymph node (SLN) identification rates and false-negative rates after NACT are comparable to those reported in patients with breast cancer who undergo upfront surgery. In the MDACC experience, SLN identification rates were 97.4% for women who underwent SNLB after NACT ($n = 575$) and 98.7% for patients treated with upfront surgery ($n = 3, 171$; $P = 0.017$), and false-negative rates were similar: 5.9% versus 4.1% ($P = 0.39$). After a median follow-up duration of 47 months, regional disease recurrence had occurred in 0.9% of the patients who underwent upfront surgery and SLNB compared with 1.2% in the NACT group—a statistically insignificant difference. This study also demonstrated that NACT could be used to downstage disease in the axilla in patients presenting with clinically node-negative T2 and T3 breast tumours, resulting in fewer axillary node dissections without compromising locoregional control: SLN-positive rates compared with upfront surgery were 20.5% versus 36.5% ($P < 0.0001$) and 30.4% versus 51.4% ($P = 0.04$) for women with T2 and T3 tumours, respectively. These data are consistent with those from NSABP B-18 [10], a randomized trial of preoperative versus postoperative chemotherapy, which showed that patients who received preoperative chemotherapy were more likely to have pathologically negative lymph nodes compared with those who underwent surgery first (58% vs. 42%; $P < 0.0001$), demonstrating that NACT can eradicate nonpalpable nodal disease in some patients.

Despite the proven ability of NACT to downstage disease in the axilla, the relative importance of pretreatment nodal stage versus postchemotherapy nodal stage on locoregional recurrence (LRR) risk and the need for adjuvant radiotherapy remain uncertain. Updated data from a combined analysis of NSABP B-18 and B-27 [64], trials of NACT in patients with operable breast cancer that did not allow regional nodal radiotherapy and/or radiotherapy to the chest wall (radiation treatment of the breast was performed in patients who underwent lumpectomy), have provided important information regarding predictors of LRR in this setting. In both trials [10, 60], approximately 70% of patients treated in the NACT

groups were clinically node negative before treatment. At 10 years of follow-up in 3,088 patients who received NACT in these trials, LRR events had occurred in 335 (10.9%) [65]; patient age, clinical tumour size, clinical nodal status before NACT, and pathological nodal status and breast tumour response after NACT were independent overall predictors of LRR. Importantly, among the clinically node-negative patients treated with lumpectomy and breast radiotherapy after NACT, rates of regional nodal recurrence were low (0.5–2.3%) and were not influenced by pathological node status nor pathological breast tumour response. Among clinically node-negative patients treated with NACT followed by mastectomy, regional nodal recurrence rates were also low, irrespective of tumour size (2.3–6.2%); however, rates of chest wall recurrence were greater in patients with clinically negative nodes but pathologically node-positive disease and were negatively correlated with breast tumour response.

Taken together, these data demonstrate that SLNB after NACT in patients with clinically node-negative disease is feasible and accurate and that NACT decreases the number of patients with a positive SLN, thereby sparing patients the morbidity of ALND, without compromising subsequent treatment recommendations or locoregional control. These findings also raise questions about current recommendations that all patients receiving NACT should undergo axillary ultrasonography with biopsy of abnormal nodes [59].

28.1.6.2 Clinically Node-Positive Disease

The success of SLNB after NACT in patients presenting with clinically node-negative disease, combined with increasing rates of pCR demonstrated in trials using modern chemotherapy regimens and targeted therapies, has led to increased interest in the use of SLNB after NACT in patients who present with clinically positive nodes. This issue is particularly relevant for patients with ER-negative and/or HER2-positive disease treated with preoperative anti-HER2 therapy, in whom pCR rates exceed 50% [66, 67]. Early evidence that this approach might be feasible came from the NSABP B-27 trial [60], which included patients with both clinically negative and positive nodes, although histological documentation of pathological nodal status was not required before NACT. After NACT, 428 of 2411 (18%) patients underwent attempted SLN identification and removal before the required ALND—23.8% of the 428 patients in whom SLN biopsy was attempted had clinically positive nodes before NACT. Among the 343 patients in whom both SLNB and ALND were performed successfully, the overall false-negative rate was 10.7% (15 of 140 node-positive patients had a negative SLNB), with no significant difference according to pretreatment nodal status (P = 0.51). Similarly, a report from a French prospective multicentre trial of SLNB after NACT found no significant difference in the false-negative rates between patients who were clinically node positive (n = 65) versus clinically node negative (n = 130) at presentation (15% vs. 9.4%; P = 0.66) [68]. These observations were not supported by smaller, single-institution case series of SLNB after NACT in patients for whom positive nodal status was documented with pretreatment biopsy [69]. The largest of these series, from the MDACC, included 150 patients with biopsy-proven nodal metastasis; 111 of these patients also underwent SLNB and ALND after NACT, and the SLN identification rate was 93% and the false-negative rate was 20.8%, leading to the conclusion that ALND remained the standard of care in this setting [70].

Three multicentre studies addressing the feasibility of SLN after NACT in patients with clinically node-positive disease have, however, challenged the conclusion that ALND is required for all clinically node-positive patients [71–73]. The Sentinel Neoadjuvant (SENTINA) trial [74], a four-arm prospective multicentre trial by the German Breast Group, included 1737 patients who all received at least six cycles of anthracycline-based NACT. All clinically node-negative patients had upfront SLNB; those who had pathologically negative SLNs had no further axillary node surgery (arm A; n = 662), and those who were SLN positive underwent a second SLNB and ALND after NACT (arm B; n = 360). Clinically node-positive patients (n = 715) underwent NACT; those who converted to clinically node-negative disease (as documented by physical examination and ultrasonography of the axilla) underwent SLNB and ALND (arm C; n = 592, pre-NACT nodal status confirmed in 149 [25%]), and the women who remained clinically node positive had ALND (arm D, n = 123). Re-operative SLNB (arm B) resulted in the lowest SLN identification rate (60.8%) and an exceedingly high false-negative rate (51.6%), clearly demonstrating that SLNB should not be performed both before and after chemotherapy. SLN identification rates were also lower than expected in arm C (80.1%) and were associated with a false-negative rate of 14.2%, although the false-negative rate was lower when three or more SLNs were removed (7.3%)—both end points were improved when SLN mapping was performed using the dual mapping technique (with radioisotope and blue dye).

The importance of SLNB technique in patients with needle biopsy-proven nodal involvement was also highlighted in the American College of Surgeons Oncology Group (ACOSOG) Z1071 trial [72], a phase II study that enrolled 756 women with T0–T4, biopsy-proven N1 or N2 disease; 663 patients had clinical N1 disease, 649 of whom completed NACT and subsequently underwent SLNB and ALND. Surgeons were encouraged to use the dual mapping technique for SLN identification and to remove at least two SLNs. The SLN identification rate was 92.9%, similar to the rate reported for SLNB after NACT in clinically node-negative patients and superior to those reported in the SENTINA trial; however, the overall false-negative rate of

12.6% was similar to the German Breast Group experience in arm C of the SENTINA study despite the fact that axillary lymph node response to NACT was not considered in selecting patients for SLNB. To be consistent with the accepted false-negative rate in patients presenting with clinically negative nodes, the prespecified criteria for success in the Z1071 trial were a false-negative rate of ≤10%; thus, the study did not meet this end point. However, as reported in the SENTINA trial, when three or more SLNs were removed, the false-negative rate was 9.1%, demonstrating that surgical technique is critical when considering SLNB in this setting and that routine imaging of the axilla post NACT might not be necessary. These findings in biopsy-proven clinically node-positive breast cancer have now also been reproduced in the smaller Sentinel Node Biopsy Following Neoadjuvant Chemotherapy (SN FNAC) study [71]. In this study, removal of one SLN was associated with a false-negative rate of 18.2%, and removal of more than two SLNs was associated with a false-negative rate of 4.9%.

The relationship between the number of SLNs removed and the false-negative rate of the procedure is not a new concept. Nearly all early prospective trials of SLN biopsy in patients with early-stage breast cancer documented the same effect: lower false-negative rates with increasing numbers of nodes removed [75–78]. However, one must also consider that the median number of SLNs removed in the SENTINA trial was 2 [71–73], as it was in NSABP B-32 and other large prospective trials of upfront SLN biopsy, suggesting that three or more SLNs cannot be identified in many patients. Indeed, in 2014, the AMAROS trial of radiotherapy versus surgery in patients with a positive SLN demonstrated that only 382 (27%) of the patients randomized had three or more SLNs identified in the setting of upfront SLN biopsy [79]. Similarly, among 641 clinically N1 patients who converted to clinically node-negative disease in the Z1071 trial and among 592 patients in arm C of the SENTINA trial, 57% and 34% of patients, respectively, had three or more SLNs removed [55, 56]. Therefore, substantial numbers of patients who convert from clinically node-positive to clinically node-negative disease after NACT are unlikely to have three or more SLNs identified after NACT and, as demonstrated in all three studies to date [71–73], omitting ALND in these patients might be associated with an unacceptably high false-negative rate. Of note, no data support random sampling of nearby axillary lymph nodes to replace SLN mapping and identification of at least three nodes following NACT; thus, surgeons will need to monitor their own performance in this regard, and until data on the clinical significance of leaving axillary lymph node disease behind after NACT are available, patients should be informed that ALND could be indicated if SLN mapping is unsatisfactory.

28.1.7 Significance of Extent of Residual Nodal Disease

The relevance of the distinction between post-NACT isolated tumour cells (ypN0i+, <0.2 mm), micrometastatic disease (ypN1mi, 0.2–2.0 mm), and macrometastatic disease (ypN+, >2.0 mm) in SLNs is another factor that remains unclear. In patients who have not received NACT, the size of the SLN metastasis is correlated with the likelihood of additional nodal disease, and low-volume SLN disease does not always mandate completion axillary node dissection [74, 80, 81]. By contrast, according to the 7th Edition of the American Joint Committee on Cancer (AJCC) staging system [82], patients treated with NACT who are ypN0i+ or ypN1mi at SLNB are considered to have residual nodal disease, and ALND remains the standard of care. In the SN FNAC study [71], SLN metastases of any size were considered positive, and no correlation between the size of the SLN metastases and the rate of positive non-SLNs was found; however, if ypN0i+ SLN disease was considered SLN negative, the false-negative rate of the procedure would have increased from 8.4% to 13.3%. The Z1071 trial investigators also reported on a subset of 470 patients who had at least two SLNs identified and for whom pathological information regarding the presence of micrometastatic disease in the SLN, identified by immunohistochemistry or haematoxylin and eosin staining, was available [83]. When micrometastatic disease was included in the definition of residual nodal disease after NACT, the pCR rate decreased from 36.0 to 33.8% and the false-negative rate decreased from 11.3 to 8.7%. As ALND was performed in all patients in the Z1071, SENTINA, and SN FNAC trials, these studies provide no information regarding the clinical significance of leaving disease behind after NACT. An important consideration is that the potentially chemoresistant disease that persists after NACT might not be associated with the same outcomes demonstrated in the NSABP B-32 and Z0011 trials of upfront surgery, in which both micrometastatic and macrometastatic diseases remaining in the axilla did not compromise locoregional control or survival [74, 80, 81].

Failure to identify residual nodal disease after NACT might also have important implications for decisions regarding radiotherapy. In the updated analysis of NSABP B-18 and B-27 trials, clinically node-positive patients who received NACT and remained pathologically node positive experienced the highest rates of LRR following ALND, ranging from 15 to 22% after lumpectomy and radiotherapy of the breast and from 17 to 22% after mastectomy [65], implying that both groups should be considered for adjuvant radiotherapy: regional nodal radiotherapy in addition to breast radiotherapy for those who undergo BCS and chest wall radiotherapy for those treated with mastectomy. The question of whether completion ALND can be omitted in

favour of axillary radiotherapy in patients with positive SLNs after NACT is being addressed in the ongoing phase III A011202 trial, conducted by the Alliance for Clinical Trials in Oncology [84]. By contrast, in the NSABP trials, patients with clinically node-positive disease who had a pCR at mastectomy (ypT0N0) experienced excellent locoregional control (0% LRR at 10 years) [65], suggesting that response to NACT can be used to select patients who do not need post-mastectomy radiotherapy. This concept is currently being tested in the NSABP B-51/Radiation Therapy Oncology Group (RTOG) 1304 (NRG 9353) trial, a phase III randomized trial of more versus less radiotherapy in women with clinically node-positive breast cancer who become pathologically node negative after NACT [85]. If additional radiotherapy in this setting does not affect the risk of LRR, NACT could become the new standard to facilitate a tailored approach to locoregional therapy in patients with operable node-positive breast cancer. For patients who remain node positive following NACT, accurate detection of residual disease is equally important, as these patients could potentially have some level of resistance to systemic therapy and, therefore, might be candidates for future trials of novel agents.

28.1.8 Conclusions

The use of NACT for the treatment of patients with breast cancer reduces the need for mastectomy and axillary dissection, decreasing the morbidity of surgery, without increasing the risk of LRR. Hormone receptor status and HER2 status can be used to select the patients most likely to experience a pCR with NACT. However, increasing rates of pCR with contemporary therapeutic agents (such as HER2-targeted therapies) have not been accompanied by a parallel increase in rates of BCS. Future trials of NACT should examine whether this pattern reflects an inability to accurately assess the extent of residual disease preoperatively or surgeon or patient preference. Improved understanding of the optimal negative margin width for BCS after NACT and the adoption of *targeted breast surgery* could also increase rates of BCS.

In patients with breast cancer who are clinically node negative at presentation, NACT often results in downstaging of axillary disease; SLNB after NACT provides an accurate indication of axillary lymph node involvement in this setting and can, therefore, guide the use of completion ALND, and this approach is associated with a low rate of LRR. The management of patients who are clinically node positive at presentation is in evolution—recent trials suggest SLNB is accurate if three or more sentinel nodes are obtained, but outcome data from patients treated with SLNB alone in this setting are lacking. Although false-negative rates for SLNB after upfront surgery of 10% are associated with a risk of LRR of <1%, whether this holds true for the potentially drug-resistant disease left behind after NACT remains unclear.

One of the great opportunities provided by NACT is the ability to tailor the extent of locoregional therapy based on the preoperative treatment response. The appropriate therapy will probably vary not only by response but also by ER, PR, and HER2 status; the failure to achieve pCR in patients with tumours that lack ER, PR, and HER2 could be indicative of a much higher risk of LRR than in patients with ER-positive tumours who receive at least 5 years of endocrine therapy or patients with HER2-positive disease who are treated with complete anti-HER2 therapy after NACT. Ongoing clinical trials will help to address these issues and to define the relative importance of pretreatment and posttreatment stage on the risk of locoregional recurrence.

The concept of *targeted breast surgery,* including five principles for breast-conserving surgery after NACT, is a recommended concept of surgical techniques optimizing local control and aesthetic outcome for patients—initially developed for primary BCS. Targeted breast surgery is a further development of the classical concept of oncoplastic breast surgery with wide local resection based on the new minimal resection margin width definition (*no ink on tumour*).

References

1. Bozzetti F, Saccozzi R, De Lena M, Salvadori B (1981) Inflammatory cancer of the breast: analysis of 114 cases. J Surg Oncol 18:355–361
2. Haagensen CD, Stout AP (1951) Carcinoma of the breast. III. Results of treatment, 1935–1942. Ann Surg 134:151–172
3. Bonadonna G et al (1976) Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 294:405–410
4. Fisher B et al (1975) 1-phenylalanine mustard (L-PAM) in the management of primary breast cancer. A report of early findings. N Engl J Med 292:117–122
5. Buzdar AU, Montague ED, Barker JL, Hortobagyi GN, Blumenschein GR (1981) Management of inflammatory carcinoma of breast with combined modality approach—an update. Cancer 47:2537–2542
6. De Lena M, Zucali R, Viganotti G, Valagussa P, Bonadonna G (1978) Combined chemotherapy–radiotherapy approach in locally advanced (T3b–T4) breast cancer. Cancer Chemother Pharmacol 1:53–59
7. Hortobagyi GN et al (1988) Management of stage III primary breast cancer with primary chemotherapy, surgery, and radiation therapy. Cancer 62:2507–2516
8. Mauri D, Pavlidis N, Ioannidis JP (2005) Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. J Natl Cancer Inst 97:188–194
9. Mieog JS, van der Hage JA, van de Velde CJ (2007) Neoadjuvant chemotherapy for operable breast cancer. Br J Surg 94:1189–1200
10. Fisher B et al (1997) Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol 15:2483–2493

11. Cortazar P et al (2014) Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 384:164–172
12. Prowell TM, Pazdur R (2012) Pathological complete response and accelerated drug approval in early breast cancer. N Engl J Med 366:2438–2441
13. van der Hage JA et al (2001) Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol 19:4224–4237
14. Bear HD et al (2003) 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 21:4165–4174
15. Baselga J et al (2012) Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. Lancet 379:633–640
16. Katz SJ et al (2005) Patient involvement in surgery treatment decisions for breast cancer. J Clin Oncol 23:5526–5533
17. Rouzier R et al (2005) Breast cancer molecular subtypes respond differently to preoperative chemotherapy. Clin Cancer Res 11:5678–5685
18. Gianni L et al (2005) Gene expression profiles in paraffin-embedded core biopsy tissue predict response to chemotherapy in women with locally advanced breast cancer. J Clin Oncol 23:7265–7277
19. Petrelli F, Barni S (2013) 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 142:227–235
20. Lips EH et al (2012) Lobular histology and response to neoadjuvant chemotherapy in invasive breast cancer. Breast Cancer Res Treat 136:35–43
21. Ataseven B et al (2015) Impact of multifocal or multicentric disease on surgery and locoregional, distant and overall survival of 6,134 breast cancer patients treated with neoadjuvant chemotherapy. Ann Surg Oncol 22:1118–1127
22. Boughey JC et al (2014) Tumor biology correlates with rates of breast-conserving surgery and pathologic complete response after neoadjuvant chemotherapy for breast cancer: findings from the ACOSOG Z1071 (Alliance) prospective multicenter clinical trial. Ann Surg 260:608–614
23. Hylton NM et al (2012) Locally advanced breast cancer: MR imaging for prediction of response to neoadjuvant chemotherapy—results from ACRIN 6657/I-SPY TRIAL. Radiology 263:663–672
24. Marinovich ML et al (2013) Meta-analysis of magnetic resonance imaging in detecting residual breast cancer after neoadjuvant therapy. J Natl Cancer Inst 105:321–333
25. Rosen EL et al (2003) Accuracy of MRI in the detection of residual breast cancer after neoadjuvant chemotherapy. Am J Roentgenol 181:1275–1282
26. Turnbull LW (2009) Dynamic contrast-enhanced MRI in the diagnosis and management of breast cancer. NMR Biomed 22:28–39
27. Yeh E et al (2005) Prospective comparison of mammography, sonography, and MRI in patients undergoing neoadjuvant chemotherapy for palpable breast cancer. Am J Roentgenol 184:868–877
28. Chen JH et al (2011) Breast cancer: evaluation of response to neoadjuvant chemotherapy with 3.0-T MR imaging. Radiology 261:735–743
29. De Los Santos JF et al (2013) Magnetic resonance imaging as a predictor of pathologic response in patients treated with neoadjuvant systemic treatment for operable breast cancer. Translational Breast Cancer Research Consortium trial 017. Cancer 119: 1776–1783
30. Straver ME et al (2010) MRI-model to guide the surgical treatment in breast cancer patients after neoadjuvant chemotherapy. Ann Surg 251:701–707
31. Charehbili A et al (2014) Accuracy of MRI for treatment response assessment after taxane- and anthracycline-based neoadjuvant chemotherapy in HER2-negative breast cancer. Eur J Surg Oncol 40:1216–1221
32. Weiss A et al (2014) Calcifications on mammogram do not correlate with tumor size after neoadjuvant chemotherapy. Ann Surg Oncol 21:3310–3316
33. Boughey JC et al (2006) 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 244:464–470
34. Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B (2001) Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. J Natl Cancer Inst Monogr 2001:96–102
35. Chen AM et al (2004) Breast conservation after neoadjuvant chemotherapy: the MD Anderson cancer center experience. J Clin Oncol 22:2303–2312
36. Clarke M, Collings R, Darby S et al (2005) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 366:2087–2106
37. Moran MS, Schnitt SJ, Giuliano AE et al (2014) SSO-ASTRO consensus guideline on margins for breast-conserving surgery with whole breast irradiation in stage I and II invasive breast cancer. Ann Surg Oncol 21:704–716
38. Houssami N, Macaskill P, Marinovich ML, Morrow M (2014) The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. Ann Surg Oncol 21(3):717–730
39. Rezai M, Veronesi U (2007) Oncoplastic principles in breast surgery. Breast Care 2:277–278
40. Kraemer S, Darsow M, Kuemmel S, Kimmig R, Rezai M (2008) Breast-conserving treatment of breast cancer. Gyn Obstet Rev 48:56–62
41. Kraemer S, Malter W (2014) Relevance of the resection margin in breast cancer surgery. Gynäkologe 47:514–520
42. Rezai M, Kraemer S, Kimmig R, Kern P (2015) Breast conservative surgery and local recurrence. Breast 24:100–107
43. Rezai M (2012) Targeted breast surgery. In Duesseldorf Breast Cancer Conference (DBCC)
44. Kraemer S, Malter W, Kirn V, Rogee K, Richters L, Mallmann P et al (2014) Targeted oncoplastic breast surgery. Anticancer Res 34:6011–6013
45. Decker MR, Greenblatt DY, Havlena J, Wilke LG, Greenberg CC, Neuman HB (2012) Impact of neoadjuvant chemotherapy on wound complications after breast surgery. Surgery 152:382–388
46. Garvey EM, Gray RJ, Wasif N, Casey WJ, Rebecca AM, Kreymerman P et al (2013) Neoadjuvant therapy and breast cancer surgery: a closer look at postoperative complications. Am J Surg 206:894–898
47. Schaverien MV, Munnoch DA (2013) Effect of neoadjuvant chemotherapy on outcomes of immediate free autologous breast reconstruction. Eur J Surg Oncol 39:430–436
48. Warren Peled A, Itakura K, Foster RD, Hamolsky D, Tanaka J, Ewing C et al (2010) Impact of chemotherapy on postoperative complications after mastectomy and immediate breast reconstruction. Arch Surg 145:880–885
49. Zweifel-Schlatter M, Darhouse N, Roblin P, Ross D, Zweifel M, Farhadi J (2010) Immediate microvascular breast reconstruction after neoadjuvant chemotherapy: complication rates and effect on start of adjuvant treatment. Ann Surg Oncol 17:2945–2950
50. Gordon CR, Rojavin Y, Patel M, Zins JE, Grana G, Kann B et al (2009) A review on bevacizumab and surgical wound healing: an important warning to all surgeons. Ann Plast Surg 62:707–709
51. Eidtmann H, Kittel K, Rezai M, Tesch H, Ulmer HU, Stirnberg S et al (2012) Surgical complications from the GeparQuinto trial

of patients receiving preoperative bevacizumab. Cancer Res 71(Suppl 24):P1-14-05
52. Gerber B, von Minckwitz G, Eidtmann H, Rezai M, Fasching PA, Tesch H et al (2014) Surgical outcome after neoadjuvant chemotherapy and bevazizumab: results from the GeparQuinto study (GBG 44). Ann Surg Oncol 21(8):2517–2524
53. Golshan M, Garber JE, Gelman R, Tung N, Smith BL, Troyan S et al (2011) Does neoadjuvant bevacizumab increase surgical complications in breast surgery? Ann Surg Oncol 18:733–737
54. Kansal KJ, Dominici LS, Tolaney SM, Isakoff SJ, Smith BL, Jiang W et al (2013) Neoadjuvant bevacizumab: surgical complications of mastectomy with and without reconstruction. Breast Cancer Res Treat 141:255–259
55. Mauri D, Palvidis N, Ioannidis JP (2005) Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. J Natl Cancer Inst 97:188–194
56. Lowery AJ, Kell MR, Glynn RW, Kerin MJ, Sweeney KJ (2012) Locoregional recurrence after breast cancer surgery: a systematic review by receptor phenotype. Breast Cancer Res Treat 133: 831–841
57. Loibl S, Jackisch C, Gade S, Untch M, Paepke S, Kuemmel S et al (2012) Neoadjuvant chemotherapy in the very young 35 years of age or younger. Cancer Res 72(Suppl):S3–S1
58. Weksberg DC, Allen PK, Hoffman KE, Litton JK, Strom EA, Shah RR et al (2013) Outcomes and predictive factors for salvage therapy after local–regional recurrence following neoadjuvant chemotherapy and breast conserving therapy. Ann Surg Oncol 20:3430–3437
59. Gradishar WJ et al (2014) Breast cancer version 3.2014. J Natl Compr Canc Netw 12:542–590
60. Mamounas EP et al (2005) Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 23:2694–2702
61. Hunt KK et al (2009) Sentinel lymph node surgery after neoadjuvant chemotherapy is accurate and reduces the need for axillary dissection in breast cancer patients. Ann Surg 250:558–566
62. van Deurzen CH et al (2009) Accuracy of sentinel node biopsy after neoadjuvant chemotherapy in breast cancer patients: a systematic review. Eur J Cancer 45:3124–3130
63. Xing Y et al (2006) Meta-analysis of sentinel lymph node biopsy after preoperative chemotherapy in patients with breast cancer. Br J Surg 93:539–546
64. Tafra L, Verbanac KM, Lannin DR (2001) Preoperative chemotherapy and sentinel lymphadenectomy for breast cancer. Am J Surg 182:312–315
65. Mamounas EP et al (2012) Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. J Clin Oncol 30:3960–3966
66. Dominici LS et al (2010) Cytologically proven axillary lymph node metastases are eradicated in patients receiving preoperative chemotherapy with concurrent trastuzumab for HER2-positive breast cancer. Cancer 116:2884–2889
67. Hennessy BT et al (2005) Outcome after pathologic complete eradication of cytologically proven breast cancer axillary node metastases following primary chemotherapy. J Clin Oncol 23:9304–9311
68. Classe JM et al (2009) Sentinel lymph node biopsy after neoadjuvant chemotherapy for advanced breast cancer: results of Ganglion Sentinelle et Chimiotherapie Neoadjuvante, a French prospective multicentric study. J Clin Oncol 27:726–732
69. Shen J et al (2007) Feasibility and accuracy of sentinel lymph node biopsy after preoperative chemotherapy in breast cancer patients with documented axillary metastases. Cancer 109:1255–1263
70. Alvarado R et al (2012) The role for sentinel lymph node dissection after neoadjuvant chemotherapy in patients who present with node-positive breast cancer. Ann Surg Oncol 19:3177–3184
71. Boileau JF et al (2015) Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. J Clin Oncol 33:258–264
72. Boughey JC et al (2013) Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA 310: 1455–1461
73. Kuehn T et al (2013) Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol 14:609–618
74. Krag DN et al (2010) Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol 11:927–933
75. Goyal A, Newcombe RG, Chhabra A, Mansel RE (2006) Factors affecting failed localisation and false-negative rates of sentinel node biopsy in breast cancer—results of the ALMANAC validation phase. Breast Cancer Res Treat 99:203–208
76. McMasters KM et al (2000) Sentinel lymph node biopsy for breast cancer: a suitable alternative to routine axillary dissection in multi-institutional practice when optimal technique is used. J Clin Oncol 18:2560–2566
77. Krag DN et al (2007) Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial. Lancet Oncol 8:881–888
78. Tafra L et al (2001) Multicenter trial of sentinel node biopsy for breast cancer using both technetium sulfur colloid and isosulfan blue dye. Ann Surg 233:51–59
79. Donker M et al (2014) Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981–22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 15:1303–1310
80. Giuliano AE et al (2011) Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 305:569–575
81. Giuliano AE et al (2010) Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg* 252:426–432
82. Edge S et al (2010) AJCC cancer staging manual, 7th edn. Springer, New York
83. Boughey JC et al (2014) Methods impacting the false negative rate of sentinel lymph node surgery in patients presenting with node positive breast cancer (T0–T4, N1–2) who receive neoadjuvant chemotherapy: results from a prospective trial—ACOSOG Z1071 (Alliance) [Poster No. P2-01-02]. Presented at the 2014 San Antonio Breast Cancer Symposium, 9–13 December 2014, San Antonio
84. NCI Community Oncology Research Program (2014) CTSU alliance A011202: a randomized phase III trial evaluating the role of axillary lymph node dissection in breast cancer patients (CT1–3 N1) who have positive sentinel lymph node disease after neoadjuvant chemotherapy [online]
85. Mamounas EP et al (2014) NSABP B-51/RTOG 1304: randomized phase III clinical trial evaluating the role of postmastectomy chest wall and regional nodal XRT (CWRNRT) and post-lumpectomy RNRT in patients (pts) with documented positive axillary (Ax) nodes before neoadjuvant chemotherapy (NC) who convert to pathologically negative Ax nodes after NC [abstract]. J Clin Oncol 32:TPS1141