Review Article

Breast surgery after neoadjuvant systemic therapy

Kate R. Pawloski, Andrea V. Barrio

Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

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Correspondence to: Andrea V. Barrio, MD. Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 300 East 66th Street, New York, NY 10065, USA. Email: barrioa@mskcc.org.

Abstract: For patients with operable breast cancer, neoadjuvant systemic therapy (NST) can be used to downstage the primary tumor in the breast and to facilitate breast-conserving surgery (BCS) in patients with large tumors who desire breast conservation. Rates of breast pathologic complete response (pCR) after neoadjuvant chemotherapy (NAC) are highest in patients with triple-negative and human epidermal growth factor receptor 2 (HER2) positive ($HER2^+$) disease; however, achieving pCR is not necessary for successful downstaging and avoidance of mastectomy, and rates of conversion to BCS-eligibility are high across all receptor subtypes. Neoadjuvant endocrine therapy (NET) can be used instead of NAC in postmenopausal patients with hormone receptor positive (HR^+)/HER2 negative ($HER2^-$) breast cancer to downstage the breast, particularly when the patient has no clear indication for systemic chemotherapy, but desires breast conservation. In patients treated with NET, rates of conversion to BCS-eligibility are similar to rates observed with NAC. The oncologic safety of BCS after NAC and NET has been established in prospective trials, and local recurrence (LR) rates are acceptably low provided negative surgical margins can be obtained. Investigation is under way to determine the feasibility and safety of omitting breast surgery in patients with responsive subtypes who have no residual invasive or *in situ* disease identified on post-treatment tumor bed biopsies; however, the significant risk of missing residual disease—which may impact selection of adjuvant systemic therapy—may preclude future adoption of this approach.

Keywords: Neoadjuvant chemotherapy (NAC); neoadjuvant endocrine therapy (NET); breast-conserving surgery (BCS); downstaging

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Introduction

Neoadjuvant systemic therapy (NST) has historically been used in women with inoperable breast cancer to decrease tumor size and improve the feasibility of surgical resection (1,2). In the modern era, NST is increasingly utilized in patients with operable disease to downstage the primary tumor and increase eligibility for breast-conserving surgery (BCS). Ideally suited patients for downstaging are those with large unifocal tumors, in whom a decrease in tumor volume is sufficient to avoid mastectomy. Reducing the extent of breast surgery is an important priority for many patients, particularly older patients who are at increased risk of functional decline after mastectomy (3). Options for surgical downstaging include neoadjuvant chemotherapy (NAC) and neoadjuvant endocrine therapy (NET), although utilization of NET remains limited (4). Initial trials focused on the overall benefit of NAC for all early-stage breast cancer patients, as understanding of tumor biology, receptor status, and response to therapy was limited, and as systemic therapy regimens across all receptor subtypes was uniform (5-7). Subsequent understanding of different molecular subtypes of breast cancer resulted in tailoring of systemic

therapies in the adjuvant and neoadjuvant setting, as well as in the introduction of targeted therapies. In addition, the emergence of genomic assays for patients with hormone receptor positive (HR^+)/human epidermal growth factor receptor 2 negative ($HER2^-$) breast cancer has allowed for discrimination of "low-risk" subsets that do not benefit from chemotherapy (8,9), rendering consideration of NAC in these subsets obsolete. In this review article, we will address the evolution of response rates in the breast with NAC over time, assess conversion rates to BCS with NAC and NET in the modern era with a focus on patient selection based on response, report the oncologic safety of downstaging, address ongoing areas of controversy in patients who downstage, and discuss whether omission of breast surgery after NST is an important research priority.

Rates of BCS with NAC in the pre-trastuzumab era

The initial randomized trials comparing NAC to adjuvant chemotherapy were performed to assess whether a survival benefit was seen with the introduction of early systemic therapy. A patient-level meta-analysis of 10 randomized trials conducted between 1983 and 2002 comparing NAC to adjuvant chemotherapy showed no difference in distant recurrence, breast cancer mortality, or death from any cause between patients receiving NAC compared to adjuvant chemotherapy. However, patients receiving NAC had a significantly higher rate of BCS (65%) compared to those who had upfront surgery followed by adjuvant chemotherapy (49%) (5), demonstrating a potential surgical advantage to NAC. Notably, BCS-eligibility at presentation for patients included in the meta-analysis was unknown, and therefore the benefit of NAC for downstaging to BCS was likely underestimated from these trials. The European Organization for Research and Treatment of Cancer (EORTC) 10902 and National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trials specifically examined BCS conversion rates with use of non-taxane-based NAC regimens in patients with operable disease felt to require mastectomy, and demonstrated conversion rates of 23–27% (6,7). As these studies were conducted in the pre-trastuzumab era with limited knowledge of receptor status and somewhat older chemotherapy regimens, they underestimate BCS conversion rates in patients receiving modern systemic chemotherapy regimens.

Rates of BCS and avoidance of mastectomy after NAC in the modern era

Over the years, the understanding that tumor biology and receptor subtype result in a differential tumor response to NAC (10,11) has allowed for identification of tumor subtypes that will benefit most from NAC for downstaging in the breast. Specifically, the American College of Surgeons Oncology Group (ACOSOG) Z1071 trial, a single-arm, prospective multicenter trial designed to assess the false-negative rate (FNR) of sentinel lymph node biopsy (SLNB) in clinically node-positive patients after NAC, retrospectively assessed rates of breast pathologic complete response (pCR) and BCS by receptor subtype. Among 694 eligible patients, rates of breast pCR were higher in patients with triple-negative and HER2 positive ($HER2^+$) breast cancer (48% and 50%, respectively), compared with $HR^+/HER2^-$ cancer (16%, $P<0.0001$). Rates of BCS were similarly higher in patients with triple-negative and $HER2^+$ cancers (47% and 43%, respectively) than in $HR^+/HER2^-$ cancer (35%, $P=0.019$) (10), highlighting the impact of receptor subtype on response and surgical procedure. Importantly, BCS-eligibility at presentation and at the completion of NAC was unknown in this retrospective analysis, limiting understanding of receptor subtype on downstaging. More recent phase III randomized neoadjuvant trials, including the Cancer and Leukemia Group B (CALGB) 40601, CALGB 40603, and BrighTNess trials specifically examined conversion rates from BCS-ineligible to BCS-eligible in patients with triple-negative and $HER2^+$ breast cancer (*Table 1*) (12-14). Collectively, these trials showed rates of conversion to BCS-eligibility of 42–53% with the use of NAC—significantly higher than the rates of conversion reported in the historic NAC trials. Because these studies included patients with clinical T4 and multicentric disease at presentation, factors traditionally considered ineligible for surgical downstaging, rates of conversion to BCS in patients with a large tumor size relative to breast size are unknown from these studies.

A single-institution study from Memorial Sloan Kettering Cancer Center (MSKCC; New York, NY, USA) specifically examined rates of conversion to BCS in patients considered BCS-ineligible because of a large tumor size relative to breast size (15). From November 2013 to March 2019, 1,328 consecutively treated patients with stage I–III breast cancer who received NAC followed by surgery were identified.

Table 1 Rates of conversion to BCS-eligibility in HER2$^+$ and triple-negative breast cancer patients receiving modern NAC regimens

Study	N	Receptor status	Conversion to BCS-eligibility	BCS attempted	BCS successful
CALGB 40601 (12)	171	HER2$^+$	43%	67%	80%
CALGB 40603 (13)	185	Triple-negative	42%	68%	91%
BrighTNess (14)	141	Triple-negative	53%	56%	–

BCS, breast-conserving surgery; HER2$^+$, human epidermal growth factor receptor 2 positive; NAC, neoadjuvant chemotherapy; CALGB, Cancer and Leukemia Group B.

Table 2 Randomized trials of NAC and NET comparing clinical response rates and BCS rates

Study	N	Clinical response rate			BCS rate		
		NET	NAC	P value	NET	NAC	P value
Semiglazov (16)	239	65%	64%	>0.5	33%	24%	0.058
GEICAM/2006-03 (17)	95	48%	66%	0.075	56%	47%	0.24
NEOCENT (18)	44	91%	77%	0.32	68%	55%	NR

NAC, neoadjuvant chemotherapy; NET, neoadjuvant endocrine therapy; BCS, breast-conserving surgery; NR, not reported.

The treating surgeon prospectively assessed BCS-eligibility pre- and post-NAC. Overall, 982 patients were considered BCS-ineligible; patients with multicentric or cT4 disease, or other contraindications to downstaging, were excluded. Overall, 600 patients were BCS-ineligible because of a large tumor size relative to breast size and comprised the study cohort. Of the 600 patients, 75% (n=450) became BCS-eligible with the use of NAC, with the highest rates of conversion in patients with triple-negative (84%) and HER2$^+$ breast cancer (79%) compared with HR$^+$/HER2$^-$ breast cancer (62%, P<0.001). Of the 450 BCS-eligible patients, 308 (68%) chose BCS, which was successful in 93% (n=285) of patients. Overall, 48% of patients with a large tumor size avoided mastectomy with the use of NAC, providing evidence of a significant clinical benefit to NAC for downstaging across all receptor subtypes. A significant contributor to the success of NAC in the breast is that, unlike the axilla in which a nodal pCR is required to avoid axillary lymph node dissection (ALND), a breast pCR is not required for avoidance of mastectomy. This is highlighted by the observation that rates of breast pCR were lower (28%) than rates of conversion to BCS-eligibility (75%), and that 70% of patients who did not achieve breast pCR became BCS-eligible with the use of NAC (15).

HR$^+$/HER2$^-$ breast cancer: NAC *vs.* NET

While the MSKCC study demonstrated a BCS-conversion rate of >60% in patients with HR$^+$/HER2$^-$ breast cancer selected for NAC, the emergence of genomic assays to inform prognosis and predict chemotherapy benefit has allowed for identification of "low-risk" subsets that do not benefit from systemic chemotherapy in the adjuvant or neoadjuvant setting. The Trial Assessing Individual Options for Treatment (TAILORx) and A Clinical Trial RX for Positive Node, Endocrine Responsive Breast Cancer (RxPONDER) trials demonstrated no additional invasive disease-free survival (DFS) benefit with chemotherapy *vs.* endocrine therapy alone for node-negative and postmenopausal node-positive patients with 1–3 positive axillary nodes and a recurrence score (RS) ≤25 (8,9). For this population of patients who derive no known oncologic benefit from systemic chemotherapy, NAC would not be indicated solely for the purpose of downstaging the breast. NET is a less-toxic alternative that can also be used to facilitate breast conservation, although its use remains limited in clinical practice (4). Three randomized trials have compared clinical response rates and BCS rates in patients with HR$^+$/HER2$^-$ breast cancer treated with NAC *vs.* NET, demonstrating similar clinical response rates and BCS rates between the two treatment arms (*Table 2*) (16-18). These studies were included in a study-level meta-analysis of 20 randomized trials and 3,490 patients; in the three randomized trials comparing NAC and NET, there was no difference in clinical response rate [odds ratio (OR), 1.08; 95% confidence interval (CI): 0.5–2.35; P=0.85] but there

Table 3 Rates of conversion to BCS with neoadjuvant AIs *vs.* tamoxifen in randomized trials

Study	Mastectomy planned	Post-treatment BCS rate		P value
		AI	Tamoxifen	
P024 (22)	337	45%	35%	0.022
IMPACT (23)	124	46%	22%	0.03
PROACT (24)	314	43%	31%	0.04

BCS, breast-conserving surgery; AI, aromatase inhibitor.

was a trend toward higher BCS rates (OR, 0.65; 95% CI: 0.41–1.03; P=0.07), slightly favoring neoadjuvant endocrine monotherapy (19).

HR$^+$/HER2$^-$ breast cancer: BCS conversion rates with NET

Evidence suggests that rates of conversion to BCS with NET among patients with HR$^+$/HER2$^-$ breast cancer deemed BCS-ineligible at presentation are similar to rates of conversion observed with NAC. ACOSOG Z1031 was a randomized phase II neoadjuvant trial of patients with stage II–III HR$^+$/HER2$^-$ cancer comparing clinical response to 16–18 weeks of letrozole *vs.* anastrozole *vs.* exemestane. In the study, 159 patients were considered "mastectomy candidates" at presentation; overall, 51% became BCS-eligible with NET (20). A retrospective study from MSKCC specifically examined downstaging rates with NET in patients considered BCS-ineligible because of a large tumor size relative to breast size. In this cohort of 47 patients treated with physician choice NET for a median duration of 4.9 months, a striking 77% of patients converted to BCS-eligibility, higher than the conversion rate with NAC (21), demonstrating the clinical efficacy of NET for downstaging in patients with HR$^+$/HER2$^-$ breast cancer.

Preferred endocrine therapy and optimal duration for surgical downstaging in the breast

Three randomized trials and a pooled analysis of seven trials comparing aromatase inhibitors (AIs) and tamoxifen have demonstrated superior efficacy of AIs compared to tamoxifen for downstaging the breast in postmenopausal HR$^+$ patients (19,22-24). The P024, IMPACT, and ProACT trials randomized postmenopausal women with HR$^+$/HER2$^-$ breast cancer in whom mastectomy was planned, to neoadjuvant AIs *vs.* tamoxifen and demonstrated a significantly higher conversion rate to BCS with AIs across all three studies (43–46%) compared with tamoxifen (22–35%) (*Table 3*) (22-24)—supporting the use of AIs as the preferred NET for downstaging. The optimal length of treatment with NET to facilitate BCS is not standardized; however, most studies have shown that longer duration of NET is associated with higher rates of conversion to BCS (4,25-27). Early NET studies employed 3–4 months of preoperative therapy that mirrored the standard duration for NAC (22,23,28). Results of prospective trials from the United Kingdom and the Netherlands indicate that treatment for a minimum of 6 months correlates with a BCS rate of approximately 70%, and that objective response rates can increase for up to 12 months of treatment (25,27). A population-based study using the National Cancer Database (NCDB) evaluated real-world utilization of NET in patients with stage II–III HR$^+$ breast cancer. In the 6,584 patients who were treated with NET, there was a dose-response relationship between duration of endocrine therapy and odds of BCS, with longer duration of therapy associated with higher odds of BCS [OR, 0.69 (95% CI: 0.62–0.77) for 1–3 months; OR, 1.59 (95% CI: 1.46–1.73) for 3–6 months; OR, 1.85 (95% CI: 1.67–2.05) for 6–12 months; OR, 2.37 (95% CI: 1.86–3.02) for 12–24 months of therapy]. Importantly, while the majority of patients exhibited a clinical response to NET, approximately 20% of patients had disease progression (4), emphasizing the importance of close clinical follow-up to assess response. In patients who exhibit progression, early identification is critical to enable prompt intervention with either surgical intervention or modification of systemic therapy.

Oncologic safety of BCS after NET

Until recently, there have been limited data on the oncologic safety of NET, particularly among patients who downstage from mastectomy to BCS. The ACOSOG Z1031 randomized phase II neoadjuvant trial, which assessed clinical response to letrozole *vs.* anastrozole *vs.*

exemestane in patients with cT2–4N0–3 HR$^+$ invasive breast cancer, published long-term locoregional recurrence data in patients treated with NET (29). Overall, 509 patients completed 16–18 weeks of AIs followed by surgery and were included in the analysis; 342 (67%) had BCS, of whom 114 (22%) were initially mastectomy candidates and downstaged to BCS. There were 12 locoregional recurrence events [seven local recurrence (LR), four regional recurrence, and one regional recurrence concurrent with a second primary cancer], with only two events occurring in patients who downstaged. The 5-year locoregional recurrence rate was 1.53% (95% CI: 0.7–3.0%), supporting the safety of BCS after NET.

Oncologic safety of BCS after NAC

For patients receiving NAC, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) patient-level meta-analysis raised concerns regarding the oncologic safety of BCS after NAC, as the meta-analysis demonstrated a significant 5.5% increase in LR in patients receiving NAC compared to upfront surgery [15-year LR rate 21.4% (NAC) *vs.* 15.9% (upfront surgery), P=0.0001] (5). This difference in LR was not solely attributed to the trials in which surgery was not performed after NAC. When including only the eight trials in which surgery was commonly performed after NAC, there remained a significant 3.2% increase in LR after NAC [10-year LR rate 15.1% (NAC) *vs.* 11.1% (upfront surgery), P=0.010]. Given the higher proportion of patients treated with BCS in the NAC group (65%) compared to the upfront surgery group (49%), this raised concerns about the safety of BCS after NAC, and the possibility that the increase in LR was secondary to the patients who downstaged from mastectomy to BCS with NAC. Importantly, the trials included in this meta-analysis pre-dated targeted systemic therapies and contemporary pathologic, radiologic, and surgical techniques, which could also account for the observed differences in LR.

Addressing this clinical area of uncertainty, Mamtani *et al.* utilized a prospective neoadjuvant database at MSKCC to compare LR rates between BCS-eligible patients and BCS-ineligible patients who downstage with modern systemic NAC regimens (30). Importantly, BCS-eligibility was prospectively assessed by the treating surgeon pre- and post-NAC. From May 2014 to December 2018, 1,136 patients with cT1–3 breast cancer received NAC. Of these, 243 were BCS-eligible prior to NAC and underwent BCS, 282 were BCS-ineligible, downstaged, and chose BCS, and 160 were BCS-ineligible, downstaged, and chose mastectomy. The mastectomy group was used as a comparator group to assess whether BCS-ineligible patients at presentation, in general, have a higher risk of LR compared to BCS-eligible patients. In the 685 patients included in the analysis, median follow-up was 35 months. The 4-year LR-free survival was 96.2% (95% CI: 94.5–97.9%) for the entire cohort, with no difference between the BCS-eligible patients, BCS-ineligible patients who downstaged and chose BCS, and those who downstaged and chose mastectomy (4-year LR-free survival 98.1% *vs.* 93.7% *vs.* 97.3%, respectively, P=0.17), supporting the oncologic safety of BCS in patients who downstage with NAC. More recently, the authors of the I-SPY2 prospective multicenter adaptive randomized NAC trial reported locoregional recurrence rates and LR-free survival between BCS and mastectomy patients enrolled on trial (31). Overall, 1,462 patients with clinical stage II–III molecularly high-risk breast cancer who had NAC followed by surgery between 2010 and 2021 were included in the analysis, with 43% undergoing BCS and 57% undergoing mastectomy per physician and patient preference. At a median follow-up of 3.5 years, the crude locoregional recurrence rate was 6.3%, with no difference between BCS patients (5.4%) *vs.* mastectomy patients (7%) (P=0.18). On multivariable analysis, there was no association between the extent of local surgery and LR-free survival (P=0.89); triple-negative receptor subtype, higher clinical T stage, and the presence of residual disease after NAC were associated with shorter locoregional recurrence-free survival. While this study was limited by the lack of information on BCS-eligibility or reason why a specific surgical procedure was chosen, it reinforces that BCS remains a safe option in patients treated with NAC.

Ongoing controversies in surgical management after NAC

Timing of surgery after completion of NAC

Following completion of NAC, patients need sufficient time prior to surgery to allow for resolution of short-term toxicities from NAC; however, a prolonged surgical delay could potentially result in tumor regrowth and worse overall outcomes. A recently published study-level meta-analysis of five studies and over 8,700 patients evaluated whether the timing of surgery after NAC impacted DFS and overall survival (OS). Patients who had surgery ≤8 weeks after NAC compared with >8 weeks had an improved DFS (OR,

Table 4 Rates of LR in patients treated with NAC followed by BCS and whole breast irradiation, stratified by margin width

Study	BCS + WBI	Margins ≤2 mm	Median follow-up (months)	LR	
				≤2 mm	>2 mm
DFCI (35)	382	27%	57	4.7%	5.8%
MSKCC (36)	582	12%	39	3%	2%

LR, local recurrence; NAC, neoadjuvant chemotherapy; BCS, breast-conserving surgery; WBI, whole-breast irradiation; DFCI, Dana-Farber Cancer Institute; MSKCC, Memorial Sloan Kettering Cancer Center.

0.71; 95% CI: 0.52–0.98; P=0.04) and an improved OS (OR, 0.47; 95% CI: 0.34–0.65; P<0.00001). However, there was no advantage to having surgery even earlier, within 4 weeks after completion of NAC, with similar DFS and OS as patients who had surgery 4–8 weeks after NAC. Importantly, rates of pCR were similar between patients who had surgery <4 weeks after NAC compared to 4–8 weeks (OR, 1.01; 95% CI: 0.80–1.28; P=0.93), suggesting that tumor regrowth was not occurring provided patients had surgery within 8 weeks after completion of NAC (32).

Is resection of entire initial tumor volume necessary?

As previously discussed, NAC facilitates breast conservation by reducing overall tumor volume, allowing for a smaller volume of resection. However, controversy remains as to whether the entire initial tumor volume needs to be resected when performing lumpectomy after NAC. Resection of the entire initial tumor volume negates the benefit of NAC and may result in unnecessary mastectomies. A retrospective study from The University of Texas MD Anderson Cancer Center (Houston, TX, USA) assessed the effect of NAC on the volume of tissue excised and the rate of re-excision after lumpectomy. Overall, 509 patients with cT1–3N0–2 disease who were enrolled in randomized chemotherapy trials at their institution were analyzed. In patients presenting with clinical T2–3 tumors, the volume of tissue resected at the time of lumpectomy was significantly smaller in those treated with NAC compared with upfront surgery (113 *vs.* 213 cm^3, P=0.0043), despite the groups having similar tumor sizes at presentation. Importantly, there was no difference in rates of re-excision between the two groups, and at a median follow-up of 33 months, there was no difference in LR. Therefore, in patients with unifocal disease who have a sufficient reduction in tumor volume to allow for breast conservation, extent of disease on post-NAC imaging and not initial tumor volume should guide volume of resection (33).

Optimal margin width after lumpectomy in patients receiving NAC

In patients with invasive breast cancer having upfront surgery with lumpectomy followed by radiotherapy, the Society of Surgical Oncology (SSO)/American Society of Clinical Oncology (ASCO)/American Society for Radiation Oncology (ASTRO) consensus guidelines endorse a margin of no tumor ink for optimal local control (34). However, these guidelines are not applicable to patients treated with NAC, due to concerns for a heavier residual tumor burden in patients with scattered disease close to the margin. The impact of margin width on LR in patients treated with lumpectomy and whole-breast irradiation after NAC was evaluated in two retrospective studies, both of which showed no difference in LR between patients with a margin width of ≤2 mm compared to >2 mm (*Table 4*) (35,36). Based on these findings, a margin of no tumor on ink is appropriate in patients receiving NAC, recognizing that the decision for re-excision in certain scenarios (i.e., multiple margins with scattered disease close to the margin) should be individualized based on the level of concern for significant residual disease in the breast.

Radiographic assessment of response to NAC

Radiographic assessment of treatment response and residual disease burden in the breast after NAC is important in guiding surgical decision making. However, the optimal imaging assessment, specifically for assessing downstaging from BCS-ineligible to BCS-eligible, remains a point of controversy. An individual patient-level meta-analysis including eight studies and 300 patients examined agreement between magnetic resonance imaging (MRI) and pathology, and MRI and standard imaging (with mammography and ultrasound) in patients treated with NAC. MRI accurately assessed the presence of residual disease in 93% of cases; MRI was less accurate in predicting

Table 5 FNRs of tumor bed biopsies after NAC reported in four prospective trials

Study	N	Eligibility	Biopsy needle gauge	FNR (95% CI)
RESPONDER TRIAL (Germany) (41)	398	Partial/complete response to NST	7–10 gauge	17.8% (12.8–23.7%)
MD Anderson/Royal Marsden/SNUH (42)	166	Partial/complete response to NAC	7–14 gauge	18.7% (10.6–29.3%)
NRG BR005 (40)	98	Partial/complete response to NAC	Not reported	50% (32.9–67.1%)
MICRA Trial (43)	167	Partial/complete response to NST	14 gauge	37% (27–49%)

FNR, false-negative rate; NAC, neoadjuvant chemotherapy; CI, confidence interval; NST, neoadjuvant systemic therapy.

pCR, with 37% of patients with a pCR having an MRI imaging abnormality. Notably, as pCR was defined as the absence of invasive disease [ductal carcinoma in situ (DCIS) allowed], the imaging findings may have been accounted for by the presence of residual DCIS. When compared to mammography and ultrasound, MRI was better at identifying residual disease, particularly when compared to mammography, where mammography more often missed tumors ≤2 cm. In addition, MRI more accurately assessed pCR compared with mammography and ultrasound (37).

More important than predicting the absence or presence of disease in the breast, is the ability of imaging to accurately predict eligibility for BCS, particularly in those patients who downstage. In a retrospective study of 111 patients treated with NAC between 2009 and 2012, all of whom had pre-and post-treatment MRIs, MRI alone correctly predicted BCS-eligibility in 88% of the 60 patients who were eligible for downstaging (38). The addition of mammography increased the predictive accuracy to 92%, likely due to the ability of mammography to detect calcifications. While MRI remains an accurate tool to assess response to NAC, its primary utility is in patients who are BCS-ineligible at presentation who are desirous of breast conservation, to assess response to treatment. In patients in whom mastectomy is indicated due to locally advanced or multicentric disease or patient choice, and in whom imaging response will not alter surgical plan, MRI can be safely avoided post-NAC.

Omission of surgery for complete responders after NAC

The high pCR rates observed in triple-negative (30–50%) and HER2$^+$ (50–60%) breast cancers, so-called "excellent responders" (10,11), have generated interest in complete avoidance of breast surgery after NAC. As imaging alone is insufficient to predict pCR (39), studies have evaluated whether tumor bed biopsies performed post-NAC can accurately predict pCR sufficiently to allow for omission of breast surgery. Four prospective studies evaluated the accuracy of image-guided tumor bed biopsies in predicting pCR, and include the MICRA, RESPONDER, NRG BR005, and MD Anderson/Royal Marsden/SNUH trials (40-43). Eligibility for these trials included a partial or complete response to NAC, and all patients had an image-guided biopsy of the tumor bed after NAC followed by surgery. Cumulatively, the FNR reported in these trials was clinically unacceptable, ranging from 18% to 50%, precluding the use of tumor bed biopsies to predict pCR and avoid surgery (*Table 5*) (40-43). The University of Texas MD Anderson Cancer Center study performed a subgroup analysis of 76 patients who had a residual imaging abnormality <2 cm and at least 6 vacuum-assisted core biopsies (VACBs) performed, and demonstrated an FNR of 3.2%. Based on these results, the authors performed a multicenter single-arm phase II trial that enrolled patients age ≥40 years with cT1–2N0M0 triple-negative or HER2$^+$ breast cancer with residual breast lesions <2 cm after NAC (44). Patients underwent a minimum of 12 VACBs with a 9-gauge needle, and surgery was omitted if no invasive or *in situ* disease was identified. All patients received whole-breast radiation. Of 50 patients enrolled, 31 had no residual disease by VACB, and at a median follow-up of 26.4 months, no ipsilateral breast tumor recurrences or other recurrence events were observed.

While these "excellent responders" may be considered for omission of breast surgery in the future, the consequences of missing residual disease have the greatest impact on outcome in patients with triple-negative and HER2$^+$ breast cancer, where data from randomized trials have shown an improvement in survival in triple-negative patients with residual disease who receive adjuvant capecitabine, and in HER2$^+$ patients who switch from trastuzumab and pertuzumab (HP) to trastuzumab emtansine (TDM-1) (45,46). While surgical downstaging in many scenarios can significantly improve quality of life, with the prime example

being avoidance of ALND, it is unlikely that avoidance of lumpectomy, with its low morbidity, will result in an improvement in quality of life, particularly given the need for more intense surveillance.

Conclusions

Both NAC and NET can significantly reduce tumor burden in the breast, resulting in high conversion rates to breast conservation. For patients who successfully downstage, BCS is oncologically safe and associated with low rates of LR if negative margins are obtained. MRI is accurate in assessing BCS-eligibility post-NAC in patients who downstage and can accurately select patients for BCS. Omission of breast surgery in excellent responders after NAC is currently under investigation, but may not be a research priority given the low morbidity of BCS and the importance of identifying residual disease after NAC to tailor adjuvant therapy.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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