Editorial Commentary

Shifting neoadjuvant chemotherapy treatment paradigms for breast cancer and its impact on axillary nodal management for clinically node-negative patients

Chandler S. Cortina[1,2]^

[1]Division of Surgical Oncology, Department of Surgery, Medical College of Wisconsin, Milwaukee, WI, USA; [2]Medical College of Wisconsin Cancer Center, Milwaukee, WI, USA

Correspondence to: Chandler S. Cortina, MD, MS, FSSO, FACS. Assistant Professor of Surgery, Division of Surgical Oncology, Department of Surgery, Medical College of Wisconsin, 8701 Watertown Plank Rd., Milwaukee, WI 53226, USA; Medical College of Wisconsin Cancer Center, Milwaukee, WI, USA. Email: ccortina@mcw.edu.

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Nodal management for breast cancer management after neoadjuvant chemotherapy (NAC) has undergone substantial change over the past decade with much progress towards safely de-escalating the extent of axillary surgery (1). However, using a NAC approach for some patients, particularly those with early-stage clinically-node negative disease (cN0) breast cancer, may result in systemic therapy or axillary surgery overtreatment (2). A retrospective multicenter cohort study by Zaborowski *et al.* was recently published in the *British Journal of Surgery* in which the authors aimed to (I) determine surgical nodal positivity rates in patients with cT1–3 cN0 breast cancer after NAC followed by surgery with sentinel lymph node biopsy (SLNB) and (II) identify factors associated with an increased or decreased odds of having node-positive disease after NAC (ypN+) (3). The cohort included 371 patients from six European centers and 12.7% of patients were found to be ypN+. Rates of ypN+ status varied by tumor receptor subtype: 29% for hormone receptor-positive (HR^+)/human epidermal growth factor receptor 2-negative ($HER2^-$) tumors, 13.8% for $HR^+/HER2^+$ tumors, 5.6% for $HR^-/HER2^+$ tumors, and 6.5% for those with triple-negative breast cancer (TNBC). The only factor associated with an increased odds of ypN+ disease on multivariable analysis was multicentric breast disease [odds ratio (OR) =2.66, 95% confidence interval (CI): 1.18–6.01, P=0.02] while a complete imaging response in the breast was associated with a decreased odds of ypN+ disease (OR =0.10, 95% CI: 0.02–0.42, P=0.002). Additionally, nearly all patients in the cohort (85%) who were found to be ypN+ underwent completion axillary lymph node dissection (ALND), the current standard of care (1,4). The findings of the Zaborowski cohort underscores the notable surgical implications of using a NAC rather than an upfront surgery approach for breast cancer patients who present with upfront cN0 disease but are found to be ypN+. While their cohort provides insightful data, there are several considerations clinicians must make in deciding which cN0 patients should undergo

^ ORCID: 0000-0002-4750-5028.

NAC *vs.* upfront surgery as well as opportunities for future work to expand the scope in how similar cohorts may be studied.

For patients who present with upfront cN0 disease, several landmark clinical trials have established that for those found to have a low pathological nodal burden on SLNB, many patients can forgo ALND as long as they receive appropriate adjuvating therapy with no differences in locoregional or distant disease control or survival (1,5-7). The landmark ACOSOG Z0011 trial demonstrated omission of ALND as an option for patients with cT–2 cN0 breast cancer undergoing upfront breast conserving surgery with 1–2 positive sentinel lymph nodes (SLNs) who receive adjuvant whole breast radiotherapy (5). The AMAROS and SENOMAC clinical trials have since expanded the role omitting ALND in cN0 but pN+ breast cancer patients undergoing upfront surgery to include patients undergoing mastectomy or those found to have additional nodal micrometastases (6,7). SENOMAC also included patients with cT3 disease and those found to have extracapsular nodal extension (7). However, unlike Z11, patients in the AMAROS and SENOMAC protocols received dedicated radiation to the axillary nodal basins. National survey data from the past several years has revealed that both the Z11 and AMAROS trials' results are being actively implemented into modern clinical practice (8,9). Notably, these trials only included patients undergoing upfront surgery and therefore these data cannot be applied to patients receiving NAC. Current standard of care for patients who are cN0, receive NAC, and undergo SLNB but are found to be ypN+, is ALND (1,4,10).

NAC has historically been used to downstage primary breast disease to facilitate breast conserving surgery or to downstage the clinically node-positive (cN+) axilla in hopes of omitting ALND if patients are found to be ypN0 (2,11). Rates of breast and axillary complete response rates after NAC vary and are notably higher for patients with HER2$^+$ or TNBC as seen in the Zaborowski cohort (3,12). However, over the past several years, novel systemic therapies for HER2$^+$ and TNBC have shifted how clinicians approach NAC as these new therapies rely upon using a NAC approach to assess disease response and dictate the role for additional systemic therapies.

The CREATE-X trial demonstrated a benefit to receiving adjuvant capecitabine for patients with TNBC who received NAC and were found to have residual disease on surgical pathology (13). Notably, CREATE-X included patients with cT1–4 cN0 TNBC in addition to those with cN+ disease. More recently, the KEYNOTE-522 trial has demonstrated the addition of pembrolizumab in the neoadjuvant setting for select TNBC patients results in improved pathological complete response rates and event-free survival for patients with early-stage TNBC and had the same inclusion criteria as CREATE-X but excluded cT1a and cT1b patients and only included cT1c patents if they were cN+ (14,15). Both the CREATE-X and KEYNOTE-522 trials demonstrated varying outcome benefits depending upon breast tumor disease and nodal burden. Recent data from the National Cancer Database (NCDB) revealed an increased use of NAC for patients with early-stage cN0 TNBC after publication of the CREATE-X trial, suggesting that these landmark systemic therapy trials are resulting in increased use of NAC for patients with TNBC (16). But with the increasing use of NAC for early-stage cN0 TNBC patients, the question then arises: does a NAC approach for these patients result in increased nodal surgery given that if patients are found to be ypN+, they are no longer Z11, AMAROS, SENOMAC eligible? Additional data from the NCDB found that while patients with cT1–2 N0 TNBC who underwent upfront surgery had higher odds of being pN0, there were no differences in ALND rates for patients who had upfront surgery *vs.* those that received NAC (2). Therefore, the decision for a NAC *vs.* upfront surgery approach in early-stage cN0 TNBC patients should rely more upon the potential benefits of a NAC approach rather than how a NAC approach may influence the need for ALND.

Significant strides have also been made in systemic therapy options for patients with HER2$^+$ breast cancer. Like the CREATE-X trial, the KATHERINE trial found a benefit to adjuvant trastuzumab emtansine (TDM-1) for patients who received NAC with trastuzumab for HER2$^+$ breast cancer and were found to have residual disease on surgical pathology (17). While the two trials had similar inclusion criteria, the KATHERINE trial did expand inclusion to those with cT1c N0 HER2+ breast cancer. Similarly, to the increased use of NAC over the past several years for TNBC, data from the NCDB has also identified an increased use of NAC in the United States for patients with HER2$^+$ breast cancer (18), but there is limited data on how this may have changed in more recent years or its impact on ALND rates in patients with early-stage cN0 HER2$^+$ breast cancer.

For patients with HER2$^+$ or TNBC who have cT1c N0 disease via clinical examination, the decision for a NAC *vs.* upfront surgery approach can be controversial. To assist in

clinical-decision making for these patients, it is reasonable to obtain a dedicated axillary ultrasound to assess for nodal involvement that may not be apparent via physical examination alone (2,19,20). If a patient with cT1c HER2$^+$ or TNBC is found to be cN+ via axillary ultrasound, treatment typically definitively shifts to a NAC approach rather than upfront surgery (19,20). This is a strength of the Zaborowski cohort as all patients had formal axillary ultrasounds to clinically stage the axilla. However, 17.3% of their cohort had cT1 disease and it is unclear how many of these were cT1a, cT1b or cT1c or what was the tumor-receptor profile of the patients with cT1 disease or what was the formal decision-making around why these patients had NAC rather than upfront surgery (3).

Notable limitations exist within the Zaborowski cohort regarding clinical context and applicability. Tumor genomic profiling currently guides the decision for systemic chemotherapy use for most patients with HR$^+$/HER2$^-$ breast cancer (21,22). It is unclear if the decision for NAC for HR$^+$/HER2$^-$ patients in the Zaborowski cohort was based upon upfront tumor genomic profiling, such as the 21-gene Oncotype DX Breast Recurrence Score® assay (21), or other clinicopathologic factors. As tumor genomic profiling of HR$^+$/HER2$^-$ breast cancer allows for an objective view of the benefit to systemic chemotherapy, its utility when considering a NAC approach for patients with HR$^+$/HER2$^-$ must be carefully considered given lower pathological response to NAC compared to the HER2$^+$ and TNBC subtypes (21). Additionally, it is a bit surprising that 20.5% of their cohort were patients with HR$^+$/HER2$^-$ cN0 breast cancer given the known lower pathologic complete response (pCR) rates for these patients. But perhaps the largest limitation is that no data is reported on the cohort's racial and ethnic makeup. Data from a United States registry have identified that while non-Hispanic Black women have lower pCR rates after NAC for TNBC, there were no differences in overall survival by race and ethnicity in those women who achieved a pCR, suggesting that survival disparities for non-Hispanic Black women with TNBC may be secondary to inferior pCR rates (23). One may assume the Zaborowski cohort is likely primarily compromised of non-Hispanic White women of European decent, but it is unknown and thus severely limits the applicability and interpretation of the study's findings to diverse patient populations seen in other areas of the world.

The decision for a NAC *vs.* upfront surgery approach in cN0 breast cancer patients, excluding those with inflammatory breast cancer (24), requires judicious and multidisciplinary decision-making. This includes shared decision-making with patients on the risks and benefits of a NAC *vs.* upfront surgery approach in terms of systemic therapy and how it may affect surgical management. As we await ongoing clinical trial results to assess if there are select patients who can forgo ALND in favor of axillary radiotherapy alone if found to be ypN+ (25), current standard of care for patients with ypN+ disease remains ALND (1,4). While there is robust data to support a NAC benefit to select patients with cN0 TNBC and HER$^+$ breast cancer, the benefits appear to be less in patients with HR$^+$/HER$^-$ breast cancer in who pCR rates are lower and a NAC approach is less likely to impact adjuvant therapy or survival outcomes.

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Footnote

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