commentaries

Role of Axillary Surgery After Neoadjuvant Chemotherapy

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INTRODUCTION

At the 2019 ASCO Annual Meeting, the optimal approach to axillary surgery for women who received neoadjuvant chemotherapy (NACT) was discussed. If residual axillary disease is detected, patients with triple-negative tumors and human epidermal growth factor receptor 2 (HER2) overexpression can be selected for additional adjuvant treatment with capecitabine or trastuzumab emtansine (T-DM1), respectively.[1,2] Failure to identify patients with residual disease can negatively affect their clinical outcome. Techniques proposed to optimize patient selection include placing clips on metastatic lymph nodes before NACT or performing axillary dissection even after a clinical complete response (CR). Does this really make sense? What role does axillary surgery play in patients for whom NACT is indicated?

UPFRONT SURGERY

Axillary status is important for local treatment of the disease and for planning systemic treatment and radiotherapy. Axillary lymph node dissection (ALND) was used for almost a century for all patients undergoing breast cancer surgery, even when clinical signs of axillary disease were absent. Since the 1990s, sentinel lymph node biopsy (SLNB) has gradually replaced systematic ALND in patients with early breast cancer and in those with clinically negative axilla. The NSABP B-32 study (ClinicalTrials.gov identifier: NCT00003830) assigned patients with clinically negative lymph nodes to SLNB or to SLNB plus ALND and reported equivalence regarding disease-free and overall survival after a mean follow-up time of 95 months.[3] Moreover, the rate of complications, particularly lymphedema in the ipsilateral upper limb, was lower in the group that did not undergo axillary dissection. Nonetheless, the 9.8% overall false-negative rate in that study increased to 17% when only one SLN was resected. Although it did not affect survival, axillary residual disease is not uncommon, even in patients with a negative SLNB.

Five randomized clinical trials (ACOSOG-Z0011 [ClinicalTrials.gov identifier: NCT00003855], IBCSG 23-01 [ClinicalTrials.gov identifier: NCT00072293], AATRM 048/13/2000 AMAROS [ClinicalTrials.gov identifier: NCT00014612], and OTOASOR) evaluated ALND versus SLNB alone or SLNB plus axillary radiotherapy in patients with clinically negative axilla and a positive SLNB. No difference was found in axillary recurrence or in overall survival in these studies other than residual non-SLN metastases in 13% to 38% of patients in the ALND arms.[4-8] In women with clinically negative axillae and low lymph node tumor load (negative SLNB or low tumor burden in the SLN at first-line surgery), ALND did not affect locoregional control and provided no relevant information for adjuvant therapy.

NACT AND CLINICALLY NEGATIVE AXILLA

Meta-analyses reported SLNB false-negative rates of approximately 10% after NACT in patients with initially clinically negative axilla (cN0), which is comparable to the rates found before NACT, irrespective of the number of lymph nodes identified or the use of dual mapping (patent blue dye and technetium).[9-11] In a retrospective analysis of cN0, T1-T3 patients who underwent SLNB after NACT (n = 575) or first-line surgery (n = 3,171), nodal recurrence was 1.2% in the NACT group, with no difference in disease-free or overall survival between groups. The false-negative rate was 5.9%.[12] In the GANEA-2 study (ClinicalTrials.gov identifier: NCT01221688), after a 36-month follow-up of cN0 patients who underwent SLNB after NACT, only one (0.2%) of 419 patients had axillary recurrence, with an 11.9% false-negative rate.[13] Therefore, a considerable proportion of patients with initial cN0 disease who are referred for NACT will have subclinical axillary disease, with residual tumor load persisting in some cases. Ultrasonography may prove to be adequate for identifying the disease in axillary lymph nodes before systemic therapy, which allows planning for radiation of the chest wall and regional lymph nodes.

NACT AND CLINICALLY POSITIVE AXILLA

In patients with positive axillary nodes at initial presentation, SLNB false-negative rates are higher after NACT compared with rates in cN0 patients. Before 2012, retrospective evaluations reported unacceptable SLNB false-negative rates of more than 20%.[14] The prospective studies ACOSOG-Z1071 (ClinicalTrials.gov identifier: NCT00881361), SENTINA (Eudra Clinical Trial No: 2006-005834-19), and SN-FNAC (ClinicalTrials.gov identifier: NCT00909441) evaluated women with positive lymph nodes before NACT who had experienced clinical CR and who underwent SLNB

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and axillary dissection.[15-17] The resulting overall false-negative rates were 12.6% to 14.2%, which is higher than the 10% rate considered safe. Subgroup analyses showed that the following techniques reduced false-negative rates to less than 10%: identifying three or more SLNs (Table 1), adding patent blue dye in a dual-mapping technique, marking the metastatic lymph node with a clip before NACT and then resecting it, and immunohistochemistry.

The SENTINA study evaluated the possibility of performing SLNB before and after NACT; however, identification and false-negative rates were unacceptable.[16] A recent meta-analysis of 1,921 women with biopsy-proven node-positive axilla before NACT showed adequate identification in 90% of the patients and an overall false-negative rate of 14%, which decreased to 11% (range, 6% to 15%) when dual mapping was used and to 4% (range, 0% to 9%) when three or more SLNs were removed.[18] These studies influenced clinical practice regarding the axilla because, although no prospective randomized studies had been conducted to investigate this issue, false-negative rates $< 10\%$ seemed to be safe. The number of lymph nodes identified began to be important, and breast surgeons maximized efforts to identify them. A real-life institutional study showed that the strategy of identifying three or more lymph nodes proved satisfactory in 86% of the patients compared with 57% in the ACOSOG-Z1071 and 34% in the SENTINA controlled studies, thus avoiding axillary dissection in almost half the patients with initially positive axillary lymph nodes.[19] The use of marker clips on the lymph node as an alternative to resecting three lymph nodes has been debated. The clip reduces false-negative rates to a slightly greater extent than resection.

In a US study, associating selective localization and removal of clipped nodes with SLN dissection, known as targeted axillary dissection, reduced false-negative rates to approximately 2% compared with 4% with removal of the clipped lymph node alone.[20] However, patients are required to undergo two procedures: placement of the clip before systemic treatment and marking it to identify the lymph node during surgery. A retrospective analysis showed that in patients with clipped lymph nodes who were referred for preoperative marking, the clip failed to be identified in 20% of those patients, even when computed tomography was used, with the additional risk of the clip not being removed during surgery.[21] Therefore, the use of clips is controversial, because it is sometimes impossible to remove the clip alone. Despite the association between the number of lymph nodes and false-negative rates, there are still no convincing data regarding clinical outcome. Small, retrospective studies have shown exceptional locoregional control. An Italian study evaluated 70 patients (cN1/N2) who achieved clinical CR after NACT and who underwent SLNB alone. After 5 years, no cases of axillary recurrence were found. The NSABP B-51 trial (ClinicalTrials.gov identifier: NCT01872975) should provide conclusive data on the subject; however, the benefits obtained from identifying three or more lymph nodes have been proven, and regional control of the disease will probably not be affected if false-negative rates are $< 10\%$. Consequently, in our opinion, there is no need to wait any longer to minimize patient morbidity. Regarding information for treatment, the decision to provide radiotherapy is currently based on previous lymph node status (ie, at this time, pathologic CR [pCR] does not affect the decision to provide radiation to the chest wall or regional lymph nodes). Conversely, lack of pCR may affect systemic adjuvant treatment.

TABLE 1. Comparison of Overall False-Negative Rates and Rates When Three or More SLNs Were Identified in the ASOCOG-Z1071, SENTINA, and SN FNAC Studies

First Author	Study Acronym	Overall False-Negative Rate, %	Three or More SLNs, %
Boughey[15]	ACOSOG-Z1071	12.6	9.1
Kuehn[16]	SENTINA	14.2	7.3
Boileau[17]	SN FNAC	13.3	4.9

NOTE. The studies assessed false-negative rates in patients with negative sentinel lymph nodes after systemic neoadjuvant therapy (ie, clinically metastatic axilla before treatment).

Abbreviation: SLNs, sentinel lymph nodes.

Until recently, no randomized studies had shown the advantage of providing adjuvant systemic therapy after NACT and surgery. The CREATEx (UMIN Clinical Trials Registry: UMIN000000843) and KATHERINE (ClinicalTrials.gov identifier: NCT01772472) studies changed this perception.[1,2] In the phase III KATHERINE study, 1,486 patients with residual HER2 disease after NACT, with or without dual anti-HER2 blockade, were randomly assigned to use trastuzumab emtansine or adjuvant trastuzumab. After 3 years, 88.3% of patients in the trastuzumab emtansine group were free of invasive disease compared with 77% in the trastuzumab group, a significant absolute difference of 11.3% with a risk ratio of 0.50 (95% CI, 0.39 to 0.64; $P < .001$) and a relative reduction in recurrence of approximately 50%. The CREATEx study randomly assigned 910 women with HER2-negative residual disease after NACT to use capecitabine or not. The study reached its primary end point and was stopped. In the women with triple-negative disease who received capecitabine, disease-free survival was 69.8% compared with 56.1% in the control group (hazard ratio, 0.58; 95% CI, 0.39% to 87%), which is a significant reduction of 42% in recurrence or death. A benefit in overall survival was also found (78.8% *v* 70.3%) with a hazard ratio of 0.52 (95% CI, 0.30 to 0.90). With these new data, it has become vital to diagnose residual disease in patients with HER2 and triple-negative disease.

The ASCO debate emphasized the use of axillary dissection and the clip, because a possible reduction in the false-negative rates of SLN detection would be welcome as a means of selecting patients for these additional adjuvant therapies, particularly because the studies of false-negative rates in the literature have shown reductions of 2% to 8%

with the use of the clip.[15,20] Even so, residual disease after NACT can be found in the breast. What would be the percentage of patients with HER2 and triple-negative tumors with pCR in the breast but in whom residual disease remains in the axilla (ypT0 ypN+)? These are the patients who would benefit from use of the clip or even axillary dissection.

A study with more than 30,000 patients from a US database evaluated lymph node positivity in women with pCR in the breast after NACT for triple-negative and HER2-positive tumors.[22] For HER2-positive tumors, pCR was achieved in the breast tissue in 43.3% of patients (with residual disease in the axilla in only 12.4%) whereas in triple-negative tumors, pCR was achieved in the breast tissue in 37% of patients (with 14.1% having residual lymph node disease). Thus, there could be a risk that residual disease in the axilla would not be identified in one of 10 women with HER2 or triple-negative tumors. Because the reduction in false-negative results with the clip has been reported as being between 2% and 8%,[15,20] the use of this technique seems unjustified. The number of patients required to undergo the intervention to benefit one patient does not justify its use. The same reasoning applies to axillary dissection. Indeed, if these numbers were relevant and they justified the use of the clip, even patients who were initially cN0 would have to undergo axillary dissection because false-negative rates are approximately 10% in these patients.[9-11,13]

POSITIVE SLNB AFTER NACT

No studies have evaluated clinical outcome in this scenario. Nevertheless, retrospective studies have shown high rates of residual disease. A recent study evaluated 181 patients with positive SLNs at frozen section after NACT, with residual disease being found in approximately 60% of patients, even in micrometastases (0.2 to 2.0 mm).[23] Another study reported similar results, with 63% of patients having additional lymph node disease when the SLN was positive.[24] Tumor size, high grade, lymphatic leakage, the size of the metastasis, and the number of positive SLNs were predictive factors for residual tumor load in axillary dissection. Conversely, the HER2 subtype was less likely to be associated with residual disease. The Alliance A11202 study (ClinicalTrials.gov identifier: NCT01901094) is currently randomly assigning patients with positive SLNB to undergo either axillary dissection with radiotherapy of the chest wall and local lymph nodes or radiotherapy without axillary surgery, irrespective of the type of breast surgery. The design of that study was similar to that of the AMAROS study with first-line surgery.

In conclusion, SLNB is safe in initially cN0 patients and is unaffected by the number of SLNs identified. In patients who were cN1/2 before NACT, systematic use of the clip or even axillary dissection in patients with clinical lymph node CR after treatment may have a much reduced effect on the locoregional control of the disease or even in the selection of patients for adjuvant treatment with capecitabine or trastuzumab emtansine. Studies are currently ongoing to increase understanding of axillary surgery under these circumstances. The identification and removal of three or more SLNs, with dual mapping, seems appropriate while we await further results. Nevertheless, when the SLN is positive after NACT, there are currently no data to enable axillary dissection to be safely omitted, irrespective of the size of the SLN metastasis.

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