Management of the positive axilla in 2017

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One of the greatest advances in breast cancer surgical management over the last few years has been the more conservative management of the axilla.

After acceptance of the Halstedian paradigm, axillary dissection (AD) became the “one size fits all” treatment modality for all stages of breast cancer. This approach was first challenged in the late 80’s by Silverstein et al. in *ductal carcinoma in situ* (DCIS) patients [1]. His report showing no axillary metastasis in any of the DCIS patients led to the omission of AD for DCIS patients.

Subsequent large trials reported that although axillary metastases can be found in 40% of clinically node-negative patients, only 15% of them became clinically perceptible if left untreated [2]. Widespread use of screening mammography in the 90’s led to further decrease in the rate of axillary positivity to 22% [3]. According to this calculation, 78% of early-stage breast cancer patients were undergoing unnecessary AD associated with a 16% risk of lymphedema [4]. Two studies investigated the possible omission of AD in elderly (>60 years old) patients revealing similar long-term outcomes with and without AD [5, 6].

AD, however, was still the treatment of choice for a clinically positive axilla and remained an essential staging procedure enabling stratification of patients, who would benefit from adjuvant therapy. In the 90’s, axillary staging was replaced by sentinel lymph node biopsy (SLNB) after this technique was validated in many studies including the

MILAN, NSABP-B32, and ALMANAC trials [7–9] limiting the use of AD for positive sentinel nodes only.

The next important advance was the omission of AD even in the presence of some axillary disease. The ACOG-Z0011 and AMAROS trials recruited patients with limited macrometastasis to the axilla [10, 11]. ACOSOG-Z0011 included patients treated with lumpectomy and adjuvant radiation therapy reporting no additional benefit in regional control of the axilla for completion AD in this specific group of patients with low recurrence risk (0.9 vs. 0.5%, $p > 0.05$). AMAROS trial compared treating SLNB positive patients with AD versus radiation treatment to the axilla. This trial also reported no additional benefit of AD compared to axillary radiation (RT) in DFS (86.9% in the AD group vs. 82.7% in the RT group, $p = 0.18$). AD, however, was associated with an approximately two-fold increase in clinical signs of lymphedema.

In parallel, the combination of SLNB and neo-adjuvant chemotherapy (NAC) was studied as well. Some proposed that the sentinel node biopsy should be performed before the chemotherapy, and some argued that it should be postponed to after the treatment. That very question was studied in a large single institutional study from MD Anderson comparing SLNB before and after NAC [12]. Identification rates (IR) and false negative rates (FNR) for SLNB before and after NAC were similar [98.7 vs. 97.4% ($p = 0.017$) and 4.1 vs. 5.9% ($p = 0.39$), respectively]. Additional multicenter studies also reported concordant results. In a retrospective analysis of NSABP B-27 data, performance of SLNB after NAC was associated with an IR of 85% and a FNR of 11% [13]. Use of radionuclide decreased FNR to 9% in comparison to 14%, which was achieved when only lymphazurin was used ($p = 0.5$). The second multicenter study was the prospectively conducted GANEA study, which reported an IR of 90% and FNR of

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11.5% for SLNB after NAC [14]. When the results of NSABP-B27 and GANEA studies were combined, an IR of 86.5% and a FNR of 10.9% were found [15]. Two meta-analyses assessed the accuracy of SLNB after NAC. The first study summarized 21 studies/1273 patients and found an IR of 90% and a FNR of 12% [16]. The second study summarized 24 studies/1799 patients and found an IR of 89.6% and a FNR of 8.4% [17]. Still yet, performing a SLNB after NAC was limited to patients who did not have a clinically positive axilla prior to treatment. Those who did have a positive axilla before NAC were treated with a mandatory AD.

The following logical step was to study whether a previously positive axilla that down-staged and became negative after NAC could be reliably staged with a SLNB alone after NAC. This question was investigated in three recent separate studies, ACOSOG-Z1071, SENTINA, and SN-FNAC, in which SLNB was followed by confirmatory AD [18–20]. In all three studies, removing ≥ 2 sentinel nodes and combining radionuclide tracer with blue dye increased sensitivity and decreased FNR. In the ACOSOG-Z1071 study, however, 1/3 of the patients had a clip placed at the time of the biopsy and before NAC in the positive axillary node. When the clipped node was identified, and excised during SLNB, the FNR decreased to 6.8% but when the clipped node was not found, the FNR was as high as 39%. These findings led to different complicated techniques described to re-localize the clipped node after NAC. Regardless, those three studies were summarized in two reviews. The first review involved 2471 patients and found an IR of 89% and a FNR of 14% [21]. According to this review usage of IHC decreased FNR to 8.7%, while without IHC, FNR was 16%. The second review included 3398 patients and reported a pCR of 39.2%, an IR of 90.9% and a FNR of 13% [22]. Long-term clinical outcomes of SLNB alone for down-staged axilla after NAC has not however been reported yet.

The coming years might bring even more changes in the management of the positive axilla. The ALLIANCE A011202 trial (<https://clinicaltrials.gov/ct2/show/NCT01901094>) is now recruiting patients with T1-3/N1/M0 at presentation and who became clinically negative after NAC. These patients undergo SLNB and if SLNB is positive get randomized to AD vs. RT.

Those very significant changes in management, however, bring also new clinical challenges to the multidisciplinary team trying to decide about the most appropriate treatment course.

First, it becomes extremely important to correctly stage the axilla at presentation. Missing the presence of a positive metastatic axillary node might lead to a decision of surgery first which will result in a positive sentinel node that might not be appropriate for observation only and

could end up in AD or RT that could have been avoided by NAC.

Second, the mere identification of axillary disease is not necessarily an indication for NAC. That would be especially true in a small luminal A or B tumor that otherwise might not need chemotherapy even after surgery and, furthermore, might have very small chances to lead to a complete response in the axilla. The different molecular signature available at the present time is focusing on survival or recurrence. New molecular signatures need to be developed that can accurately predict the nodal response to chemotherapy in order to correctly guide the patients.

How to reassess the axilla after NAC is a challenging issue as well. Since even the presence of micrometastasis after NAC is predictive of residual axillary disease in up to 98% of the patients [22], the most accurate reassessment of the axilla for residual disease would minimize the risk of an unplanned AD concomitant or subsequent to the SLNB.

In our institution, we have implemented and are currently studying a systematic sonographic axillary staging at presentation, preferentially by the surgeons. Needle biopsies are then preformed of suspicious nodes. At completion of NAC, the axilla is again systematically staged sonographically, taking into account the pre-treatment disease locations. Any residual morphologically suspicious node undergoes a repeat needle biopsy. If there is evidence of residual disease, the patient is scheduled for AD. If there is no detectable residual disease, the patient is scheduled for a SLNB.

Prediction of likelihood of a certain metastatic axillary disease to fully respond to NAC is done currently based on the following criteria.

(a) The indication for chemotherapy in the adjuvant setting. If a patient will need chemotherapy anyway in the adjuvant setting and metastatic axillary disease is identified, NAC will be offered to the patient in an attempt to avoid AD.

(b) The molecular signature of the tumor. For those patients who would not necessarily need chemotherapy, we use some of the available molecular signatures in an attempt to be predictive about the axillary response but further refinement is necessary. Furthermore, the currently published information regarding preoperative use of hormonal modulation is insufficient to accurately predict a complete axillary response. Hopefully, further refinement in the molecular signature assays will help better manage the positive axilla.

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Compliance with ethical standards

Conflict of interest There are no conflicts of interest.

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