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Commentary

What we learned in axillary management of breast cancer patients at the American society of clinical oncology (ASCO) 2020 virtual meeting? The EUBREAST point of view

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ABSTRACT

In 2020, the American Society of Clinical Oncology (ASCO) annual meeting was held as a virtual conference. Overall, 461 abstracts focused on breast cancer management. As European Breast Cancer Association of Surgical Trialists (EUBREAST) we summarize and comment the results of these abstracts dealing with axillary management in breast cancer patients and offer an interpretation on how these findings may be incorporated into clinical practice and further research.

Because of the COVID-19 pandemic restrictions, in 2020 the American Society of Clinical Oncology (ASCO) annual meeting was held as a virtual conference. As European Breast Cancer Association of Surgical Trialists (EUBREAST), we provided our point of view on the most relevant results presented on the management of the axilla, among the over 450 abstracts focusing on breast cancer (Table 1).

One of the abstracts determined the accuracy of sentinel lymph node (SLN) mapping in patients with invasive lobular carcinoma (ILC) [1]. The false negative rate (FNR) was 8.97% and the sensitivity was 91%, comparing well with that reported for invasive ductal carinoma (IDC). A high percentage (37.7%) of clinically node negative patients (cN0) had axillary disease after surgery (pN+), highlighting the challenges posed by ILC of the breast. In our opinion, patients with ILC should be offered the same surgery as patients with IDC. However, further de-escalation of axillary surgery, up to complete omission of SLN biopsy, should be approached with supplementary caution either the ILC subgroup being evaluated separately in studies.

Several abstracts evaluated the performance of nomograms in determining the risks of identifying metastases in non sentinel lymph nodes (NSLN). Of the seven nomograms evaluated, only three (MD Anderson Cancer Center, Memorial Sloan Kettering Cancer Center and Cambridge nomograms) had an AUC>0.7. Overall, sensitivity and specificity were poor and the false negative rate high [2]. A nomogram combining clinical data with genome profiling was presented. Two SNP clusters, molecular subtype, N stage, number of positive and negative SLNs were found to be significant predictors of metastasis in

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NSLNs [3]. Nowadays, the omission of axillary lymph node dissection (ALND) is widely accepted for patients with disease limited to the SLNs who undergo breast conserving therapy and radiation therapy (RT). We do not expect nomograms calculating NSLN involvement to influence clinical practice in this setting. In patients undergoing mastectomy, and therefore not subjected to postoperative RT, nomograms may be of use in predicting in which patients with metastatic SLN an ALND can safely be omitted.

In the primary systemic therapy (PST) setting, the omission of SLN in initially node-negative breast cancer patients, the axillary conversion rate in initially node-positive breast cancer patients, and the omission of ALND in node-positive breast cancer patients, were three hot topics.

Clinico-pathological factors (ER, PgR, HER2, Ki-67) on needle biopsy and tumor size on MRI before and after PST in initially node-negative breast cancer patients were compared [4]. At the multivariate analysis, MRI-complete response of the primary tumor and high Ki67 were independent predictive factors of axillary response after PST (ypN0) ($p < 0.01$). This was especially true for patients with HER2-positive disease. Therefore, pathologic complete response (pCR) in the breast in high-proliferative disease is a good predictor for complete response in the lymph nodes. EUBREAST initiated a clinical trial evaluating the omission of SLN biopsy in triple-negative and HER2-positive breast cancer patients with pCR in the breast after PST that will soon start enrollement [5].

In a subgroup analysis of the SENTINA trial, the association between clinical/pathological parameters and axillary conversion after PST was reported [6]. Univariate logistic regression analysis showed that small tumor diameter after PST ($p = 0.0038$), achievement of breast pCR ($p = 0.0001$) and lack of LVI ($p = 0.00009$) were associated with axillary conversion to ycN0. This finding underlines the role of breast pCR to predict a clinical conversion from *N+* to N0. Further research is required to identify patients who convert from cN1 to ycN0 and have a low risk of axillary involvement to allow further de-escalation of axillary surgery. The optimal surgical approach for patients converting from cN+ to ycN0 through PST is not yet defined. EUBREAST initiated an international cohort study (EUBREAST-3/AXSANA) to compare different surgical staging techniques [7].

Patients with involved lymph nodes after PST (ypN+) who were treated with postoperative regional nodal irradiation have been analyzed. Five-year-OS was similar in patients undergoing ALND and those in the SLN biopsy-only group (73% vs.76%; $p > 0.05$) [8]. At the Cox regression analysis, neither type of surgery nor clinical-pathological factors were associated with OS, suggesting that ALND does not improve survival in ypN+ patients receiving nodal irradiation.

More data on this issue are awaited from the Alliance 011,202 trial. The EUBREAST-2/INDAX trial, will further investigate whether it is safe to omit ALND in ypN+ patients who have undergone TAD, SLNB or TLNB and receive RT [9].

Finally, the biologic significance of nodal micrometases after PST (ypN1mic) was investigated [10]. Recurrence rates for ypT0N0 and ypT0N1mic were 4% and 29% respectively. Median disease free survival was not reached for the ypT0N0 group and was 28 months (95%CI: 21.6−34.4 months) for the ypT01mic group (HR: 16.55, 95%CI: 2.68−102.37; $p = 0.003$). Overall survival did not differ between the groups. The biological significance of micrometastasis in SLN after PST seems to differ from that of micrometastasis diagnosed at primary surgery. Therefore, in contrast to the primary surgery setting, omission of ALND should be critically discussed with ypN1mic

Table 1
: Key trials on axillary surgical management.

Authors	Abstract ID	Study type	Setting	Number of patients	Primary endpoints	Results
Ruby Guo et al. 1	E12604	Retrospective	Invasive lobular breast cancer undergoing SLN biopsy	196	Validation of the tecnique	FNR 8.9% Sensitivity 91%
Asha Reddy et al.2	568	Retrospective	Validation of nomograms to predict NSLN metastasis in positive SLN breast cancer	2350	AUC Sensitivity specificity FNR	MDA, MSKCC, Cambridge AUC> 0.7 (0.77, 0.77, 0.74) Sensitivity 62.3, 56.1, 60.7 Specificity 84.5, 86, 72.4 FNR 37.7, 43.9, 27.6
Liling Zhu et al. 3	E12577	Retrospective	Nomogram based on genetic and clinicopathologic features to predict NSLN metastases in positive SLN breast cancer	310	Factors associated to NSLNs metastasis	Two SNP clusters, molecular subtype, N stage, number of positive and negative SLNs significantly predict NSLNs metastasis
Atsushi Yoshida et al. 4	564	Retrospective	Initially node-negative breast cancer patients undergoing PST	419	Clinico-pathological factors and MRI characteristics associated with ypN0 after PST	MRI-complete response on primary tumor and high Ki67 were independent predictive factors of ypN0 ($p<0.01$)
Hans-Christian Kolberg et al. 6	567	Retrospective	Initially node-positive breast cancer patients undergoing PST	716	Factors associated to axillary conversion	small tumor diameter after PST ($p = 0.0038$), breast pathologic complete response ($p = 0.0001$) and lack of LVI ($p = 0.00009$) were positively associated to axillary conversion to ycN0
Michael Kharouta et al. 8	572	Retrospective	Node-positive breast cancer patients after PST: SLN biopsy versus ALND both followed by radiation to the axilla	1411	OS	SNL biopsy 73% vs ALND 76%, ($p>0.05$)
Esmeralda Garcia Torralba et al. 10	E12524	Retrospective	Oncologic outcome of ypT0N0 versus ypT0N1mic	106	OS and DFS at 39 months	DFS was not reached for the ypT0N0 group, 28 months (95%CI: 21.6−34.4 months) for the ypT0N1mic group (HR: 16.55, 95%cI: 2.68−102.37; $p = 0.003$); OS $p = 0.77$

patients. The non-inferiority NEONOD-2 trial will further clarify the role of micrometastases after PST.

In conclusion, despite significant advances in the understanding of axillary disease, numerous clinical questions still remain unanswered. Ongoing clinical trials will shed more light on these issues.

Declaration of Competing Interest

The authors declare no conflict of interest related to this paper

Contributors

ML Gasparri: drafting the manuscript, screening of the abstracts and data selection, review of the literature and comments. M Banys-Paluchowski: Tables editing. EA Bonci, R. Di Micco, R. Condorelli: review of the literature. Z. Matrai, P. Dubsky: critical comments. T. Kuehn: conceiving the idea. P. Poortmans, OD Gentilini: final revisions

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