Editorial Commentary

Risking arm lymphedema in more than a hundred patients to benefit one patient—is it worth it?

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Axillary lymph node dissection (ALND) can result in multiple complications, of which arm lymphedema, which could be permanent (1), is the most dreaded morbidity. It can occur in 20–25% of patients undergoing ALND (2). Though ALND could remove the metastatic axillary nodal burden and allow accurate staging of the axilla, it has not been shown to improve survival in patients with early breast cancer (3). As a result, in patients with no evidence of nodal involvement, a sentinel lymph node biopsy (SLNB) was introduced in the 1990s to stage the axilla and an ALND was performed only when the axillary lymph node was positive (4).

In the 2010s, however, there has been further de-escalation of axillary surgery, since it was demonstrated that SLNB alone, with omission of ALND, even in patients with limited nodal burden, did not affect survival (5-10). As such, ALND should be reserved for patients with heavy nodal burden of >2 metastatic lymph nodes.

While de-escalation of the axillary surgery was beneficial to the patients, it now posed a diagnostic dilemma for the medical oncologists. Since the number of sentinel lymph nodes which should be harvested to accurately stage the axilla was not defined in the de-escalation trials (5-10) and harvesting ≤2 sentinel lymph nodes alone in patients with limited nodal burden also did not seem to compromise survival (11), establishing the true nodal status of the patient, i.e., pathological 1–3 axillary nodal metastases (pN1) versus ≥4 axillary nodal metastases (pN2/N3), has become a challenge. This, in turn, could affect the patient's treatment regime. This was especially the case when only one sentinel lymph node was harvested, and that node was positive.

Without knowledge of the true nodal status, a dilemma arose when deciding on the use of CDK4/6 inhibitors for patients with T1–2, estrogen receptor-positive (ER^+), human epidermal growth factor receptor 2-negative ($HER2^-$) and grade 1 or 2 breast cancer without high risk factors, as in a group in cohort 1 of the monarchE trial [Endocrine Therapy With or Without Abemaciclib (LY2835219) Following Surgery in Participants With Breast Cancer (monarchE) (ClinicalTrials ID: NCT03155997)] (12). It was shown that addition of adjuvant abemaciclib to endocrine therapy in patients with 4–9 pathological nodal disease could improve 4-year invasive disease-free survival rates to 88.2% from 81.3% for those receiving hormonal therapy alone (13), though overall survival benefit has not yet been demonstrated.

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To identify pN2/3 disease, an ALND could be performed for staging but is it worth it? Based on a similar cohort in the phase 3 randomised SENOMAC trial [Sentinel Node Biopsy in Breast Cancer: Omission of Axillary Clearance After Macrometastases. A Randomized Trial (ClinicalTrials ID: NCT02240472)] (14), this implied that to prevent an invasive disease-free survival event at 5 years with 2 years of abemaciclib, 104 patients would need to have a completion ALND for staging, of which 17 would require lymphedema treatment. In another cohort which also used the monarchE criteria, 139 women needed to undergo a completion ALND for 1 woman to benefit from abemaciclib (15). In addition, using real world data, the incidence of having >3 metastatic axillary nodes in patients who met cohort 1 of monarchE trial criteria without high-risk factors and had limited positive sentinel lymph nodes was 11–13% (2,15). When analysed based on the number of positive sentinel lymph nodes, only 10% and 24% of patients with 1 and 2 positive sentinel lymph nodes respectively had pN2/3 disease which were eligible for CDK4/6 inhibitors.

Though pN2/3 nodal status was used in the monarchE trial as an indicator for CDK4/6 inhibitors, ALND need not be the staging tool used. In this case, an axillary ultrasound can be an adjunct diagnostic tool to guide the identification of patients with pN2/N3 disease whereby ALND was warranted. In a study which examined the use of axillary ultrasound in patients with $ER^{+}HER2^{-}$ breast cancer and metastatic nodal disease, having >5 abnormal lymph nodes on ultrasound was predictive of pN2/N3 disease (16). This study however was not truly reflective of cohort 1 of monarchE trial without risk factors, since it included patients with T3 and grade 3 disease and those aged 50 years old and above only. Conversely, in patients with a normal axillary ultrasound and T1–2 disease, only 6.1% would have >2 metastatic lymph nodes and require completion ALND (17). A normal axillary ultrasound could then reassure the treating physician that the probability of such a patient having pN2/3 disease and be eligible for abemaciclib, despite SLNB staging only, would be low. This study was however not confined to patients with luminal cancers only and investigated for patients with >2 instead of >3 lymph nodes. Despite so, axillary ultrasound has its limitations and can be less sensitive in cases with invasive lobular cancers, lower grade, and smaller breast tumors (18). Another study which examined the $ER^{+}HER2^{-}$ subtype concluded that having both a negative axillary ultrasound and magnetic resonance imaging would indicate a low probability of ≥4 positive lymph nodes pathologically, supporting their potential use in axillary nodal assessment (19).

Before we try hard to determine with certainty the patient's true nodal status, there were also other practical considerations. These included the compliance rate of patients with CDK4/6 inhibitors and its cost. In the monarchE trial, 6.4% and 5.3% of patients discontinued abemaciclib due to its adverse effects and patients' decision respectively (12). In addition, abemaciclib is costly (20) and may not be affordable for all eligible patients. This is true in the Asian setting which had experienced a surge in breast cancer rates in recent years (21,22) and there are vast inequities in the availability of healthcare resources in the low- and middle-income countries (23). These factors hence made the pursuit of completion ALND for staging purposes futile in these groups of patients, if they had no access or could not afford it in the first instance.

Moving forward, this ongoing controversy of whether an ALND should be performed to determine candidacy for abemaciclib in this group with low-risk features and limited positive sentinel lymph nodes might soon become a matter of little importance, given the findings from the NATALEE trial [A Trial to Evaluate Efficacy and Safety of Ribociclib With Endocrine Therapy as Adjuvant Treatment in Patients With HR+/HER2- Early Breast Cancer (NATALEE) (ClinicalTrial ID: NCT03701334)] (24). This trial demonstrated a 90.4% versus 87.1% invasive disease-free survival benefit at 3 years in the group who received ribociclib and hormonal therapy compared to hormonal therapy alone (25). Compared to the monarchE trial, a broader study population of patients with pN1 disease or had negative nodes and additional risk factors were included. As a result, once ribociclib is approved in adjuvant setting, ALND should not be performed in patients with low-risk features and 1–2 positive sentinel lymph nodes since these patients would have qualified for the use of ribociclib based on their pN1 status.

In conclusion, only a small group of patients with up to two positive sentinel lymph nodes, in luminal early breast cancer and favourable characteristics had pN2/3 disease. As a result, doing a completion ALND for the identification of patients suitable for abemaciclib was not justified, given the high morbidities associated with ALND and low rate of patients who would benefit from abemaciclib in this setting. When planning future trials to define the indication of novel agents, efforts must be made to use minimally invasive modalities, such as SLNB or imaging, etc., to decide on the eligibility of these novel agents, so that maximal gain

and minimal risk could be achieved for our patients. Last but not least, with the shift to omitting axillary dissection in patients with limited positive sentinel nodes, it may be timely to revisit the Tumor, Node, Metastasis (TNM) staging classification of breast cancer to classify this group of patients who are clinically node-negative (cN0) with 1–3 axillary nodal metastases on SLNB (pN1[sn]) as a distinct category, which has a low likelihood of pN2/3 disease that should not undergo axillary dissection for staging purposes.

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