Editorial

Regional nodal management in the light of the AMAROS trial

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The last decade witnessed the gradual adoption of sentinel lymph node biopsy (SLNB) to stage the axilla of breast cancer (BC) patients presenting with clinically negative lymph nodes; aiming to minimize the complications of the formal (gold standard) axillary lymph node dissection (ALND). Although abandoning ALND in pathologically negative sentinel node (SN) became the current standard of care, a similar consensus remains lacking in patients with positive SN.

The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial was, perhaps, among the most influential studies in steering the wheel towards a minimalistic approach. This non-inferiority phase III trial demonstrated no significant difference in overall survival (OS) and disease free survival (DFS) in 856 BC patients with macroscopic disease in one to two positive SN with or without additional ALND. Furthermore, the axillary recurrence was remarkably low (0.9%) in both arms where the majority of patients had systemic therapy and all received whole breast radiotherapy (RT) (1). The study had several limitations (such as inability to meet accrual, unexpectedly low events rate, poorly characterized radiotherapy fields and high proportion of patients lost to follow up), yet it strongly suggests that a less aggressive approach is justified. This minimalistic approach, however, collides with the results of different studies where a more comprehensive approach—including ALND and regional nodal irradiation (RNI)—not only reduce axillary failure but also reduces distant failure and potentially improves survival. In the modern systemic therapy era, the National Cancer Institute of Canada (NCIC) MA.20 reported significant decrease in locoregional failure (LRF) (3.2% *vs.* 5.2%; P=0.02) and distant metastases rates (8.4% *vs.* 12.7%; P=0.002) with a trend to OS improvement in patients randomized to RNI (*vs.* no RNI) after lumpectomy and ALND (2). Similarly, the 10-year results of the European Organization for Research and Treatment of Cancer (EORTC) 22922-10925 demonstrated a significant DFS benefit (72.1% *vs.* 69.1%, respectively; P=0.044) and an OS trend (82.3% *vs.* 80.7%, respectively; P=0.056) when comprehensive RNI is added to whole breast or chest wall radiation in 4004 patients with early stage breast cancer with axillary node involvement or high risk node negative disease treated surgically by lumpectomy or mastectomy (3). As recently reported by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (4), these two studies affirm that comprehensive nodal management may benefit women with low axillary lymph node disease burden (N1 stage) where micrometestesis probability is low and for whom, reduction of LRF with local modalities has a higher potential impact on the overall prognosis. Yet, an explanation is needed to reconcile the results of Z0011-lacking ALND and comprehensive RNI-vis-à-vis the outcome of EORTC 22922 and MA.20; especially when the percentage of patients with four or more positive lymph nodes is comparable in the three studies (Z0011, 13%; MA.20, 15% and EORTC 22922, 12%). Indeed, the low axillary failure observed in Z0011 may be multifactorial; inclusion of a favorable subset of patients with low axillary disease burden, systemic therapy effects, in addition to incidental radiation to axillary level I-II with high tangential fields and/or supraclavicular field. The post-hoc central review of the radiation field design in Z0011 determined that 19% received a third field directed to the supraclavicular region and nearly half of the patient received breast irradiation via high tangents (5). Unfortunately, this non-systematic RNI adoption complicates rather than clarifies this controversy.

Obviously, a trial randomizing patients with positive SNB to axillary radiotherapy (AxRT) or no AxRT is needed to clarify the role of RNI in this setting. Yet, the EORTC after Mapping of the Axilla: Radiotherapy or Surgery? (AMAROS) (6) (10981/22023) publication may help to seal the gap between the minimalistic approach of Z011 and the comprehensive approach of EORTC 22922 and MA.20.

Analogous to Z0011, AMAROS addressed ALND omission: BC patients with clinical T1-2N0—with one to two positive SN—were randomly assigned to AxRT or ALND. Yet, congruent with the comprehensive approach of EORTC 22922 and MA.20, RNI, including the undissected axilla, was delivered in all patients assigned to the AxRT arm. The median tumor size was 17 mm and the median age was 56 years in the AMAROS patients' population where 1,425 patients out of the 4,806 accrued were found to have positive SNB and, very similar to Z0011 patient's population, the majority had low-volume residual axillary disease (77% of patients had one positive sentinel lymph node, 40% had micrometastatic disease). Also, these two studies shared a comparable percentage of additional positive lymph nodes detected in the ALND arm (32.8% in AMAROS and 27% in Z0011). In both studies, systemic therapy was delivered in most of the patients (60% received chemotherapy) and in both studies the axillary recurrence was very low; under powering the 5-year axillary recurrence primary end point. Yet, due to non-significant difference in—per protocol—5-year DFS (82.7% *vs*. 80.5%; P=0.39), OS (89.9% *vs*. 89.5%; P=0.82) and axillary recurrence (0.33% *vs*. 1.3%; P=0.09) in the ALND *vs*. AxRT arms, respectively, the authors concluded that AxRT should be the treatment of choice in these patients due to lower lymphedema incidence (13% *vs*. 6%; P=0.0009). However, the AxRT reported superiority is weakened by the fact that the patients did not have a significant difference in shoulder movement impairment or quality of life reported outcomes. Although, AMAROS investigators are to be commended for including per protocol (in addition to intent to treat) analysis, the unexpected low number of axillary recurrence events in a non-inferiority design led to insufficiently powered comparison weakening the confidence in the interpretation of the final results. From a clinical perspective, however, the results are an important contribution that clearly impacts practice.

Hence, patients with low volume axillary disease can be spared the morbidity of ALND without increase in failure rates; a conclusion suggested by AMAROS results and reinforced by Z0011 recommendation. Yet, the same Z011 findings (including the non–systemic RNI) suggest that the low risk of nodal failure in this selected population doesn't even justify RNI in these patients who can appropriately be managed without ALND or AxRT.

Accordingly, considering or omitting AxRT must be recommended only after proper patient selection and weighting risk of recurrence against toxicity. The biology driven pattern of failure guided by molecular profiling may provide a unique insight on steering RNI clinical decision making with further research.

The next dilemma in axillary nodal management controversy may evolve around a similar question: RNI in the neoadjuvant setting [Alliance A11202 trial (NCT01901094)] or dropping SLNB altogether while depending on high quality imaging [SOUND trial (Sentinel node *vs.* Observation after axillary Ultra-SouND)].

As the future continues to unravel, the premise of individualized patient care continues to evolve and AMAROS, through suggesting a strong alternative to ALND, provides important information on that subject.

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