

## Z-11 trial and rethinking axillary reverse mapping

Masakuni Noguchi

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Axillary lymph node dissection (ALND) was an integral part of the surgical procedure of breast cancer in the era of radical mastectomy. However, a randomized clinical trial has demonstrated that it does not reduce systemic recurrence or improve survival. Therefore, ALND was regarded as a surgical procedure for assessing nodal status and preventing axillary recurrence. Recently, sentinel lymph node (SLN) biopsy has become a standard method for assessing nodal status in breast cancer. Several randomized studies confirmed that SLN biopsy achieves the same survival and regional control as ALND in SLN-negative patients with invasive breast cancer. This procedure can avoid unnecessary ALND in SLN-negative patients, thereby minimizing arm lymphedema. However, SLN-positive patients who undergo ALND do not benefit from SLN biopsy.

In 2011, the American College of Surgeons Oncology Group (ACOSOG) reported the results of the Z-11 trial. This trial was designed to address whether ALND is necessary in SLN-positive patients who underwent breast-conserving surgery (BCS) with whole-breast irradiation and systemic therapy [1]. The results indicated a remarkably low rate of axillary recurrence in SLN-positive patients who did not undergo ALND. At a median follow-up of 6.3 years, axillary recurrence rates were similar between each arm with 4 (0.9 %) patients in the SLN

biopsy group compared with 2 (0.5 %) in the ALND group, and there was no trend towards improvement of disease-free or overall survival with ALND. Morrow et al. [2] stated that ALND could be safely omitted in selected women with T1-2, clinically node-negative (cN0) breast cancer who undergo SLN biopsy and BCS with whole-breast irradiation and appropriate systemic therapy.

The Z-11 trial is a landmark study. Even in patients with positive SLNs, ALND is not a critical component of surgical therapy. In ACOSOG Z-11, regional recurrence after SLNB alone was <0.1 %, despite the fact that 27 % of patients randomized to the ALND arm of the study had additional metastases identified [1]. However, this trial did not lead to the abandonment of SLN biopsy itself in cN0 patients, even if ALND can be avoided irrespective of the SLN status. It demonstrated that SLN biopsy with whole-breast irradiation and systemic therapy can replace ALND in preventing axillary recurrence in patients with macro-metastatic SLNs. Thus, a combination therapy of surgical resection and irradiation is effective not only for the primary breast cancer but also for the axillary metastases.

Obviously, ALND should not be omitted in patients who underwent total mastectomy, patients who received neo-adjuvant therapy, and patients who underwent BCS without breast radiotherapy. Currently, nipple- or skin-sparing mastectomy with immediate breast reconstruction using breast implant has become increasingly popular for patients with multicentric and multifocal tumors. However, either breast or axillary irradiation would not be preferable for these patients because of the increasing rate of capsular contracture. Therefore, ALND remains the standard procedure of treating regional disease in these patients. Nevertheless, conventional ALND is frequently associated with morbidities, including arm lymphedema, seroma, disturbance of shoulder movement and sensory loss. Arm

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M. Noguchi (✉)  
Department of Breast and Endocrine Surgery, Kanazawa  
Medical University Hospital, Uchinada, Daigaku-1-1, Kahoku,  
Ishikawa 920-0293, Japan  
e-mail: nogumasa@kanazawa-med.ac.jp

lymphedema is among the most serious chronic complications in patients following axillary surgery.

The axillary reverse mapping (ARM) technique has been developed for identifying and preserving lymphatic drainage from the arm during ALND, thereby expecting to minimize arm lymphedema. The ARM procedure is the reverse of SLN biopsy that serves to identify and then remove the lymph nodes draining from the breast. It is based on the hypothesis that there are two distinct lymphatic pathways in the axilla and a medial chain draining the breast and a lateral chain draining the arm. However, ARM nodes could be involved in patients with clinically positive nodes ( $cN \geq 1$ ). Due to oncological concern, therefore, ARM lymphatics/nodes within the boundaries of a standard ALND should be resected in these patients. On the other hand, in cN0 patients, the metastatic ARM nodes may be actually SLN-ARM nodes [3]. Deng et al. [3] reported that ARM nodes metastasis occurred in 6 of 69 patients. In these 6 patients, all metastatic ARM nodes coincided with SLN-ARM nodes. In 50 of 69 patients whose ARM nodes did not coincide with SLNs, all ARM nodes were negative, even in 12 patients with metastatic SLNs. They suggested that all of the ARM node involvements occur only in patients whose ARM nodes were SLN-ARM nodes, and crossover SLN-ARM nodes may be the main reason for ARM node involvement. Similarly in our recent study (unpublished data), the ARM nodes were involved in 11 of 64 cN0 patients whose ARM nodes coincided with SLNs (Concordance type). On the other hand, all of the ARM nodes were not involved in 174 cN0 patients whose ARM nodes did not coincide with SLNs, even in 21 patients with positive SLNs (Separate type). If ALND is required in SLN-positive patients who do not meet the Z-11 criteria, therefore, conservative ALND with ARM procedure will be the next procedure.

The oncological safety of the ARM procedure has not yet been confirmed. Nevertheless, Kodama et al. [4] performed lower ALND without using either the ARM procedure or SLN biopsy to prevent arm lymphedema. In the lower ALND, axillary lymph nodes were partially dissected below the second intercostal brachial nerve (ICBN).

They reported that the 5-year overall and disease-free survival rates were 95.6 and 89.7 %, respectively, in 1043 cN0 patients who underwent lower ALND from 2001 to 2008. Axillary recurrence was developed only in 6 patients (0.6 %) with a median follow-up of 72 months, while no lymphedema occurred. These survival rates were not significantly different from those of 1084 cN0 patients who underwent conventional ALND from 1994 to 2000 (94.9 and 88.4 %, respectively). Since the majority of ARM nodes are located between the axillary vein and the second ICBN, these data have suggested that the ARM procedure is oncologically feasible in cN0 patients.

In patients with cN0, ALND can be avoided not only in patients with negative SLNs but also in those with positive SLNs, who meet with the Z-11 criteria. However, conservative ALND with ARM procedure will be indicated in patients with positive SLN who do not meet the Z-11 criteria. On the other hand, conventional ALND remains a standard method of treating axillary disease in patients with  $cN \geq 1$ . Therefore, surgical treatment of the axilla can be individualized on the basis of the axillary nodal status.

**Conflict of interest** The author indicated no potential conflicts of interest.

## References

1. Giuliano AE, McCall L, Beitsch P, Whitworth PW, Blumencranz P, Leitch AM, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg.* 2011;252:426–33. doi:[10.1097/SLA.0b013e3181f08f32](https://doi.org/10.1097/SLA.0b013e3181f08f32).
2. Morrow M, Giuliano AE. To cut is to cure: can we really apply Z11 in practice? *Ann Surg Oncol.* 2011;18:2413–5.
3. Deng H, Chen L, Jia W, Chen K, Zeng Y, Rao N, et al. Safety study of axillary reverse mapping in the surgical treatment for breast cancer patients. *J Cancer Res Clin Oncol.* 2011;137:1869–74. doi:[10.1007/s00432-011-1064-3](https://doi.org/10.1007/s00432-011-1064-3).
4. Kodama H, Mise K, Kan N. Partial lower axillary dissection for patients with clinically node-negative breast cancer. *J Int Med Res.* 2012;40:2336–45. doi:[10.1177/030006051204000632](https://doi.org/10.1177/030006051204000632).