

# To Dissect or Not to Dissect? The Surgeon's Perspective on the Prediction of Greater Than or Equal to 4 Axillary Lymph Node Metastasis in Early-Stage Breast Cancer

## A Comparative Analysis of the Per-Protocol Population of the SINODAR-ONE Clinical Trial

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Over the past few decades, the management of axillary surgery in breast cancer (BC) has undergone a significant evolution, shifting away from routine axillary lymph node dissection (ALND) toward more selective approaches or even omission of axillary surgery altogether in appropriately selected patients.<sup>1</sup> The shift toward a less aggressive approach to axillary management is strongly supported by a substantial body of literature. The National Surgical Adjuvant Breast and Bowel Project B-04 trial randomly assigned clinically node-negative (cN0) BC patients to receive either radical mastectomy, total mastectomy, or total mastectomy and regional radiotherapy. After 25 years of follow-up, no significant difference in disease-free survival and overall survival (OS) was observed among the different groups of cN0 women.<sup>2</sup> The European Organization for Research and Treatment of Cancer 10981-22023 AMAROS trial investigated whether axillary radiotherapy could replace ALND in patients with cN0 T1-2 BC and positive sentinel lymph node (SLN). After 10-year follow-up, both the axillary radiotherapy and ALND groups showed excellent axillary recurrence (0.9% vs 1.6% in the ALND and axillary radiotherapy group, respectively) and OS rates (14.0% vs 16.4% in the ALND and axillary radiotherapy group, respectively).<sup>3</sup> The American College of Surgeons Oncology Group Z0011 trial randomized 891 women with cN0 BC and up to 2 positive SLNs detected after breast-conserving surgery (BCS) to either ALND or observation.

No statistically significant difference in OS was found after 9.3 years of follow-up.<sup>4</sup> The SINODAR-ONE randomized clinical trial was designed to overcome the limitations of the Z0011 study, enrolling BC patients undergoing BCS or mastectomy. The initial study results reported that patients with cN0 T1-2 BC and 1–2 macrometastatic SLNs treated with BCS, omission of ALND, and adjuvant treatment did not present worse 3-year survival, regional, or distant recurrence rates than those treated with ALND.<sup>5</sup> Only a few routine indications for ALND remain in current clinical practice.<sup>6</sup> However, de-escalation of axillary surgery, especially in BC patients with 1–3 positive SLNs challenges the recently established criteria for adjuvant treatment. The RxPONDER trial investigated the effectiveness of utilizing the Oncotype DX recurrence score in assessing the benefits of chemotherapy in patients diagnosed with hormone receptor-positive, human epidermal growth factor receptor 2-negative BC and having 1–3 positive lymph nodes.<sup>7</sup> The monarchE trial evaluated abemaciclib in the adjuvant setting for patients with high-risk (ie,  $\geq 4$  pathologically positive axillary nodes or 1–3 positive nodes and at least one of the following: tumor dimension  $\geq 5$  cm, G3, or Ki67  $\geq 20\%$ ) early-stage BC.<sup>8</sup> Importantly, the Z0011 and SINODAR-ONE clinical trials showed that the rate of axillary tumor-burden left behind in early-stage BC when omitting ALND was at least 1 positive lymph node in 27% and 44% of cases respectively, as assessed by the ALND groups.<sup>4,5</sup> Considering the significance of nodal disease extent in these studies, the question remains as to whether these patients should undergo further ALND to determine whether  $\geq 4$  nodes are positive to guide subsequent adjuvant therapies. To further investigate the latest controversies in axillary management of early-stage BC patients and predict the presence of  $\geq 4$  axillary lymph node metastasis, we evaluated patients with  $\geq 4$  positive nodes in the per-protocol population of the SINODAR-ONE clinical trial.

The SINODAR-ONE trial is a prospective noninferiority multicenter randomized study aimed at assessing the therapeutic role of ALND in patients undergoing either BCS or mastectomy for cN0 T1-2 BC with 1–2 positive SLNs. Patients were randomly assigned to either the removal of  $\geq 10$  axillary level I/II nodes followed by adjuvant therapy (standard arm) or no further axillary surgery (experimental arm). We evaluated patients in the standard arm of the per-protocol population and a comparison of characteristics between patients with  $\geq 4$  metastatic lymph nodes and patients with 1–3 metastatic lymph nodes was performed. A multivariate analysis was performed using a logistic regression model to identify independent predictors of  $\geq 4$  axillary lymph node metastasis.

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Overall, 403 cN0 T1-2 BC patients in the per-protocol population were randomized to receive ALND. Of these, 65 and 338 patients presented with  $\geq 4$  or 1–3 axillary lymph node metastasis, respectively. The following factors were found to significantly increase the probability to present  $\geq 4$  axillary lymph node metastasis: lobular histology versus other histology [odds ratio (OR) = 4.185], G3 versus G1-2 (OR = 5.930), pT2 versus pT1 (OR = 5.260), and 2 positive SLNs versus 1 positive SLN (OR = 13.188). Univariate and multivariate analyses are detailed in Supplemental Table 1, <http://links.lww.com/AOSO/A298>.

The findings of the monarchE trial, which evaluated the use of abemaciclib in high-risk early-stage BC, have sparked discussions regarding the necessity of ALND in specific cases. In this trial, high-risk patients, including those with  $\geq 4$  positive lymph nodes or 1–3 positive lymph nodes along with additional high-risk features such as tumor size  $\geq 5$  cm, G3, or Ki67  $\geq 20\%$ , were randomly assigned to receive standard endocrine therapy with or without abemaciclib. The trial demonstrated a significant improvement in 2-year invasive disease-free survival with the addition of abemaciclib.<sup>8</sup> Additionally, on the basis of the findings from the RxPONDER trial, it is recommended that premenopausal patients with 1–3 positive nodes undergo chemotherapy irrespective of their Oncotype DX recurrence score.<sup>7</sup> The ongoing question persists as to whether patients who have 1–3 positive SLNs without any additional risk factors should undergo ALND to ascertain the presence of  $\geq 4$  positive lymph nodes. We suggest that a minority of cN0 T1-2 BC patients may be understaged if ALND is not performed. Nevertheless, the improvements and increasing effectiveness of combination therapies may sufficiently control and treat the axillary tumor-burden left behind, potentially reducing the need for extensive axillary surgery, as demonstrated by the promising 3-year oncological outcomes of the SINODAR-ONE trial. While ALND may still be considered, particularly in cases presenting with specific risk factors for additional axillary disease (such as lobular histology, G3 grading, pT2 stage, and the presence of 2 positive SLNs), our study suggests a refined perspective. Specifically, in instances where 3 out of the 4 identified predictive factors are present, we advocate for a proactive approach, recommending the performance of ALND. We believe that such a decision, made after multidisciplinary team discussion, contributes to a more

comprehensive understanding of nodal involvement, balancing the risk of complications associated with ALND with the need for correct axillary staging for guiding personalized treatment strategies.

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