



Invited Commentary | Oncology

## Distant Lymph Node Metastases From Breast Cancer— Is it Time to Review TNM Cancer Staging?

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Using the Surveillance, Epidemiology, and End Results (SEER) registries database, Hong Pan et al<sup>1</sup> retrospectively analyzed 2033 patients who were diagnosed with breast cancer between 2010 and 2014. Patients were allocated into 3 cohorts, namely the distant lymph node metastases (DLNM) cohort, ipsilateral supraclavicular lymph node metastases (ISLM) cohort, and distant metastases (DLNM excluded) cohort. Their results revealed that 3-year breast cancer-specific survival rate (BCSS) and overall survival (OS) rate were similar between patients in the DLNM and ISLM cohorts. In addition, patients with DLNM did not show worse BCSS (HR, 0.93; 95% CI, 0.64-1.36;  $P = .72$ ) and OS (HR, 0.81; 95% CI, 0.59-1.10;  $P = .17$ ), compared with those with ISLM. Therefore, the authors concluded that DLNM of breast cancer may be a regional rather than a metastatic disease. Plus, it was recommended to reestablish the staging criteria for breast cancer, and offer patients with DLNM more aggressive locoregional treatments.

As one of the paramount factors in breast cancer staging, status of lymph node metastasis guides therapeutic strategies and is used to assess prognosis for patients, particularly those with distant metastases. Patients with ISLM have been categorized as stage III according to the tumor-node-metastasis classification, owing to their comparable clinical course and prognosis with those of patients with stage III locally advanced breast cancer.<sup>2</sup> A better OS has been found for patients with contralateral axillary lymph node metastasis (CALNM), currently classified as an M1 stage IV disease, compared with those with distant lymph node metastasis at other sites.<sup>3</sup> Owing to the fact that lymph node metastases of several sites are now redefined as locoregional instead of distant disease, is it necessary to reconsider DLNM as a local disease as well? Fortunately, this cohort study provides critical evidence.<sup>1</sup> The results showed that locoregional treatments for ISLM, which is staged as IIIC, were also effective for DLNM. Primary surgery and radiotherapy rather than distant surgery improved the BCSS and OS of patients with DLNM. In addition, better outcomes were obtained from primary surgery for both luminal and triple-negative subtypes. Overall, it indicates that more locoregional treatments should be considered for patients with DLNM, which may further improve the OS rate and prognosis of these patients.

Whether primary tumor resection (PTR) should be performed on patients with breast cancer with distant metastases has long been a controversial issue. In our previous meta-analysis of 30 observational studies,<sup>4</sup> PTR was associated with significantly improved OS among patients with stage IV breast cancer (HR, 0.65; 95% CI, 0.61-0.70;  $P < .001$ ). The benefits of primary tumor surgery, were limited according to the results of randomized controlled trials.<sup>5,6</sup> In fact, this contradictory outcome could be attributed to the selection bias in retrospective studies. Patients with smaller tumor size, oligometastasis, or bone-only metastasis were more likely to undergo PTR in cohort studies. Similarly, Pan et al<sup>1</sup> reported that primary surgery was associated with improved BCSS and OS among patients with DLNM, but no statistical test was performed to eliminate the difference in baseline characteristics between the 2 cohorts. In such a case, selection bias may also exist in their study, which can lead to unreliable conclusions. Therefore, the effectiveness of primary tumor or distant lymph node resection in patients with DLNM has yet to be proven with more clinical trials and high-quality pair-matching studies.

Several strengths in the study by Pan et al<sup>1</sup> should be recognized. It is the first study that compares the difference of real-world survival between patients with DLNM and ISLM breast cancer.

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Given the large sample size, results are credible, and lead to considerations on reviewing the current TNM staging for breast cancer. However, a few limitations that affect the quality of this study cannot be omitted. First, selection bias is inevitable, given the differences in baseline characteristics (age, treatment principles, subtype) among 3 cohorts. Furthermore, details of the treatment were not compared because the specific chemotherapy regimen and radiotherapy dose are unavailable from the SEER database. Second, this study only analyzed samples from the SEER database, which lacks data of other ethnic populations. Chinese patients account for 12.2% of all newly diagnosed breast cancers in the world,<sup>7</sup> thus it is important to include the Chinese population and other major populations for determining the prognosis of DLNM breast cancer. Finally, the median follow-up (27 months) was short, which could affect the final survival outcomes. Hence, more multicenter randomized clinical trials and observational studies with high quality, large sample size, multivariable analysis, and adequate follow-up are required for further validation.

### ARTICLE INFORMATION

**Published:** March 16, 2021. doi:[10.1001/jamanetworkopen.2021.2026](https://doi.org/10.1001/jamanetworkopen.2021.2026)

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**Conflict of Interest Disclosures:** None reported.

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