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Lymph Node Micrometastases Do Influence Breast Cancer Outcome

TO THE EDITOR: The study by Mittendorf et al[1] and the associated editorial[2] published in *Journal of Clinical Oncology* renewed the debate on the prognostic relevance of isolated tumor cells (pN0(i+)) and micrometastases (pN1mi) in sentinel lymph nodes (SLNs) from patients with breast cancer.

Patients from MD Anderson Cancer Center (MDACC; n = 3,474; median follow-up, 6.1 years) and from the American College of Surgeons Oncology Group Z0010 trial (n = 4,590; median follow-up, 9 years) were analyzed.[1] In both cohorts, there were modest, nonsignificant differences between stage IA (pN0) and IB (pN0(i+)/pN1mi) patient-cases for relapse-free survival (RFS), distant disease–free survival, and overall survival (OS). These findings led the authors to conclude that there is no prognostic difference between stage IA and stage IB disease and that this categorization should be reconsidered.

However, as the authors remarked,[1,2] adjuvant chemotherapy was administered to larger fractions of stage IB patients than stage IA patients (70.5% *v* 26.9% in the MDACC cohort; 52.6% *v* 38.1% in the Z0010 trial, respectively[1]). Further, clinicians at MDACC were provided with patient staging and might have recommended systemic therapy accordingly.[1,2]

We had previously analyzed the prognostic value of a pN0(i+)/pN1mi status in a single-institution, consecutive series (n = 702; median follow-up, 8 years).[3,4] Hematoxylin and eosin (H&E) pN0 cases were step-sectioned every 200 μm (n = 6,676) and reassessed by immunohistochemistry (IHC). Accordingly, 13% of patients were restaged to pN0(i+) or pN1mi. The hazard ratio (HR) for disease relapse for pN0(i+)/pN1mi versus pN0 cases was 2.16 (95% CI, 1.42 to 3.28; $P < .001$), and the pN0(i+)/pN1mi status was shown to account for 50% of metastatic recurrences.

In the MIRROR (Micrometastases and Isolated Tumor Cells: Relevant and Robust or Rubbish?) study (median follow-up, 5.1 years),[5] SLNs from 3,181 patients with breast cancer were serially sectioned every 150 μm, $\geq$ 3 levels, and analyzed by H&E/IHC. Untreated pN0 cases (n = 856) were compared with untreated (n = 856) or treated (n = 995) pN0(i+)/pN1mi cases. The HR for RFS of untreated pN0(i+) versus untreated pN0, was 1.50 (95% CI, 1.15 to 1.94); that of pN1mi was 1.56 (95% CI, 1.15 to 2.13). However, HRs were markedly reduced by adjuvant therapy, in a parallel manner for pN0(i+) (HR, 0.66; 95% CI, 0.46 to 0.95) and pN1mi (HR, 0.50; 95% CI, 0.35 to 0.72) cases. Thus, systemic therapy effectively erased the added risk associated with a pN0(i+)/pN1mi status.[5]

De Boer et al[6] extended these findings in a meta-analysis of 58 studies that included single-section examination of axillary lymph nodes (n = 285,638 patients), H&E/IHC re-examination of lymph nodes previously judged negative (n = 7,740 patients), and SLN-only H&E/IHC analyses (n = 4,155 patients). Random effects meta-analysis was used to estimate pooled HRs. At 5 years of follow-up, pN0(i+)/pN1mi cases had worse outcomes than pN0 cases, both for RFS (HR, 1.55; 95% CI, 1.32 to 1.82) and for OS (HR, 1.45; 95% CI, 1.11 to 1.88).

In the NSABP B-32 (National Surgical Adjuvant Breast and Bowel Protocol B-32) randomized prospective study,[7] pathologically negative SLNs were centrally evaluated for occult metastases by H&E/IHC. Treating physicians were unaware of the evaluation results, and restaging was not used for therapeutic decisions. Occult metastases were detected in 15.9% of 3,887 patients. The associated HRs were 1.40 for OS (95% CI, 1.05 to 1.86; $P = .03$), 1.31 for RFS (95% CI, 1.07 to 1.60; $P = .02$), and 1.30 for distant disease–free survival (95% CI, 1.02 to 1.66; $P = .04$). Occult metastases were shown to be an independent prognostic variable and were found to lead to a 1.2% reduction of OS at 5 years.[7]

Giuliano et al[8] reassessed SLNs from 3,326 pN0 patients in the Z0010 trial. A low fraction (10.5%) of IHC–re-evaluated nodes was found to contain occult metastases, and these were not associated with increased odds of death or recurrence. However, only single-section analysis was performed, and, as the authors remarked, the smaller number of IHC-positive patients might have been insufficient to detect differences in survival. Moreover, 78.3% of patients received adjuvant therapy in the NSABP B-32 benchmark trial versus 86.2% in the Z0010 trial, and therapy intensity could have attenuated the association between occult metastases and survival in the Z0010 trial.[8] Moreover, IHC-positive cases in the Z0010 trial were administered more frequent therapeutic procedures than IHC-negative cases (+12.7% overall),[8] further blunting the detection of the pN0(i+)/pN1mi-associated risk.

The SEER database was queried for the prognostic significance of pN1mi in pM0 in patients with breast cancer with fewer than four axillary nodes affected by macroscopic disease (n = 209,720).[9] In multivariable analyses, pN1mi was found to be a significant prognostic indicator across all patients, with an HR of 1.35 versus pN0 cases ($P < .001$).[9]

In summary, stage IB patients consistently seem to be at significantly greater risk of experiencing disease relapse than stage IA patients when treatment effect is taken into account. As Mittendorf et al[1] argue, distinct biologic contexts[10] do modulate the benefit of adjuvant therapy. At the same time, though, stage IB consistently remains one of the key, predictive parameters of response from systemic therapy.[5] Hence, it correspondingly remains important to rigorously identify patients with stage IB breast cancer to provide them with effective therapeutic procedures.

Laura Antolini
University of Milano-Bicocca, Monza, Italy

Elia Biganzoli
University of Milano, Milan, Italy

Patrizia Querzoli
University of Ferrara, Ferrara, Italy

Mauro Piantelli and Saverio Alberti
University of Chieti, Chieti, Italy

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Laura Antolini
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Patrizia Querzoli
No relationship to disclose

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No relationship to disclose

Saverio Alberti
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