EDITORIAL

Sentinel-Lymph-Node Biopsy in Early-Stage Breast Cancer — Is It Obsolete?

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The role of axillary surgery in the management of breast cancer has changed. Sentinel-lymph-node biopsy is used to identify nodal metastases, but recognition of the lack of therapeutic benefit of this approach, coupled with the emphasis on tumor biology for decisions about systemic therapy, has led to trials examining the elimination of sentinel-lymph-node biopsy in early-stage breast cancer.

Two trials involving clinically node-negative patients with breast cancer treated without axillary surgery have now provided outcome data: Reimer et al. present in the *Journal* results from the INSEMA (Intergroup Sentinel Mamma) trial,[1] and data from the SOUND (Sentinel Node versus Observation after Axillary Ultrasound) trial were published in 2023.[2] Both trials enrolled patients who planned to undergo breast-conserving surgery, and both required the use of axillary ultrasonography, but they had no restrictions on eligibility based on receptor subtype or menopausal status. The SOUND trial included patients with cancer staged as clinical T1 (cT1; tumor size, ≤2 cm) and node negative (N0); the INSEMA trial also included patients with cT2 cancers (tumor size, >2 cm to ≤5 cm). Despite the broad criteria for eligibility, approximately 95% of the women in both trials had hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer, and approximately 90% were postmenopausal. This selection of older patients with luminal breast cancer reflects the importance of nodal status in the choice of systemic therapy for HER2-overexpressing or triple-negative breast cancers, as well as for HR-positive, HER2-negative breast cancers in premenopausal women.

The INSEMA and SOUND trials showed that for survival outcomes, the omission of sentinel-lymph-node biopsy was not inferior to the use of sentinel-lymph-node biopsy. Among patients with cT1N0 cancers and normal ultrasonography results, pathological N2 (pN2) disease (in which cancer has spread to four to nine axillary lymph nodes) is present in less than 1%. Although approximately 9% of the patients in the SOUND trial and 11% of those in the INSEMA trial who underwent sentinel-lymph-node biopsy had macrometastases in one to three axillary nodes, axillary recurrence was seen in only 0.4% and 1.0%, respectively, of patients in the SOUND and INSEMA trials who did not undergo axillary surgery.

Questions about the safety of omitting sentinel-lymph-node biopsy in the treatment of patients with T2 tumors remain: only 19.2% of the patients in the per-protocol population in the INSEMA trial had pT2 tumors (median size, 2.5 cm). Both the likelihood and the number of nodal metastases increase with increasing tumor size; 20.8% of the patients with T2 tumors had macrometastases, as compared with 10.6% of those with T1 tumors, a finding that arouses concern about higher rates of axillary recurrence if this approach is adopted for larger T2 tumors. The elimination of sentinel-lymph-node biopsy in the treatment of patients with higher-risk disease — including those with grade 3 tumors, who were underrepresented (accounting for 3.6% of the total number of patients) in the INSEMA trial — may result in suboptimal recommendations with regard to adjuvant therapy.

Guidelines from the National Comprehensive Cancer Network encourage consideration of regional nodal irradiation in patients with one to three axillary nodal metastases,[3] an approach that may result in undertreatment in approximately 9 to 11% of patients treated without sentinel-lymph-node biopsy, according to the data from the SOUND and INSEMA trials. By contrast, patients with T1 tumors are often candidates for accelerated partial-breast irradiation; however, current guidelines for partial-breast irradiation specify that patients be histologically node negative,[4] a standard that leads many clinicians to pursue whole-breast radiation therapy when they are faced with uncertain nodal status. Data from the prospective single-group LUMINA (Local Recurrence Following Breast-Conserving Surgery and Endocrine Therapy in Low-Risk Luminal A Breast Cancer)[5] and IDEA (Individualized Decisions for Endocrine Therapy Alone)[6] trials suggest that whole-breast radiation therapy could be eliminated entirely in postmenopausal women with HR-positive, HER2-negative, biologically low-risk tumors. This concept is being studied in randomized trials, but all the patients involved in the LUMINA and IDEA trials had histologically negative nodes; in the future, we will need to identify the de-escalated treatment that should be prioritized.

Potential undertreatment with cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors is a subject of similar concern. Abemaciclib was the first CDK4/6 inhibitor approved for adjuvant therapy, on the basis of improved disease-free survival in the MonarchE (Endocrine Therapy with or without Abemaciclib Following Surgery in Participants with Breast Cancer) trial, which included, in addition to a group of patients with high-risk disease, patients with involvement of one to three nodes and T1 or T2, grade 1 or 2 tumors[7]; that trial aroused concern about a loss of benefit from abemaciclib in the absence of sentinel-lymph-node biopsy. Some of this concern was mitigated with the approval of adjuvant ribociclib for use in both node-negative and node-positive cancers, a development that decreased reliance on nodal status for decision making. Given that CDK4/6 inhibitors are not without additional toxicity and are associated with substantial cost as compared with endocrine therapy alone, their value in patients with very-low-risk disease — such as those enrolled in the INSEMA trial — is probably small.

Together, the INSEMA and SOUND trials (as well as two additional, ongoing trials with results yet to be reported[8,9]) provide a glimpse into the future. Sentinel-lymph-node biopsy is associated with low but measurable morbidity,[10] and elimination of the procedure decreases the treatment burden on patients. But if the omission compromises recommendations for adjuvant therapy and leads to whole-breast irradiation in a candidate for partial-breast irradiation or to the omission of CDK4/6 inhibitor therapy because of uncertainty about nodal status, is this the most appropriate course? Successful de-escalation of any therapeutic approach requires multidisciplinary consideration of the effects on the entire treatment plan; INSEMA and SOUND data provide a strong foundation for consideration of how to incorporate the elimination of sentinel-lymph-node biopsy into practice. At present, patients with grade 1 or 2, cT1 tumors are ideal candidates for this approach. If surgical pathological examination reveals a larger T2 tumor, a high-grade tumor, or lymphovascular invasion — factors that increase the likelihood of nodal metastases and are indicative of worse prognosis — patients can then undergo sentinel-lymph-node biopsy. This approach will avoid axillary surgery for the majority while minimizing undertreatment. Patient-reported outcomes are needed to determine which therapies patients prefer to de-escalate as we increasingly face a choice of which therapies to omit.

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