Validation of sentinel lymph node (SLN) dissection (SLND) as an alternative to axillary lymph node dissection (ALND) has been a significant advance in the surgical management of breast cancer. As detailed in the review by Pilewskie and Morrow, clinical trials have proven that in clinically node-negative patients, SLND provides accurate staging with less morbidity, and that ALND can be omitted in patients with negative SLNs without diminishing disease-free survival, overall survival, or local-regional control. Moreover, in patients with micrometastases, and in select patients with SLN macrometastases, use of ALND has not improved local-regional control or survival. One constant finding in these trials is low axillary recurrence rates—consistently less than 3%.

As surgical trials have been exploring the possibility of reducing the extent of surgery, use of adjuvant systemic therapy has increased. Treatment decisions are now guided by receptor status, molecular subtypes, and genomic tools; thus, the results of the SLND are often not necessary to guide management. This trend has extended to the node-positive patient population: in the RxPONDER trial, the 21-gene recurrence score assay is being used to risk-stratify patients with hormone receptor–positive disease for purposes of chemotherapy decision making. This trial gets at the crux of the argument that Drs. Pilewskie and Morrow are making—namely, that the biology of the primary tumor is the most important determinant of treatment and outcome. This strategy of looking beyond the anatomy and focusing on biology has led some to ask whether nodal status needs to be determined at all in patients who present with a clinically negative axilla. That question is being addressed in the SOUND (Sentinel Node vs Observation After Axillary Ultrasound) trial, which is enrolling patients with tumors < 2 cm with a clinically negative axilla on physical examination for whom breast-conserving therapy is planned. Axillary ultrasound is performed, and patients with suspicious nodes are excluded. The remaining patients are randomized to SLND or no axillary staging. The primary endpoint is distant disease–free survival; 1,560 patients will need to be enrolled to determine whether no axillary treatment is not inferior to SLND. Although the morbidity of SLND is significantly less than that of ALND, there are long-term effects, and lymphedema rates of approximately 8% have been reported with SLND. If the SOUND trial demonstrates that no axillary treatment is required for clinical T1 tumors, this would spare many patients long-term effects from a procedure that has a low likelihood of affecting survival.

One group of patients not discussed by Pilewskie and Morrow are clinically node-negative patients who are receiving neoadjuvant chemotherapy. This is likely due to the lack of randomized trials evaluating SLND in this population. There have been a number of single-institution studies, and two meta-analyses have shown that SLND is feasible and accurate after neoadjuvant chemotherapy. The meta-analysis by van Deurzen et al included 27 studies and more than 2,100 patients; it reported an SLN identification rate of 93% in clinically node-negative patients. The false-negative rate (FNR) was 10.5%; this is consistent with the FNR in the National Surgical Breast and Bowel Project (NSABP) B-32 trial (9.8%), which established the efficacy of SLND in clinically node-negative patients undergoing surgery as their initial intervention. In the MD Anderson experience with 575 clinically node-negative patients, the SLN identification rate after neoadjuvant chemotherapy was 97.4% and the FNR was 5.9%. These results compared favorably with the identification rate (98.7%) and FNR (4.1%) in 3,171 patients who underwent upfront surgery. Importantly, in patients with clinical T2 or T3 tumors who received neoadjuvant chemotherapy, there were fewer positive SLNs, which resulted in fewer ALNDs. After a median follow-up of approximately 4.5 years, regional recurrences rates were 1.2% in patients who received neoadjuvant therapy and 0.9% in those who underwent surgery first. These data are consistent with those from NSABP B-18, which showed that patients who received neoadjuvant chemotherapy were
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less likely to have node-positive disease at surgery compared with those who had surgery first.[22] Taken together, these data suggest that neoadjuvant chemotherapy clears occult disease and may spare patients having to undergo ALND. Use of the neoadjuvant platform and assessment of pathologic response as a surrogate endpoint is part of a new strategy being used to support accelerated approval by the US Food and Drug Administration.

Pilewskie and Morrow conclude that further research is necessary to identify patients who will benefit from more aggressive local-regional treatment. Traditionally, node-positive patients are candidates for more aggressive treatment, including ALND. Studies have shown that up to 40% of node-positive patients who receive neoadjuvant chemotherapy will have a complete response in the axilla, with even higher rates in patients with human epidermal growth factor receptor 2 (HER2)-positive tumors treated with trastuzumab and chemotherapy.[23,24] The question that arises is which patients can avoid ALND after achieving a clinically node-negative status with chemotherapy? The American College of Surgeons Oncology Group (ACOSOG) Z1071 trial was a phase II study that enrolled patients with clinical T0-T4,N1-N2,M0 breast cancer for whom SLND and completion ALND were planned following neoadjuvant chemotherapy.[23] The primary objective was to determine the FNR in clinical N1 patients with at least 2 SLNs removed. Of 525 patients with 2 or more SLNs, the FNR was 12.6%. The FNR decreased to 10.8% when both blue dye and radioactive colloid were used to identify the SLNs and decreased further, to 9.1%, when 3 or more SLNs were removed.[23] Results from the Sentinel Neoadjuvant (SENTINA) [25] and the Sentinel Node Biopsy Following Neoadjuvant Chemotherapy in Biopsy-Proven Node-Positive Breast Cancer (SN FNAC)[26] trials were similar, suggesting that surgical technique plays a critical role in lowering the FNR in this setting. Ongoing trials are investigating axillary management following neoadjuvant chemotherapy in patients with clinically node-negative disease. The NSABP B-51/ Radiation Therapy Oncology Group (RTOG) 1304 trial is randomizing patients converted to pathologically node-negative after neoadjuvant chemotherapy to regional nodal irradiation (RNI) or no RNI, with a primary aim of determining whether RNI will significantly reduce the invasive breast cancer recurrence–free interval. The Alliance A011202 trial is randomizing patients with a positive SLN after chemotherapy to ALND plus RNI or to RNI alone. The A011202 trial is a noninferiority trial designed to determine whether axillary radiation is not inferior to axillary radiation plus ALND with respect to invasive breast cancer recurrence–free survival. These trials will provide information regarding whether response to treatment can be used to guide local-regional therapy recommendations. The review by Pilewskie and Morrow highlights that much has been learned from clinical trials, and clinicians are encouraged to consider participation in these ongoing studies.

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