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ASO PERSPECTIVES

At the Speed of SOUND: The Pace of Change for Axillary Management in Breast Cancer

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Just when we thought axillary management for patients with breast cancer had reached a peak of convolution, new data come to the horizon. Starting in the early 20th century, historical surgical dogma prioritized pathologic nodal status, as this was the guiding force behind adjuvant systemic therapy and radiation therapy recommendations. Despite the lack of survival benefit of axillary lymph node dissection (ALND) being demonstrated in NSABP B-04 in the 1970s,[1] a true understanding of tumor biology was in its infancy and nodal status was necessary for both prognostication and treatment planning. Development and validation of the sentinel lymph node biopsy (SLNB) allowed for de-escalation of surgical nodal staging in clinically node-negative women following publication of NSABP B-32 in the 1990s,[2] but ALND remained the mainstay for both clinically and pathologically node-positive patients. As our understanding of the morbidity of ALND evolved, its need in patients with low nodal disease burden was questioned and disproven with ACOSOG Z0011 and AMAROS in the 2010s,[3,4] forever changing the landscape of surgical axillary management in breast cancer. The advent of molecular genomic testing further minimized the importance of pathologic nodal status with publication of the RxPONDER trial, illustrating how Oncotype DX testing can be used, even in the node-positive postmenopausal patient, to determine the benefit of chemotherapy.[5] With this knowledge, as well as improvements in breast imaging and expansion of systemic therapy options, the natural next question became ‘do we even need surgical nodal staging?’ Enter the SOUND (Sentinel Node vs. Observation after axillary UltraSound) trial.[6]

Published in JAMA Oncology in September 2023, the SOUND trial sought to evaluate the oncologic safety of omitting axillary surgery in patients with cT1N0 breast cancer and a negative preoperative axillary ultrasound who were undergoing breast-conserving surgery followed by radiation. From 2012 to 2017, 1405 patients from 18 hospitals in Italy, Spain, Switzerland and Chile were randomized to either observation or SLNB. The primary endpoint was 5-year distant disease-free survival (DDFS), with secondary endpoints of cumulative incidence of distant recurrences, cumulative incidence of axillary recurrence, DFS, overall survival (OS), and adjuvant treatment recommendations. If a suspicious lymph node was found on ultrasound, fine needle aspiration (FNA) was performed. If no disease was detected, the patients were randomized accordingly. If micrometastases or macrometastases were seen on FNA, they were excluded. Exclusion criteria also included multiple suspicious nodes seen on ultrasound, extensive multifocality or multicentricity, bilateral breast cancer, distant metastases at diagnosis, prior history of breast cancer, pregnant or breastfeeding, or if there would be obstacles to obtaining consent or undergoing regular follow-up. With a non-inferiority study design, assuming a 96.5% 5-year DDFS for the SLNB arm, patients underwent 1:1 randomization to no axillary surgery or SLNB. Although the reasoning is unclear, as the trial was established after ACOSOG Z0011 had been published, an amendment to the initial protocol mandated that all patients with any macrometastases in the SLN(s) underwent an ALND. There were no age, menopausal status, or tumor biology requirements for enrollment. No description of the sonographic criteria to characterize a lymph node as normal or suspicious was given.

Clinicopathologic features of the two arms were very similar. In both groups, nearly 80% were peri/postmenopausal with ductal histology. Around 88% were luminal

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A-like, with around 6% being HER2-positive and 6% being triple-negative. The median interquartile range for age was 60 years, with enrolled patients ranging from < 40 years of age to > 65 years of age. In the 708 patients in the SLNB arm, 61 (8.6%) had macrometastases, 4 (0.6%) of whom had four or more positive nodes, and 36 (5.1%) had micrometastases. Recommendations for and receipt of adjuvant chemotherapy, radiation therapy and hormone therapy were nearly the same between the two cohorts.

With a median follow-up of 5.7 years, no significant differences were found in 5-year DDFS (97.7% in the SLNB arm vs. 98% in the no axillary surgery arm), DFS (94.7% vs. 93.9%), OS (98.2% vs. 98.4%), cumulative incidence of distant metastases (2.3% vs. 1.9%), or cumulative incidence of axillary recurrences (0.4% in both groups). The authors conclude that these data support the safety of omitting axillary surgery in postmenopausal women with a negative axillary ultrasound, cT1cN0, estrogen receptor (ER)-positive, HER2-negative breast cancer.

Considering this study, what do we currently know about axillary ultrasound? Initially described for use in patients with breast cancer in 1989[7] as a non-invasive, cost-effective modality offering no radiation exposure, it has become the most common form of axillary imaging. Compared with clinical examination, axillary ultrasound has a much higher negative predictive value (NPV; 76–84% for ultrasound vs. 50–62% for examination) and is less limited by body habitus. Sonographic suggestions of metastatic disease include cortical thickening > 3 mm, loss of fatty hilum and irregular margins, which, in experienced hands, are readily detected.[8,9] While it was reflexively performed when breast imaging was concerning for a malignancy in the past, axillary ultrasound fell out of favor due to fear of unnecessarily committing a patient to ALND who otherwise met ACOSOG Z0011 criteria. However, in patients with one suspicious lymph node on axillary ultrasound, sensitivity and NPV have been reported to be 92%, with a false-negative rate of 8%, which is comparable with that of SLNB, to predict limited disease burden.[10,11] Following the implementation of targeted axillary dissection, removal of a biopsy-proven positive lymph node, along with a standard SLNB, axillary ultrasound is now used more frequently since these patients can be treated according to Z0011. The timing of the SOUND trial publication seems to be perfect.

Can we implement these data into clinical practice now? The short answer is yes, but with caution and on an individual basis.

Questions to ask yourself and your colleagues:

1. How will this change your diagnostic workflow? Will an axillary ultrasound be performed for all patients in whom a biopsy is recommended? Should it only be done once a biopsy confirms breast cancer? Will this delay surgical planning? What would be the most cost-effective strategy?
2. Ultrasound is operator-dependent. Are your radiologists comfortable and competent with axillary ultrasound to guide decision making?
3. Will deferring surgical nodal staging impact adjuvant therapy recommendations? Will your multidisciplinary team change treatment based on surgical pathology, despite the SOUND trial showing that 86.3% of patients with a negative axillary ultrasound had a negative SLNB? We do not want unnecessary escalation of adjuvant therapy as we de-escalate surgical therapy.
4. Can these results be generalized to my patient population? This trial was mainly performed in Europe with most patients coming from Italy. Could or should that make a difference?
5. Will deferring nodal staging preclude some patients from enrollment in other clinical trials? For instance, NRG BR007, a phase III trial evaluating de-escalation of breast radiation after lumpectomy in patients with low Oncotype scores, requires nodal staging for enrollment.
6. What should be done with ‘borderline’ lymph nodes? Ones that do not necessarily meet criteria to be deemed suspicious, but simply do not look perfectly normal. How should we define ‘borderline’? Should they all undergo core biopsy? Should that mean SLNB is necessary?
7. Although around 88% of patients in the SOUND trial were ER-positive and HER2-negative, can we generalize these data across all tumor subtypes? Especially considering that ER-negative tumors are less likely to be node-positive, should we not interpret the ultrasound findings with the same confidence that the trial suggests for ER-positive tumors?
8. For women aged 70 years and older, surgical nodal staging can be safely deferred in those with cT1N0, ER-positive tumors according to the Choosing Wisely guidelines.[12] When should women in this age group undergo axillary ultrasound? Is it ever indicated?
9. How young is too young to defer nodal staging? We know that women under age 50 years who are found to be node-positive have a benefit to chemotherapy, regardless of Oncotype score, according to the RxPONDER trial.[5] Is axillary ultrasound enough to guide systemic therapy recommendations in women under age 50 years?
10. Can we consider axillary ultrasound a surrogate to SLNB? It is important to note that the false negative rate (FNR) of axillary ultrasound in this trial was 13% (8.6% for macrometastases), which is not far from the FNR of SLNB at close to 9%. Is the difference in FNR

enough to justify the additional cost and potential morbidity of SLNB?

The SOUND trial should spark very interesting multidisciplinary conversations. This study will undoubtedly change axillary management as we currently know it and be the foundation for innumerable research projects and publications in the future. For the benefit of our patients, and honestly the healthcare system at large, we need to be ready to put practice-changing data into effect as soon as it becomes available. Just do not set your algorithms into stone—this will not be the last revision to the axillary management guidelines for patients with breast cancer. I think we are just getting started.

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