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ORIGINAL ARTICLE – BREAST ONCOLOGY

Real-World Implications of the SOUND Trial

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ABSTRACT

Background. The SOUND trial demonstrated that omission of sentinel lymph node biopsy (SLNB) is noninferior to axillary staging in patients with early-stage breast cancer (BC) and negative axillary ultrasound (AxUS). We examined the generalizability of these findings in patients with hormone receptor (HR)+HER2− disease.

Methods. Patients with cT1N0M0, HR+HER2− BC and negative AxUS undergoing breast conservation with SLNB from 2016 to 2023 were identified from a prospectively maintained database. Clinicopathologic characteristics, disease burden, adjuvant treatment, and oncologic outcomes were examined and compared with the SLNB arm of the SOUND trial. In postmenopausal patients, the impact of nodal status and 21-gene recurrence score on chemotherapy recommendations were also examined.

Results. Of 3972 patients with cT1N0M0 HR+HER2− breast cancer, 544 underwent AxUS; 312 met SOUND eligibility criteria. Median age was 57 (interquartile range [IQR] 48–64) years, and 199 (63.8%) were postmenopausal. Median (IQR) tumor size was 1.3 (0.9–1.7) cm, and 260 (83.3%) tumors were grade 1 or 2. Sentinel lymph node biopsy was positive in 38 (12.2%) patients. Only three (0.4%) had ≥ 4 positive lymph nodes. At a median follow-up of 26.2 (IQR 10.8–38.2) months, there were no axillary recurrences and one (0.3%) distant recurrence. Among postmenopausal women with recurrence score ≤ 25, chemotherapy recommendations were not associated with nodal status.

Conclusions. Examination of our real-world HR+ HER2− "SOUND-eligible" population suggests that nodal disease burden and oncologic outcomes are similar to the SOUND trial population, supporting careful implementation of trial results into multidisciplinary practice. In postmenopausal patients, omission of SLNB does not appear to impact adjuvant chemotherapy recommendations.

Keywords SOUND trial · Sentinel lymph node biopsy · Axillary ultrasound · HR+HER2 breast cancer

The indications for and extent of axillary surgery in breast cancer have evolved significantly over the past two decades and remain an area of active research and debate. Sentinel lymph node biopsy (SLNB) has replaced axillary lymph node dissection (ALND) for patients with clinically negative axillae. In the setting of upfront surgery, omission of ALND in the presence of 1–2 positive sentinel lymph nodes (SLN) is well supported by multiple prospective clinical trials.[1–4] Although SLNB is less morbid than ALND, the procedure is still associated with short- and long-term arm morbidity and a 3–5% lifetime risk of developing lymphedema.[5–9] Therefore, identifying patients who can safely omit SLNB is critical.

The Sentinel Node versus Observation after Axillary Ultrasound (SOUND) trial randomized breast cancer patients with tumors smaller than 2 cm, clinically negative axillae, and negative preoperative axillary ultrasound (AxUS) to SLNB or no axillary surgical staging. The

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primary endpoint, distant disease-free survival (DDFS) at 5 years, was not different between the two groups (97.7% vs. 98.0%, $p = 0.67$), demonstrating that omission of SLNB is noninferior to surgical staging of the axilla in this patient population.[10] Although the SOUND trial included patients of any age, the study cohort was predominantly comprised of postmenopausal patients (79.4%) and patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+HER2−) breast cancer (87.8%), suggesting an initial opportunity to expand age considerations for omission of SLNB beyond the traditionally considered Cancer and Leukemia Group B (CALGB) 9343 population, supported by the Choosing Wisely campaign.[11–14]

Unlike in HER2+ and triple-negative breast cancer, multidisciplinary care has evolved away from relying on nodal status as a key determinant for systemic therapy approach in HR+HER2− disease, particularly in postmenopausal patients, as the RxPONDER trial demonstrated no benefit to chemotherapy among patients with one to three positive nodes and recurrence score (RS) < 25.[15] However, selecting patients for whom omission of surgical axillary staging is oncologically safe and will not compromise adjuvant treatment decisions remains critical. To examine the generalizability of the SOUND trial results in real-world practice, we examined nodal disease burden and oncologic outcomes in patients meeting SOUND trial eligibility criteria treated at our institution, focusing specifically on patients with HR+HER2− disease.

METHODS

Following institutional review board approval, the Dana-Farber Brigham Cancer Center (DF/BCC) prospective clinical outcomes quality database was used to identify patients with primary cT1N0M0, HR+HER2− breast cancer treated from January 2016 to March 2023. Within this group, patients meeting the following criteria as allowed by eligibility criteria for the SOUND trial were considered the "SOUND-eligible" cohort: women planning for breast-conserving surgery and SLNB with either a negative preoperative AxUS or a single abnormal lymph node on AxUS and a negative needle biopsy.[10] Patients without axillary US, those with more than one abnormal lymph node on AxUS, a positive or nondiagnostic axillary node biopsy, and those undergoing upfront mastectomy were excluded from the "SOUND-eligible" cohort.

Datapoints collected from the DF/BCC database included patient demographics (age, race/ethnicity and menopausal status), tumor characteristics (histology, grade, clinical and pathologic size, percent estrogen receptor [ER] positivity [ER > 1% considered positive]), AxUS findings (performed, number of abnormal lymph nodes), fine needle aspiration and core needle biopsy results (negative, positive, non-diagnostic), type of initial breast surgery (lumpectomy or mastectomy), type of final breast surgery, type of axillary surgery (SLNB alone or SLNB+ALND), number of positive SLN, total number of positive lymph nodes if ALND, adjuvant systemic treatment (endocrine therapy [ET], chemotherapy, CDK4/6 inhibitor, radiation), 21-gene RS, any recurrence (local, axillary, distant), and survival. Menopausal status is captured per patient report at the initial surgical consultation; no specific age criteria or biochemical testing are used. For SOUND-eligible patients, any missing data were collected by chart review.

During the study timeframe, AxUS was not routinely performed in this patient population at our center; chart review was performed to identify the indications for the exam and investigate potential selection bias. Although in the SOUND trial, ALND was performed in the event of any positive SLN, our practice is to perform ALND only for those with 3 or more positive SLN per the American College of Surgeons Oncology group (ACOSOG) Z0011.[2] Also of note, at our institution, the 21-gene RS has been routinely obtained since late 2016 for women with T1c or greater N0 and N1 HR+HER2− breast cancer, regardless of menopausal status.

Within the entire cohort of T1N0M0 HR+HER2− breast cancer patients, patient and tumor characteristics and oncologic outcomes were compared between patients with and without preoperative AxUS. Chi-square testing was used for analysis of categorical variables, and Kaplan-Meier estimates were used to compute survival estimates. Within the SOUND-eligible cohort, clinicopathologic and treatment characteristics were compared with the reported SLNB arm of the SOUND trial.[10] Kaplan-Meier estimates were again used for oncologic outcomes, including locoregional recurrence rates and distant metastasis, for our SOUND eligible cohort. Lastly, among postmenopausal SOUND-eligible patients, the association between nodal status, RS, and chemotherapy recommendations were explored.

RESULTS

Axillary US versus No Axillary US Cohort Comparison

A total of 3,972 patients with cT1N0M0 HR+HER2− breast cancer were identified. Preoperative AxUS was performed in 544 (13.7%) patients; of whom 312 (57.3%) would have met all of the SOUND trial eligibility criteria and formed our SOUND-eligible cohort (Fig. 1).

Among the 544 patients with a preoperative AxUS, 437 (80.3%) were performed prior to presentation to our institution. The remaining 107 (19.7%) had either other abnormal imaging findings warranting AxUS or AxUS was performed at the surgeon's discretion. Compared with patients who did not undergo AxUS (n = 3428), patients with an AxUS were younger (median age 59 vs. 63 years, p < 0.001), more

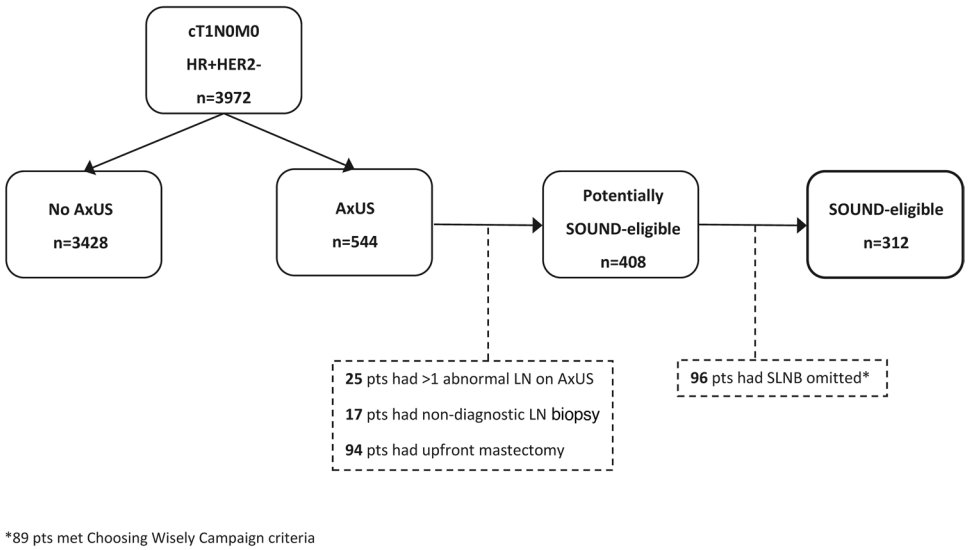

FIG. 1 CONSORT diagram. *HR* hormone receptor; *HER2* human epidermal growth factor receptor 2; *AxUS* axillary ultrasound; *pts* patients; *LN* lymph node; *bx* biopsy; *SLNB* sentinel lymph node biopsy

likely to be premenopausal (33.8% vs. 24.3%, $p < 0.001$), to have larger tumors (median tumor size 1.3 cm vs. 1.0 cm, $p < 0.001$), to have higher-grade tumors ($p < 0.001$), and to have undergone mastectomy (20.6% vs. 13.2%, $p < 0.001$; Table 1). The majority of both cohorts were White (87.8% vs. 90.6%); the remainder were African American (3.3% vs. 2.9%), Asian/Pacific Islander (5.1% vs. 3.1%), American Indian/Aleutian/Eskimo (0.5% vs. 0.1%), and other/unknown (3.1% vs. 3.1%). Patients of Spanish/Hispanic origin comprised 2.4% of the AxUS cohort and 3.2% of the No AxUS cohort. Kaplan-Meier estimates of oncologic outcomes at 3 years, including locoregional recurrence (0.0 vs. 0.03%, $p = 0.51$), distant recurrence (DR, 1.0% vs. 0.03%, $p = 0.43$), invasive disease-free survival (iDFS, 98.0% vs. 98.5%, $p = 0.54$), and overall survival (OS, 98.9% vs. 98.9%, $p = 0.86$) did not differ between patients with and without preoperative AxUS.

SOUND-Eligible Cohort Comparison

Patient and tumor characteristics of our SOUND-eligible cohort and of the SLNB arm of the SOUND trial are shown in Table 2. Numerically, our SOUND-eligible cohort was younger (median age 57 vs. 60 years) and included more premenopausal patients (36.2% vs. 20.5%). The most common histology in both cohorts was invasive ductal carcinoma (IDC), median tumor size in our cohort was 1.3 cm (vs. 1.1 cm in the SOUND trial), and more than 80% of the tumors in both cohorts were grade 1 or 2. Breast-conserving surgery was performed in 308 (98.7%) patients in our SOUND-eligible cohort, and 272 (87.2%) received RT (vs. 98% in the SOUND trial).

Nodal disease burden for our SOUND-eligible cohort and the SLNB arm of the SOUND trial is shown in Table 3. In our cohort, any SLNB was positive in 38 (12.2%) patients; 8 (2.6%) patients with 3 or more positive SLN underwent ALND and only 3 (0.9%) had 4 or more total positive nodes. In the SLNB arm of the SOUND trial, 97 (13.7%) had a positive SLNB, 45 (6.4%) underwent ALND, and only 4 (0.6%) had ≥4 total positive lymph nodes. Although we cannot make a direct comparison to the SOUND trial population, tumor characteristics in our node-positive SOUND-eligible patients are shown in Supplementary Table S1. Notably, 21 of 38 (55%) node-positive patients had LVI on final pathology.

Adjuvant hormonal therapy was the single systemic treatment received in 80.1% of our patients and 77.5% of the SOUND trial SLNB arm (Table 2). Chemotherapy, either alone or combined with hormonal therapy, was received by 30 (9.6%) patients in our cohort. Docetaxel or paclitaxel with cyclophosphamide was the regimen in 23 (76.7%) patients, 5 (16.7%) received doxorubicin with cyclophosphamide, and 1 patient received cyclophosphamide/methotrexate/5-fluorouracil.

In terms of disease outcomes in our SOUND-eligible cohort, four (1.3%) patients in our SOUND-eligible cohort experienced a local recurrence (LR) at a median follow-up of 26.2 (range 10.8–38.2) months. Of the four patients who developed a LR, three were postmenopausal and all were node-negative. One postmenopausal patient with LR had an invasive lobular carcinoma (ILC) and a RS of 22. The other three patients did not have RS performed. All patients received WBRT, one received endocrine therapy, and none received chemotherapy. There were no axillary recurrences, and only one (0.3%) patient developed distant disease. In the SLNB arm of the SOUND trial, 9 (1.3%) patients experienced LR at a median follow-up of 69.6 (range 60–82.8) months, 5 (0.7%) experienced an axillary recurrence, and 13 (1.8%) had distant metastases. There were no deaths from breast cancer in either cohort (Table 3).

TABLE 1 Population characteristics by use of preoperative axillary ultrasound

Characteristics	Patients, No (%)		
	AxUS (n= 544)	No AxUS (n= 3428)	*p*
Age at surgery (years)			
Median age	59 (22-91)	63 (26-95)	< 0.001
< 40	37 (6.8)	91 (2.7)	< 0.001
40–49	114 (21.0)	489 (14.3)	
50–65	204 (37.5)	1353 (39.5)	
≥ 65	189 (34.7)	1495 (43.6)	
Menopausal status			
Premenopausal	184 (33.8)	833 (24.3)	< 0.001
Postmenopausal	352 (64.7)	2545 (74.2)	
Unknown	8 (1.5)	50 (1.5)	
Clinical tumor size (cm)			
Median tumor size	1.3 (0.2-16)	1.0 (0.06-16)	< 0.001
Histology			
Ductal	363 (66.7)	2290 (66.8)	0.611
Lobular	74 (13.6)	437 (12.7)	
Other	107 (19.6)	701 (20.4)	
Grade			
G1	169 (31.1)	1484 (43.3)	< 0.001
G2	287 (52.8)	1576 (46.0)	
G3	87 (16.0)	339 (9.9)	
Unknown	1 (0.2)	29 (0.8)	
No. positive SLN			
0	370 (68.0)	2280 (66.5)	0.125
1–2	67 (12.3)	302 (8.8)	
≥ 3	6 (1.1)	19 (5.5)	
No SLNB	101 (18.6)	815 (23.8)	
Failed SLNB	0 (0.0)	12 (0.4)	
ALND			
ALND performed	18 (3.3)	54 (1.6)	0.005
Additional positive nodes found	13 (2.4)	34 (1.0)	0.01
Final surgery			
Lumpectomy	431 (79.2)	2975 (86.8)	< 0.001
Mastectomy	112 (20.6)	451 (13.2)	
Adjuvant systemic treatment			
None	60 (11.0)	351 (10.2)	0.006
Hormone therapy only	426 (78.3)	2842 (82.9)	
Chemotherapy only	16 (2.9)	48 (1.4)	
Hormone therapy and chemotherapy	42 (7.7)	187 (5.5)	
Oncologic outcomes			
Median follow-up (months)	23.6 (0.3-84.4)	29.9 (0.1-126.1)	
3-yr LRR	0.0%	0.03%	0.515
3-yr DR	1.0%	0.03%	0.432
3-yr iDFS	98.0%	98.5%	0.540
3-yr OS	98.9%	98.9%	0.857

AxUS axillary ultrasound; *SLN* sentinel lymph node; *SLNB* sentinel lymph node biopsy; *ALND* axillary lymph node dissection; *LRR* local recurrence rate; *DR* distant recurrence rates; *iDFS* invasive disease-free survival; *OS* overall survival

TABLE 2 Patient and tumor characteristics of our SOUND-eligible cohort and SLNB arm of the SOUND trial

Characteristics	Patients, No. (%)	
	SOUND-eligible (n = 312)	SLNB arm SOUND trial (n = 708)
Age at surgery (years)		
Median (IQR) age	57 (48–64)	60 (52–68)
< 40	20 (6.4)	10 (1.4)
40–49	70 (22.4)	114 (16.1)
50–64	150 (48.1)	324 (45.8)
≥ 65	72 (23.1)	260 (36.7)
Menopausal status		
Premenopausal	113 (36.2)	145(20.5)
Postmenopausal	199 (63.8)	558 (78.8)
Histology		
Ductal	217 (69.5)	551 (77.8)
Lobular	39 (12.5)	61 (8.6)
Other	56 (117.9)	96 (13.6)
Clinical tumor size (cm)		
Median (IQR) tumor size	1.4 (1–1.8)	N/A
Pathologic tumor size		
Median (IQR) tumor size (cm)	1.3 (0.9–1.7)	1.1 (0.8–1.5)
pT1mic or pT1a	16 (5.1)	71(10.0)
pT1b	85 (27.2)	251 (35.5)
pT1c	173 (55.4)	355 (50.1)
pT2	37 (11.9)	31 (4.4)
pT3	1 (0.3)	0 (0.0)
Grade		
G1	102 (32.7)	194 (27.4)
G2	158 (50.6)	377 (53.2)
G3	52 (16.7)	130 (18.4)
Final surgery		
Lumpectomy	308 (98.7)	703 (99.3)
Mastectomy	4 (1.3)	5 (0.7)
Radiation treatment		
Yes	272 (87.2)	694 (98.0)
No	40 (12.8)	14 (2.0)
Partial breast irradiation	7 (2.2)	76 (10.7)

SLNB sentinel lymph node biopsy; *IQR* interquartile range

Subset Analysis of SOUND-Eligible Cohort by Menopausal Status

Among 199 postmenopausal SOUND-eligible patients, 178 (89%) were node-negative by SLNB. Overall, 101 (50.7%) had RS performed, including 80 (44.9%) node-negative patients and all 21 node-positive patients (Supplementary Fig. S1). Among the node-negative group, 16 (20%) had a RS ≥ 26 and 11 (69%) received chemotherapy. Among the node-positive group, three (14.2%) had a RS ≥ 26 and all three received chemotherapy. Chemotherapy was not recommended for any of the patients with RS ≤ 25 regardless of nodal status. Overall, only two (1.0%) SOUND-eligible postmenopausal patients had 4 or more positive lymph nodes, including one patient with IDC and a total of 5 positive lymph nodes and one patient with mixed IDC and ILC had a total of 24 positive lymph nodes. This patient received adjuvant CDK4/6 inhibitor therapy Both patients had RS ≤ 25, and chemotherapy was not recommended.

Among 113 SOUND-eligible premenopausal patients, 96 (85%) were node-negative by SLNB. Among the 17 node-positive patients, three had 3 positive SLN and returned to the operating room for ALND with no additional positive nodes. Recurrence score was obtained for all 17 node positive patients, and all were <26. Of these, 15 (88.2%) received either endocrine therapy plus ovarian suppression (n = 13) or chemotherapy (n = 2).

DISCUSSION

In this real-world population of SOUND-eligible patients with cT1N0 HR+HER2− breast cancer, clinical characteristics and nodal disease burden were very similar to patients in the SLNB arm of the SOUND trial. Notably, 87.8% (vs. 84.6%) of patients had negative lymph nodes, and less than 1% in both cohorts had 4 or more positive nodes. Receipt of systemic therapy and radiation therapy was also similar between groups, and although our length of follow-up is limited, oncologic outcomes were excellent. Given there was no difference in oncologic outcomes between the two arms of the SOUND trial, it is reasonable to extrapolate that our SOUND-eligible patients would have had equally good outcomes without SLNB. These findings indicate that the SOUND clinical trial population is representative of similar patients treated in real-world practice and support careful implementation of the SOUND trial results in multidisciplinary care.

There has long been debate over the importance of axillary imaging to truly define a clinically node-negative population. While not required in the landmark studies that led to the omission of ALND in cN0 patients with 1–2 positive SLN (ACOSOG Z0011, AMAROS), many centers have continued to advocate for AxUS in clinical practice.[2,3] The SOUND trial demonstrates that AxUS can be used to define a very low-risk patient population in which the omission of any axillary surgical staging did not impact treatment recommendations or oncologic outcomes. The false-negative rate (FNR) of AxUS in the SOUND trial was 13.7%; 8.6% of patients with a negative AxUS had macrometastatic nodal disease. Similarly, in our cohort, the FNR of AxUS for macrometastases was 7.3%, performance characteristics that are very similar to the widely accepted FNR of 10% for the SLNB procedure.[16] Historically, the

TABLE 3 Nodal status, adjuvant treatment and oncologic outcomes of the SOUND-eligible cohort and SLNB arm of the SOUND trial

Characteristics	Patients, No. (%)	
	SOUND-eligible (n = 312)	SLNB arm SOUND trial (n = 708)
No. positive SLNs*		
0	274 (87.8)	599 (84.6)
1	29 (9.3)	83 (11.7)
≥ 2	9 (2.9)	14 (2.0)
ALND performed	8 (2.6)	45 (6.4)
No. total positive LN		
0	274 (87.8)	599 (84.6)
1–3	35 (11.2)	93 (13.1)
4–9	2 (0.6)	2 (0.3)
≥ 10	1 (0.3)	2 (0.3)
False-negative rate of AxUS**		
All nodal disease	12.2%	13.7%
Macrometastatic nodal disease	7.3%	8.6%
Adjuvant systemic treatment		
None	32 (10.3)	17 (2.4)
Hormone therapy only	250 (80.1)	549 (77.5)
Chemotherapy only	9 (2.9)	49 (6.9)
Hormone therapy and chemotherapy	21 (6.7)	93 (13.1)
Median (IQR) follow-up (months)	26.2 (10.8-38.2)	69.6 (60-82.8)
Oncologic outcomes		
Ipsilateral breast recurrence alone	4 (1.3)	7 (1.0)
Axillary recurrence alone	0 (0.0)	3 (0.4)
Ipsilateral breast and axillary recurrence	0 (0.0)	2 (0.3)
Distant metastasis	1 (0.3)	13 (1.8)
Death from breast cancer	0 (0.0)	0 (0.0)
Death from unknown cause	1 (0.3)	21 (3.0)

*In the SLNB arm of the SOUND trial, SLNB was not performed in 12 (1.7%) patients

**Defined as rate of nodal positivity following a negative axillary US or a negative fine-needle aspiration following axillary US showing one abnormal node

SLN sentinel lymph node; *SLNB* sentinel lymph node biopsy; *ALND* axillary lymph node dissection; *LN* lymph nodes; *AxUS* axillary ultrasound; *IQR* interquartile range

presence of micrometastatic nodal disease was associated with slightly worse outcomes that were offset by standard adjuvant treatments amongst all-comers[17,18]; however, adjuvant treatment recommendations among patients with early-stage HR+HER2− breast cancer are now largely driven by genomic assays, particularly among postmenopausal patients, which supports the use of AxUS instead of SLNB for this population.

Data to support omission of surgical axillary staging in women 70 years and older with HR+HER2− cT1N0 breast cancer have been available for decades and supported by the Choosing Wisely campaign.[11,12,14,19,20] Despite this, a systematic review of the literature from 2016–2019 demonstrated that rates of SLNB in women 70 years or older with low-risk breast cancer remain persistently greater than 80%, potentially owing to uncertainty about the impact of unknown nodal status on adjuvant chemotherapy decisions.[13] While the SOUND trial further validates these recommendations and in fact supports lowering the age cutoff for omission of SLNB, an additional concern is that omission of SLNB might affect decisions regarding adjuvant radiation therapy (RT), leading to higher rates of RT recommendations in women who would have otherwise been eligible for omission of RT based on CALGB 9343 and the PRIME II trials.[14,21]

Surgical axillary staging and confirmed pathological N0 status were required in the PRIME II trial, which demonstrated that adjuvant RT can be safely omitted in women 65 years or older who have T1 or T2 (tumor size ≤3 cm) estrogen receptor-high (>50%) cancers treated with breast-conserving surgery and plan to complete adjuvant ET.[21] In contrast, the CALGB 9343 trial also showed that among

women 70 years or older, with clinical T1N0, estrogen receptor-positive breast cancer, the addition of adjuvant RT to ET did not significantly increase survival, regardless of axillary surgical staging.[14] In fact, 62% of patients in the CALGB 9343 cohort did not undergo axillary staging. To date, nodal status remains an important factor in selecting candidates for accelerated hypo-fractionated breast radiotherapy or partial breast irradiation (PBI) as adjuvant treatment options. The FAST-Forward trial, which demonstrated the oncologic equivalency of 26 Gy delivered in five fractions to a standard 15-fraction regimen for early breast cancer patients, did allow pN1 disease; however, axillary surgical staging, either with SLNB or ALND, was a requirement.[22] ASTRO guidelines regarding PBI eligibility also call for axillary surgical staging and negative nodes before considering PBI in patients otherwise meeting guidelines (tumor size ≤2 cm, grade 1–2 disease, estrogen receptor-positive histology, and age ≥40 years).[23,24] Thus, the potential trade-offs in local therapy decision making—surgical axillary staging versus radiation therapy options—requires careful consideration and will benefit from future investigations incorporating patient preferences and estimates of individualized risks of side-effects from SLN biopsy versus whole breast radiation therapy.

With respect to adjuvant systemic therapy decisions, the RxPONDER trial demonstrated no benefit for the addition of chemotherapy to ET in postmenopausal patients with HR+HER2−, N1 breast cancer and RS ≤ 25.[15] Although our cohort included patients treated before the publication of RxPONDER, it had been our practice to obtain RS in node-positive patients during the timeframe of this study. Previous studies from our institution have shown that in postmenopausal women with T1-2, N0-1 HR+HER2− breast cancer and RS ≤ 25, SLNB alone was adequate for chemotherapy decisions.[25–27] Per ACOSOG Z0011 criteria, completion ALND in our cohort was performed only in patients with 3 or more positive sentinel lymph nodes, potentially underestimating the total extent of nodal disease in a small number of patients. However, in the SOUND trial, where ALND was performed for any positive SLN, only four (<1%) patients had 4 or more positive nodes. This is in contrast to ACOSOG Z0011, where AxUS was not mandated and, in the ALND arm of the trial, 13.7% of patients had 4 or more positive nodes. Nonetheless, in this analysis of postmenopausal SOUND-eligible patients, nodal status did not appear to affect chemotherapy recommendations, with the exception of a single patient with extensive nodal involvement who received a CDK4/6 inhibitor. Overall, decisions regarding chemotherapy treatment appeared to be driven by RS, indicating that surgical axillary staging could be omitted in this patient population without affecting adjuvant chemotherapy recommendations.

In younger patients with HR+HER2− breast cancer and in those with high-risk disease characteristics, nodal staging will likely continue to provide important information for adjuvant systemic therapy recommendations. The RxPONDER trial showed that premenopausal patients with 1–3 positive lymph nodes and a RS ≤ 25 experience longer iDFS and overall survival benefit with addition of chemotherapy to ET.[15] Moreover, nodal status was part of the eligibility criteria in initial clinical trials investigating the benefit of adding CDK4/6 inhibitors to ET for early HR+/HER− breast cancers.[28,29] The monarchE trial investigated the addition of adjuvant abemaciclib to standard adjuvant ET in patients with either ≥4 positive axillary lymph nodes or 1–3 positive axillary lymph nodes and either grade 3 disease, tumor size ≥ 5 cm, or Ki-67 index ≥ 20%.[28] The trial's primary objective was iDFS. At 36 months, there was a statistically significant improvement in iDFS, 86.1% for those receiving abemaciclib plus ET versus 79.0% for those receiving ET alone, an absolute benefit of 7.1%, leading to the U.S. Food and Drug Administration approval of adjuvant abemaciclib with ET for patients meeting monarchE eligibility criteria.[30] Based on updated survival analyses, the Ki-67 testing requirement was subsequently removed.[31,32] At the most recent report of data from the monarchE trial, after a median follow-up of 54 months, the iDFS rate for patients receiving abemaciclib was 83.6% versus 76.0% for those receiving ET alone, a 5-year absolute improvement of 7.6%.[33] The NATALEE trial investigated the benefit of adding the CDK4/6 inhibitor ribociclib to adjuvant ET in patients with HR+HER2− anatomic stage II or III breast cancer. This trial's primary endpoint was also iDFS, and at 3 years, the iDFS rate was 90.4% for patients receiving ribociclib versus 87.1% for those receiving ET alone (hazard ratio = 0.75; 95% CI 0.62–0.91, $p = 0.003$). Of note, 28.1% of patients enrolled on the NATALEE trial had N0 disease.[34] At the time of this writing, Ribociclib has not yet been approved by the FDA for use in patients with early-stage HR+/HER2− disease.

Special consideration should be given to tumors of lobular histology before applying the SOUND trial results in practice. A minority (8.5%) of patients on the SOUND trial had ILC. In addition, there is controversy in the literature regarding pathologic patterns and extent of nodal involvement in patients with ILC, with variable reports on surgical and oncologic outcomes.[35–40] Additionally, the FNR of AxUS has been shown to be significantly higher among patients with ILC compared with IDC, indicating that sonographic assessment of the axilla, a critical component of the SOUND trial, may not be as accurate for this population.[41] Given the reported increased frequency of higher nodal disease burden (≥3 positive nodes) in patients with ILC, higher reported FNR of AxUS and their underrepresentation in the SOUND trial, in our opinion the inclusion of patients

with ILC in early implementation efforts warrants careful consideration.[40,41]

Another pathologic factor that should be addressed when considering SOUND implementation is the presence of lymphovascular invasion (LVI). Lymphovascular invasion has been suggested to be a predictor of heavy nodal disease burden defined as 3 or more positive nodes, even with a negative AxUS. Thus, caution should be taken when AxUS is used in lieu of SNLB for these patients.[42–44] Additionally, the presence of LVI is a conditional recommendation against PBI, so definitive nodal status in patients with LVI can be important for determining optimal adjuvant RT.[23] Granular data regarding LVI were not reported in the SOUND trial, yet more than half of our node-positive SOUND-eligible patients had LVI on final pathology. As such, LVI remains another factor that requires careful consideration in multidisciplinary treatment planning.

This study has several limitations. Our cohort was obtained from a retrospective review of a prospectively maintained database with relatively short follow-up compared with the SOUND trial (median follow-up 26.2 vs. 69.6 months). There was selection bias in the use of preoperative AxUS, because we did not routinely use AxUS in this population during the timeframe of this study. However, we attempted to address his limitation by performing a comparison of those with and without AxUS, demonstrating no difference in oncologic outcomes. Moreover, many patients older than 70 years with HR+HER2− breast cancer who would have been eligible for the SOUND trial were excluded from our SOUND-eligible cohort, because we routinely omit SLNB in this group per Choosing Wisely recommendations. Finally, although the time period of our study largely predates the publication of RxPONDER, more than 50% of our postmenopausal SOUND-eligible patients (including all node-positive patients) had RS performed based on our institution's consensus criteria, and adjuvant chemotherapy decisions appeared to be driven by RS, regardless of nodal status for this population. Because this is a single institution database, systemic therapy selection reflects practice patterns at a single institution only and may not be generalizable.

CONCLUSIONS

We believe that these findings support careful implementation of omission of surgical staging of the axilla in postmenopausal patients with cT1N0, HR+HER2− breast cancer and a negative AxUS. At our institution, we have adopted this approach for patients aged 60–69 years with grade 1–2 IDC, ER > 10%, and no LVI. These criteria were the result of multidisciplinary discussions taking into account the continued importance of axillary surgical staging for some adjuvant therapy decisions. Future work will continue to measure the impact of omission of surgical axillary staging and the potential to expand these criteria.

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DATA AVAILABILITY De-identified data are available with proper institutional approval, upon request.

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