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Sentinel Lymph Node Biopsy for Patients With cN1 HR+/HER2− Breast Cancer and Palpable Adenopathy
A Nonrandomized Clinical Trial

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IMPORTANCE Randomized trials established the safety of omitting axillary lymph node dissection (ALND) among patients with clinically node-negative breast cancer and less than 3 positive sentinel lymph nodes (+SLNs) having upfront surgery and adjuvant radiation. Patients with palpable mobile level I/II axillary adenopathy (cN1) were not eligible for these studies. Presently, more than 80% of patients with HR+/HER2− cN1 disease undergo ALND either at upfront surgery or after neoadjuvant therapy, despite evidence that 50% to 60% will have only 1 or 2 positive nodes.

OBJECTIVE To determine upfront sentinel lymph node biopsy (SLNB) feasibility and evaluate ALND rate among patients with HR+/HER2− cN1 breast cancer selected with axillary ultrasound (AUS).

DESIGN, SETTING, AND PARTICIPANTS This nonrandomized clinical trial involved patients with cTx/cT1-2 cN1 HR+/HER2− breast cancer with 3 or fewer morphologically abnormal nodes on AUS at 4 centers. The trial began on April 20, 2021, and the database for this report was frozen on September 26, 2024.

INTERVENTIONS Patients underwent upfront lumpectomy/mastectomy and SLNB, with single/dual-tracer mapping. ALND was indicated for 3 or more positive SLNs.

MAIN OUTCOMES AND MEASURES The primary outcome was ALND rate. Secondary outcomes were frequency of palpable nodes being radioactive/blue and locoregional recurrence.

RESULTS Among 78 enrolled patients, the median (IQR) age was 58 (49.0-66.5) years. Most tumors were cT1 (37 [47%]) or cT2 (40 [51%]), 56 patients (72%) had ductal histology, and 59 tumors (76%) were moderately differentiated. On AUS, 39 patients (50%) had 1 abnormal-appearing node, 33 (42%) had 2, and 6 (8%) had 3. Median (IQR) pathologic tumor size was 2.3 (1.6-3.3) cm, 50 patients (64%) had lymphovascular invasion, and 54 (69%) had extracapsular extension. SLNB was performed with dual tracer in 68 (87%), and 3 or more SLNs were retrieved in 75 (96%). The palpable diseased nodes were blue and/or radioactive in 107 of 161 instances (66.5%). Overall, 24 patients (31%) had 1 +SLN, 30 patients (38%) had 2 +SLNs, and 24 patients (31%) had 3 or more +SLNs. SLNB alone was performed in 59 patients (76%), while 19 (24%) had ALND; indicated ALND was deferred in 5 cases. Among those with 12 months or more follow-up (n = 68; median, 25 months), there have been no isolated axillary or locoregional recurrences.

CONCLUSIONS AND RELEVANCE This study found that SLNB is feasible among patients with cN1 HR+/HER2− disease and that resection of palpable nodes is necessary to minimize false-negative rates. This approach affords the opportunity to omit ALND and minimize morbidity among patients with cN1 cancer and limited nodal burden.

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Invited Commentary

Supplemental content

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The omission of axillary lymph node dissection (ALND) among patients with early-stage, clinically node-negative (cN0) breast cancer with 1 or 2 positive sentinel lymph nodes (SLNs) undergoing upfront surgery and adjuvant radiotherapy is routine based on results of the landmark trials American College of Surgeons Oncology Group (ACOSOG) Z0011, After Mapping of the Axilla: Radiotherapy or Surgery (AMAROS), and Sentinel Node Biopsy in Breast Cancer: Omission of Axillary Clearance After Macrometastases (SENOMAC).[1-3] Patients with palpable mobile ipsilateral adenopathy (cN1) were not eligible for these studies because of a presumed heavy underlying nodal disease burden unlikely to be controlled by adjuvant therapies. As a result, ALND remains standard for patients with cN1 cancer who are undergoing upfront surgery. Although neoadjuvant therapy allows avoidance of ALND if a nodal pathologic complete response is achieved, nodal pathologic complete response in the hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2−) subset is seen in only 20% to 30% of patients.[4-6]

There remains a significant unmet need for approaches to decrease the use of ALND in patients with cN1 HR+/HER2− disease. A growing body of evidence suggests that up to 50% to 60% of patients with cN1 cancer will have only 1 or 2 total positive lymph nodes. In the early National Surgical Adjuvant Breast and Bowel Project trials of patients with node-positive breast cancer, 60% to 70% of those with cN1 disease had 1 to 3 positive lymph nodes.[7-9] Similarly, in a contemporary single-institution analysis of 180 patients with cT1-3N1 HR+/HER2− tumors, 50% to 60% had only 1 or 2 positive lymph nodes at upfront surgery,[10] and the finding of fewer than 3 morphologically abnormal nodes on preoperative axillary ultrasound (AUS) was independently predictive of pN1 disease. These findings suggest an opportunity for axillary de-escalation in select patients with cN1 HR+/HER2− disease and limited nodal burden on AUS. In this multicenter, single-arm clinical trial, we prospectively evaluated the use of sentinel lymph node biopsy (SLNB), and the rates of subsequent ALND, among patients with cN1 HR+/HER2− disease who are treated with upfront surgery.

Key Points

Question What is the feasibility of upfront sentinel lymph node biopsy (SLNB) and the rate of axillary lymph node dissection (ALND) among patients with HR+/HER2− cN1 breast cancer selected with axillary ultrasound?

Findings In this nonrandomized clinical trial including 78 consecutive patients with cTx/cT1-2 cN1 HR+/HER2− breast cancer with palpable, biopsy-proven nodal metastases, SLNB was feasible among patients with cN1 HR+/HER2− disease, with 3 or more SLNs retrieved in 96% of cases, and nearly 70% of patients meeting criteria for SLNB alone and able to avoid ALND.

Meaning This approach affords the opportunity to omit ALND and minimize morbidity among cN1 patients with limited nodal disease burden.

Methods

Patient Characteristics

This prospective, single-arm trial was registered with the National Cancer Institute and approved by the institutional review board of each participating center (see the trial protocol and statistical analysis plan in Supplement 1). All patients provided written informed consent to participate; Transparent Reporting of Evaluations With Nonrandomized Designs (TREND) reporting guidelines were followed. Adult patients with cTx or cT1-2, HR+/HER2− breast cancer with cN1 (palpable, and biopsy-proven) nodal metastasis with preoperative in-house AUS demonstrating up to 3 morphologically abnormal lymph nodes were eligible for participation. A clipped node was not required for study entry. HR positivity was defined as being positive for estrogen receptor (ER) and/or progesterone receptor (PR) staining indicated by 1% or greater immunoreactive tumor nuclei, while HER2 negativity was defined by immunohistochemistry assay demonstrating no or faint staining in 10% or less of tumor cells (immunohistochemistry 0 or 1+) or negative by dual-probe in situ hybridization assay. Morphologically abnormal nodes were characterized by sonographic features of cortical thickening, rounded or irregular shape, loss of fatty hilum, hilar displacement or effacement, nonhilar cortical blood flow, and/or presence of microcalcifications: these criteria were specified in protocol documents and reviewed with all participating sites. Patients who were pregnant; patients with nonpalpable nodal disease detected by sonogram only; and patients with a history of prior ipsilateral breast cancer, advanced nodal disease (defined as >3 abnormal nodes on ultrasound or evidence of supraclavicular or internal mammary involvement), or stage IV disease, were excluded.

Study Design and End Points

Patients meeting eligibility criteria underwent upfront surgery, including SLNB with single- or dual-tracer lymphatic mapping, using technetium-99m sulfur colloid and either isosulfan blue or methylene blue dye, per routine institution standards. SLNs were defined as nodes that were radioactive, blue, or palpably abnormal. No minimum number of SLNs was required, and preoperative localization of clipped nodes and the use of frozen section were permitted per surgeon preference. For patients with a clipped node, an intraoperative specimen radiograph was obtained. ALND was not mandated if the clip was not identified in the palpable diseased node. Intraoperative node findings were recorded by the operating surgeon on a standardized form, which was compiled along with standard clinical and pathologic data into a prospective study database that was compliant with the Health Insurance Portability and Accountability Act.

An SLN was considered positive if it contained micrometastases or macrometastases, while a node with isolated tumor cells was considered negative. Completion ALND was required if metastases were present in 3 or more SLNs, for the presence of gross extracapsular extension or matted nodes, or if no metastases were identified in the SLNs indicating failure to identify the biopsy-proven positive node (**Figure 1**).

Figure 1. Study Schema

ALND indicates axillary lymph node dissection; BCS, breast-conserving surgery; cN1, palpable mobile ipsilateral adenopathy; cT, clinical tumor stage; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; SLNB, sentinel lymph node biopsy.

The primary study end point was the rate of ALND. Secondary end points included the frequency of detection of the palpable metastatic node using technetium-99m sulfur colloid and/or blue dye, and locoregional recurrence (LRR)-free survival among those treated with SLNB alone. LRR was defined as in-breast or ipsilateral axillary, internal mammary, or supraclavicular nodal disease recurrence; other disease sites were defined as distant metastases.

Statistical Analysis

Study sample size was calculated based on an anticipated 40% ALND rate with the use of upfront SLNB on study, which would constitute a clinically meaningful reduction from the 80% rate of ALND reported in prior studies among patients with cN1 HR+/HER2− disease who were treated with traditional neoadjuvant chemotherapy followed by surgery. A sample size of N = 78 was determined to produce a 1-sided 95% upper limit CI with a distance from the sample proportion to the upper limit that is equal to 0.059 when the sample proportion is 0.74. The study database was frozen on September 26, 2024. The ALND rate was estimated using binomial exact 1-sided 95% CIs. Two-sided *P* values less than .05 were considered statistically significant, and no corrections were made for multiple testing. All analyses were performed using SAS version 9.4 TS1M6 (SAS Institute).

Results

Patient Characteristics

From April 2021 to August 2024, 132 patients with cTx or cT1-2, cN1, HR+/HER2− breast cancer were identified at participating centers. Of these, 54 (41%) were ineligible because of preoperative AUS demonstrating more than 3 morphologically abnormal nodes. Seventy-eight patients met enrollment criteria with AUS demonstrating 3 or fewer morphologically abnormal lymph nodes and were enrolled in the study: 65 (83%) were enrolled at Memorial Sloan Kettering Cancer Center, 5 (6%) at University of Michigan, 5 (6%) at Lehigh Valley Topper Cancer Institute, and 3 (4%) at Hartford HealthCare.

The median (IQR) patient age was 58 (49.0-66.5) years, 1 patient (1.3%) had an occult (cTx) tumor, 37 (47%) had cT1 tumors, and 40 (51%) had cT2 tumors. Most patients had ductal histology (56 [72%]) and moderately differentiated (59 [76%]) tumors. On preoperative AUS, 39 patients (50%) had only 1 abnormal-appearing node, 33 (42%) had 2, and 6 (8%) had 3. Patient and tumor characteristics are summarized in the **Table**.

Surgical Treatment and Nodal Burden

Breast-conserving surgery (BCS) was performed in 68% of cases, while 32% had mastectomy. All enrolled patients underwent planned SLNB at upfront surgery, which was performed with dual-tracer lymphatic mapping in 68 cases (87%), while 10 (13%) had single-tracer lymphatic mapping. At least 3 SLNs were retrieved in 96% of cases, with a median (IQR) of 5 SLNs (3-6) removed. Overall, a total of 161 palpable nodes were found among 78 enrolled patients. The palpable diseased nodes were excised and confirmed positive on final pathology in all cases, with no cases of failure to identify the palpable diseased nodes. The palpable nodes were intraoperatively recorded as also being blue and/or radioactive in 107 of 161 instances (66.5%), while in 54 instances (33.5%), the palpable node was neither blue nor radioactive. Specimen x-ray of the palpable node was performed for those who had a clipped node (n = 49). Of these, the clip was identified in 41 cases (84%), and no clip was found in 8 cases (16%), all of which had either biopsy site changes seen (5/8), or tumor replacing the node (3/8).

Overall, 24 patients (31%) had 1 positive SLN, 30 (38%) had 2 positive SLNs, and 24 (31%) had 3 or more positive SLNs. On final pathology, the median (IQR) pathologic tumor size was 2.3 (1.6-3.3) cm, 50 patients (64%) had lymphovascular invasion, and 54 (69%) had microscopic extracapsular extension in 1 or more of the SLNs. SLNB alone was performed in 59 patients (76%), of whom 54 had only 1 or 2 positive SLNs, and of whom 5 had 3 or more positive SLNs but declined the recommended ALND. The remaining 19 patients (24%) underwent the prescribed ALND due to 3 or more positive SLNs (**Figure 2**). Completion ALND was performed at the initial operation in 13 of 19 cases (68%) and at a second operation in 6 cases (32%). When comparing patients with limited nodal burden (1-2 positive nodes) to those with heavy nodal burden (≥3 positive nodes), clinicopathologic features of age (median, 58 years, in both groups), premenopausal status (17 [31%] vs 5 [21%]), presence of pure lobular histology (2 [4%] vs 1 [4%]), and Oncotype DX score (median score, 18, in both groups) were similar; small sample size precluded formal statistical analysis.

All patients received radiotherapy: 13 (17%) received whole breast radiotherapy, 40 (51%) received whole breast radiotherapy and regional nodal irradiation, and 25 (32%) received

Table. Clinicopathologic Characteristics Among Enrolled Patients With cTx/cT1-2, cN1 HR+/HER2− Disease and Preoperative Axillary Ultrasound Demonstrating up to 3 Morphologically Abnormal Lymph Nodes

Characteristic	Study population (N = 78), No. (%)
Age, median (IQR), y	58 (49.0-66.5)
Clinical tumor stage	
cTx	1 (1.3)
cT1	37 (47)
cT2	40 (51)
Histology	
Ductal	56 (72)
Lobular/mixed	18 (23)
Other	4 (5)
Differentiation	
Well	3 (4)
Moderate	59 (76)
Poor	16 (21)
No. of morphologically abnormal nodes on preoperative axillary US	
1	39 (50)
2	33 (42)
3	6 (8)
Pathologic tumor size, median (IQR), cm	2.3 (1.6-3.3)
Lymphovascular invasion	50 (64)
Microscopic ECE present	54 (69)
Size of ECE	
None	24 (31)
≤2 mm	19 (24)
>2 mm	35 (45)
Oncotype DX score, median (range)	15 (3-48)
Pathologic tumor stage	
pTx	1 (1)
pT1	27 (35)
pT2	47 (60)
pT3	3 (4)
Pathologic nodal stage	
pN1	61 (78)
pN2	12 (15)
pN3	5 (6)
No. of positive SLNs	
1	24 (31)
2	30 (38)
≥3	24 (31)
Breast surgery performed	
Breast-conserving surgery	53 (68)
Mastectomy	25 (32)

Abbreviations: cN1, palpable mobile ipsilateral adenopathy; cT, clinical tumor stage; ECE, extracapsular extension; pN, pathologic nodal stage; pT, pathologic tumor stage; SLNs, sentinel lymph nodes; US, ultrasound.

postmastectomy radiotherapy with regional nodal irradiation. Systemic therapy was received as indicated: 43 patients (55%) received adjuvant chemotherapy, 76 patients (97%) are receiving adjuvant endocrine therapy (2 patients declined), and 33 patients (42%) are undergoing or have completed treatment with a CDK 4/6 inhibitor.

Disease Outcomes

Among patients with at least 12 months of follow-up (n = 68; median, 25 months), there have been no isolated axillary or locoregional recurrences; 2 patients have developed distant disease, both with metastasis to bone diagnosed at 5 months and 18 months after surgery.

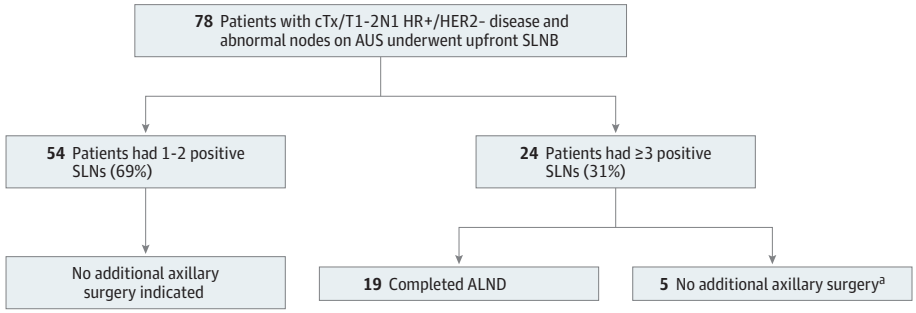
Discussion

Remarkable progress has been made over the past 3 decades in the de-escalation of axillary surgery among patients with node-positive breast cancer. This is largely due to the use of SLNB alone for patients with low-volume nodal disease undergoing upfront surgery and high rates of nodal downstaging with neoadjuvant therapy among those with chemoresponsive subtypes, allowing for management with SLNB alone. However, there is a lack of effective options for patients with cN1 HR+/HER2− disease. These patients continue to undergo frequent ALND because neoadjuvant chemotherapy, when indicated, yields low rates (20%-30%) of nodal pathologic complete response.[4-6] Furthermore, results from the phase 3 RxPONDER trial have confirmed that a subset of patients with node-positive HR+/HER2− disease do not benefit from chemotherapy, rendering this a suboptimal choice with avoidable toxicities for many such patients.[11] New approaches to decrease the use of ALND in this subset are needed; our single-arm clinical trial is, to our knowledge, the first to prospectively evaluate the feasibility of upfront SLNB among patients with cN1 HR+/HER2− cancer. We observed that by using ultrasound to select patients with limited nodal burden, nearly 70% of study participants had only 1 or 2 positive nodes and avoided ALND with this approach.

Omission of ALND is routine among patients with T1-T2, cN0 cancer with 1 or 2 positive SLNs based on early clinical trials, including the ACOSOG Z0011 and AMAROS studies, which demonstrated no added benefit from ALND in locoregional control or overall survival among patients treated with SLNB alone.[1,2] Subsequent studies expanded and validated the applicability of this approach to patients with T3 disease, microscopic extranodal disease, and those undergoing mastectomy.[3,12,13] However, patients with cN1 cancer were excluded from all of these trials because of the assumption that these patients harbor a heavier underlying nodal burden, and because of uncertainty regarding the feasibility and applicability of SLNB in this setting.

A growing body of evidence suggests that many patients with cN1 disease in fact have limited pathologic nodal burden. Two small retrospective studies demonstrated that 40% to 45% of patients with cN1 HR+/HER2− breast cancer had pN1 disease, with both studies demonstrating larger tumor size to be associated with a heavier nodal burden.[14,15] Similarly, in a larger study of 180 patients with cT1-3N1 HR+/HER2− tumors treated with upfront ALND, Crown et al[10] found that 43% had only 1 or 2 positive lymph nodes and that cT stage and number of suspicious nodes on AUS were independently associated with nodal burden at surgery. While AUS adds little value to the assessment of patients with clinically node-negative

Figure 2. Nodal Positivity and Rate of Axillary Lymph Node Dissection



ALND indicates axillary lymph node dissection; AUS, axillary ultrasound; cTx/T1-2N1 HR+/HER2−, clinical T1 or T2 or occult primary tumor, clinically node–positive (palpable ipsilateral mobile adenopathy), and hormone receptor–positive/human epidermal growth factor receptor 2–negative; SLNB, sentinel lymph node biopsy; SLNs, sentinel lymph nodes.

[a]ALND was deferred in 5 cases because of patient preference or surgeon discretion.

(cN0) disease, in patients with cN1 disease, it can be used to identify those with a limited nodal burden. In our current study of such patients selected by AUS, 69% had only 1 or 2 diseased lymph nodes and avoided ALND.

The applicability of SLNB in patients with palpable nodal disease has been uncertain, but feasibility was confirmed in the current study with successful retrieval of at least 3 SLNs in 96% of cases using standard lymphatic mapping techniques. Importantly, while the palpable diseased node was also blue and/or radioactive in the majority of cases, it was neither blue nor radioactive in 33.5% of cases. Among 54 lymph nodes that were identified by palpation alone, dual-tracer lymphatic mapping was used in 94% of cases. Palpation of the axilla has always been an important component of the SLNB procedure but is particularly important in the setting of cN1 disease to minimize the false-negative rate of the procedure. Among those with a clipped node (n = 49), 16% did not have the clip identified on specimen x-ray, potentially due to clip migration or placement into the extranodal fat as suggested by the presence of biopsy changes in most such cases. This is consistent with prior studies that have reported 7% to 30% rates of failure to identify the clip despite varying localization techniques, albeit among patients who received neoadjuvant chemotherapy before surgery.[16-18] It is unlikely that preoperative localization, which was performed in only 2 cases, would add value in the setting of palpable adenopathy. Although there were no instances of failure to remove a palpable diseased node in this study, such a scenario would warrant axillary dissection. Further validation for the use of SLNB among patients with cN1 cancer having upfront surgery is anticipated from the ongoing European TAXIS trial (NCT03513614).[19] This trial of patients with cN+ disease undergoing either upfront surgery or neoadjuvant therapy, with tailored axillary surgery consisting of SLNB and removal of palpable, suspicious nodes, randomizes patients to receive axillary radiation therapy vs ALND and radiation therapy.[19] In a planned preliminary analysis of 500 patients who were randomized to receive ALND, a median of 5 SLNs were removed with localization of a clipped node as compared with a median of 4 SLNs removed without localization (P = .30), with no significant difference in either the number of positive SLNs (median, 2) or the presence of additional nodal disease.[19] In our trial, a similar median 5 SLNs were removed despite infrequent use of preoperative localization of the node/clip. To our knowledge, this study is the first to prospectively establish the feasibility of SLNB in this setting and broadens the application of SLNB to include select patients with cN1 disease having upfront surgery.

Avoidance of ALND among patients with cN1 HR+/HER2− disease and limited (pN1) nodal burden selected by AUS is applicable to patients undergoing either BCS or mastectomy, provided that radiotherapy is received. Importantly, these results should not be extrapolated to patients with locally advanced breast cancer, such as those with cT3-T4 or cN2-N3 disease, who were not included in the current study. Although longer follow-up is needed, there have been no LRRs observed at a median 2-year follow-up. While past studies among pN1 patients with only 1 or 2 positive nodes have shown no survival benefit to ALND,[1,2] results from the prospective TAXIS trial will provide definitive data on LRR and survival outcomes. In a retrospective study of 57 823 T1-T2 patients from the American Cancer Society/American College of Surgeons National Cancer Database treated with upfront SLNB or ALND, among those found to be pN1, there was no difference in overall survival among those who were cN0 vs cN1 (hazard ratio, 1.13; 95% CI, 0.93-1.37; P = .22), suggesting that patients with cN1 disease who otherwise appear to be candidates for ALND omission should still be considered eligible if pathologic nodal burden is limited.[20] Similarly, in another National Cancer Database analysis of patients with T1-T2 cN1 cancer, Cocco et al[21] observed no difference in 5-year overall survival among those treated with SLNB and radiation (N = 3030; 88%) vs those treated with ALND and radiation (N = 5446; 86%), respectively. Concerns about elimination of ALND among patients with HR+/HER2− disease and 1 or 2 positive SLNs have included the challenge of then identifying those with heavier nodal burden who may qualify for abemaciclib[22] or undertreatment among those with low Oncotype DX scores who would qualify for chemotherapy based on nodal burden.[11] In a post hoc analysis of the SENOMAC trial including patients with T1-T2 cN0 HR+/HER2− disease and 1 or 2 positive SLNs, and using data extracted from the monarchE and AMAROS trials, de Boniface et al[23] calculated that ALND would be required in 104 patients to avoid a single disease-free survival event at 5 years, while 9 patients would experience significant arm morbidity. Furthermore, results from the phase 3 NATALEE trial demonstrated disease-free survival benefit with the addition of ribociclib to endocrine therapy in both patients who were node-negative and node-positive, broaden-

ing the indication for the use of CDK 4/6 inhibitors.[24] Accordingly, systemic therapy decision-making should be based on known nodal information, and unnecessary axillary surgery should be avoided in the absence of any clear survival benefits.

Limitations

Limitations of our study include its single-arm design and relatively short follow-up thus far. However, this prospective trial had a rigorous eligibility criterion with standardized surgical/technical methods and was carried out in a broad population of patients with cN1 HR+/HER2− disease at 4 participating metropolitan and nonmetropolitan centers. Widespread adoption of the reported surgical approach will have a substantial and meaningful impact on the modern treatment paradigm for patients with node-positive HR+/HER2− disease.

Conclusions

In this prospective, multicenter, single-arm trial of patients with cTx/cT1-2 cN1 HR+/HER2− disease and limited nodal burden suggested by preoperative AUS, SLNB was feasible, with 3 or more SLNs retrieved in 96% of cases. This approach affords the opportunity to omit unnecessary ALND and minimize morbidity among patients with cN1 cancer and limited nodal disease burden.

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Data Sharing Statement: See Supplement 2.

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