



Cost-effectiveness analyses demonstrate that observation is superior to sentinel lymph node biopsy for postmenopausal women with HR + breast cancer and negative axillary ultrasound

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Abstract

Purpose To evaluate the cost-effectiveness of axillary observation versus sentinel lymph node biopsy (SLNB) after negative axillary ultrasound (AUS). In patients with clinical T1-T2 N0 breast cancer and negative AUS, SLNB is the current standard of care for axillary staging. However, SLNB is costly, invasive, decreasing in importance for medical decision-making, and is not considered therapeutic. Observation alone is currently being evaluated in randomized clinical trials, and is thought to be non-inferior to SLNB for patients with negative AUS.

Methods We performed cost-effectiveness analyses of observation versus SLNB after negative AUS in postmenopausal women with clinical T1-T2 N0, HR⁺/HER2⁻ breast cancer. Costs at the 2016 price level were evaluated from a third-party commercial payer perspective using the MarketScan® Database. We compared cost, quality-adjusted life years (QALYs), and net monetary benefit (NMB). Multiple sensitivity analyses varying baseline probabilities, costs, utilities, and willingness-to-pay thresholds were performed.

Results Observation was superior to SLNB for patients with N0 and N1 disease, and for the entire patient population (NMB in US\$: \$655,659 for observation versus \$641,778 for SLNB for the entire patient population). In the N0 and N1 groups, observation incurred lower cost and was associated with greater QALYs. SLNB was superior for patients with > 3 positive lymph nodes, representing approximately 5% of the population. Sensitivity analyses consistently demonstrated that observation is the optimal strategy for AUS-negative patients.

Conclusion Considering both cost and effectiveness, observation is superior to SLNB in postmenopausal women with cT1-T2 N0, HR⁺/HER2⁻ breast cancer and negative AUS.

Keywords Breast cancer · Staging · Axilla · Ultrasound · Sentinel lymph node biopsy · Cost-effectiveness

Introduction

Sentinel lymph node biopsy (SLNB) is currently the standard of care for axillary staging in patients with cT1-T2 N0 breast cancer. However, the role of SLNB has been questioned for multiple reasons. First, in patients with clinically negative axilla, there is no survival benefit associated with

surgical clearance of the axilla, even for patients with positive SLNB. The ACOSOG Z0011 trial randomized patients with 1–2 positive lymph nodes to either axillary lymph node dissection (ALND) or no further axillary intervention. No significant difference in the rates of axillary recurrence or survival was observed despite the presence of macrometastases (> 2 mm) in non-sentinel nodes in 27.3% of patients in the ALND group [1]. Second, although SLNB offers information about the extent of disease, tumor biology and patient factors are more informative for selection of systemic adjuvant therapy [2]. Gene expression profiles, such as Oncotype DX, are increasingly used in both node-negative and node-positive patients to predict a patient's likelihood of recurrence and their response to treatment [3–9]. Third, although SLNB is associated with less morbidity

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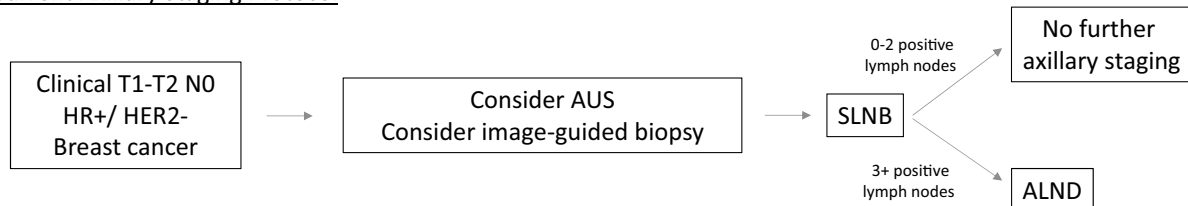
than ALND, risks of the procedure include lymphedema (in approximately 5–10% of patients), dye reactions, nerve damage, range of motion deficits, as well as acute complications such as infection and seroma [10–20].

Axillary ultrasound (AUS) has been proposed as a non-invasive alternative to SLNB for axillary staging (Fig. 1), because it has a high negative predictive value [21–26]. In one study, AUS had a sensitivity of 76% and negative predictive value (NPV) of 89% for detection of macrometastases (> 2 mm) [27]. Interim results from the Intergroup-Sentinel-Mamma (INSEMA) trial demonstrated a negative predictive value of 98.4% for ≥ 3 positive lymph nodes in 755 cT1-2 N0 women with negative AUS undergoing SLNB [28]. Although the most appropriate management algorithm following positive AUS (image-guided biopsy versus SLNB versus ALND) remains a topic of debate, we and others have proposed that observation is superior to SLNB in AUS-negative patients.

The differences in quality-of-life outcomes (especially related to potential complications) and costs between observation and SLNB are substantial [29–31]. There are two ongoing randomized controlled trials (NCT02167490 and NCT02466737) comparing observation to SLNB in AUS-negative patients [28–32]. These trials will not consider critical information related to cost and quality of life, and may not provide detailed analyses for the HR +/

HER2- subtype in which observation is likely most appropriate. To date, cost-effectiveness analyses have focused on the role of AUS-guided biopsy in AUS-positive patients [30–33]. To our knowledge, there have been no cost-effectiveness analyses comparing observation to SLNB in AUS-negative patients. Providers are likely unaware of the potential economic burden patients incur due to SLNB given the lack of accessible, easily interpretable, and detailed healthcare cost data in the U.S. The costs of SLNB may not be justified considering possible quality-of-life detriments [31], and the minimal impact of axillary staging information on recurrence and survival for most postmenopausal, HR⁺/HER2⁻ patients. cT1-T2N0, postmenopausal, HR⁺/HER2⁻ patients represent a very large and low-risk subset of breast cancer patients who are unlikely to develop recurrence or progressive disease [34]. HR⁺/HER2⁻ is the most common subtype of breast cancer, and postmenopausal women are the most common age group [35, 36]. This group is also the most well represented in the patient population studied in clinical trials which have supplied data for the decision analytic model [1, 4, 28]. In these patients, a direct comparison of disease outcomes, quality of life, and financial costs associated with observation and SLNB is needed. Therefore, we have performed cost-effectiveness analyses comparing observation to SLNB in cT1-T2N0, postmenopausal, HR⁺/HER2⁻, breast cancer patients with negative AUS.

Current Axillary Staging Protocol



Proposed Axillary Staging Protocol

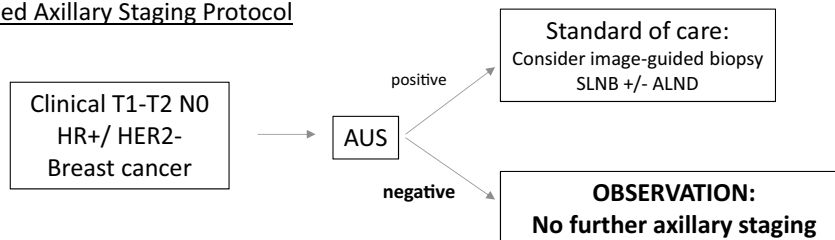


Fig. 1 Current versus Proposed Axillary Staging Protocols. Currently, SLNB is the standard of care for staging of the axilla for patients with early stage breast cancer. However, surgery does not improve survival in patients without clinically apparent disease, and may lead to complications including lymphedema and surgical site

infections. In the proposed staging algorithm, negative AUS can be used to exclude disease in the axilla, and identify those patients who can forego SLNB. *AUS* axillary ultrasound, *SLNB* sentinel lymph node biopsy, *ALND* axillary lymph node dissection

Methods

Target population

The study population was postmenopausal women with cT1-T2 N0, HR⁺/HER2⁻ invasive breast cancer and negative AUS. This population represents the largest subset of breast cancer patients [35, 36], and potentially the best candidates for non-invasive staging for multiple reasons. First, postmenopausal women with HR⁺/HER2⁻ disease have very low risks of disease recurrence or progression compared to pre-menopausal women and those with HR disease [34]. Furthermore, in this subset, medical decision-making is less dependent on surgical staging, and radiation therapy has not demonstrated significant benefit. We stratified these patients into six subpopulations: pT1a N0, pT1a N1, pT1a N2+, pT1b-T2 N0, pT1b-T2 N1, and pT1b-T2 N2+ (Fig. 2) to best accommodate stage-specific standards of care. Due to the inconsistency between the Z0011 definition of low nodal burden (1–2 nodes) and the 8th edition AJCC definition (N1 = 1–3 nodes), we defined women with 1–2 or 1–3 positive nodes as N1, and women with > 3 positive nodes as N2+ (pN2-pN3) [37].

Decision analytic model

We constructed decision analytic models to compare observation versus SLNB for each of the six subpopulations (Fig. 2). Observation was defined as the standard of care and surveillance that breast cancer patients receive after initial diagnostic work-up as recommended by the 2019 NCCN breast cancer guidelines [35, 38]. Markov models were used to simulate potential events and outcomes patients could experience for 10 years (each cycle length = 1 year) after breast cancer diagnosis and initial treatment, which would be poorly represented accurately modeled using simple decision trees [39]. The Markov models consisted of five mutually exclusive and collectively exhaustive health states: healthy (no recurrence), local recurrence, regional recurrence, distant recurrence, and deceased (Table 1, Fig. 3, S-VI).

Input parameters: probabilities

To populate parameters in the decision analytic models, literature reviews were conducted using PubMed, Ovid Medline, Embase, Scopus, Clinicaltrials.gov, and Cochrane Database of Systematic Reviews. A meta-analysis was also performed to assess the performance characteristics of AUS, particularly related to the false-negative rate associated with a high burden of nodal disease (N2+ or ≥ 3 positive lymph nodes).⁴⁰ This included 14,383 patients in 14 studies from

various settings (academic medical centers, population-based studies, and international studies). Whenever available, we used probability values specific to patient age, T-stage, N-stage, recurrence score, and hormonal subtype (exceptions outlined in S-II). When > 1 data sources were available, the data from the best evidence (better study design, larger sample size) was used [39].

In the Markov models, transition probabilities were derived from relevant survival analyses in the literature (Table 1, S-VI). Patients with false-negative AUS may be undertreated due to their unrecognized axillary disease. To account for the fact that patients with false-negative AUS results may have a higher likelihood of regional and/or distant recurrence than patients with the same stage identified as positive by SLNB, we applied a “multiplier” to the related transition probabilities. These multipliers were estimated based on the risk ratios of recurrence associated with the appropriate systemic therapy and/or radiation therapy for the stage. For example, hazard ratios for recurrence from a recent randomized clinical trial by Whelan et al., and relative risks from a meta-analysis by the Early Breast Cancer Trialists’ Collaborative Group were used to inform the multiplier estimates for the transition probability from the healthy state to the distant recurrence state [41, 42]. These multipliers were calibrated and validated by comparing our predicted survival curves to survival analyses from clinical trials. We also examined values within a wide range for each of these multipliers in the sensitivity analyses (see Sect. 2.4).

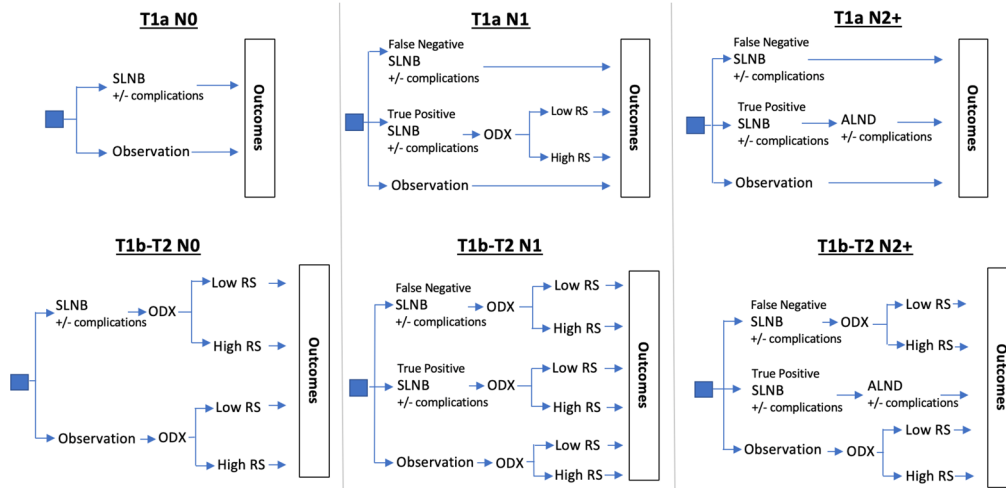
Input parameters: costs

Healthcare costs from the payer perspective were derived from the IBM® MarketScan® Commercial Database. Women at least 52 years of age coded with an International Classification of Diseases (ICD)-9/10 diagnosis code(s) for invasive breast cancer on a pathologist’s claim(s) were identified, and Current Procedural Terminology, 4th edition (CPT) codes for procedures of interested were captured within 180 days of diagnosis. From our cost analysis, the costs of AUS, Oncotype DX testing, SLNB, and ALND were \$164; \$3,912; \$6,430; and \$7,367, respectively (S-IV). Costs were adjusted to 2016 U.S. dollars using the medical care cost component of the consumer price index, and were each at 3% as recommended by the US Panel on Cost-Effectiveness in Health and Medicine [43, 44].

Input parameters: utilities

Utility values for each health state of the Markov models were obtained from published data. When multiple values were available, arithmetic averages were used.

Stage-specific models



Population-level model

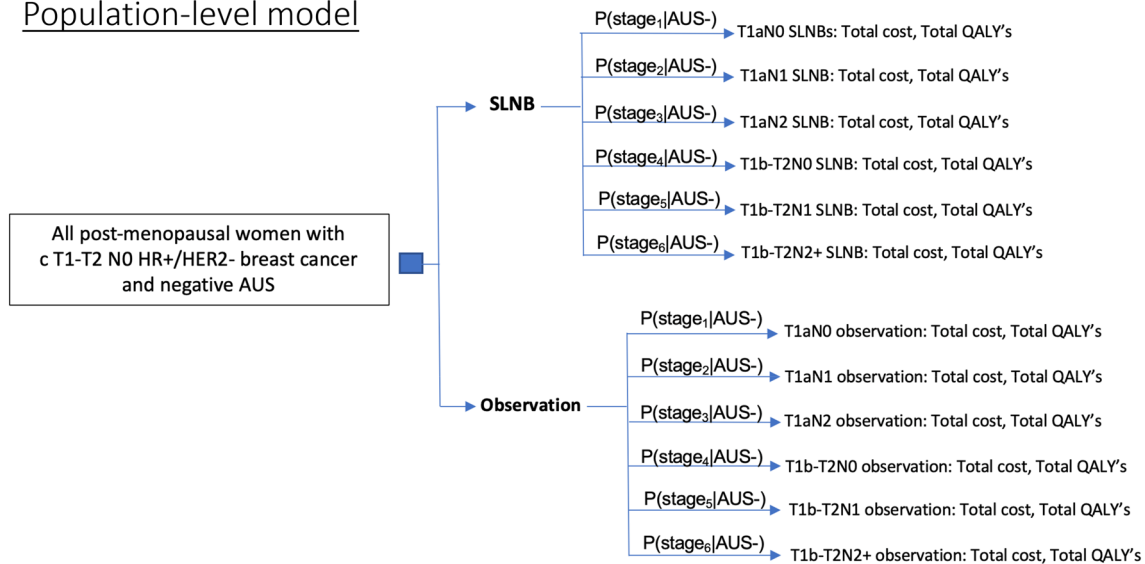


Fig. 2 Decision Analytic Model Structures. All models featured the same initial decision node: SLNB versus observation after negative AUS. T1b-T2N0 and N1 patients received Oncotype DX testing. N2+ patients whose axillary disease was correctly identified by SLNB proceeded to ALND. N1 and N2+ patients whose axillary disease was not correctly identified by AUS or SLNB (false negatives) were treated as if they were N0. Treatment was modeled based on Oncotype Dx recurrence score and observed stage, in accordance with NCCN guidelines (S-III). Stage-specific cost-effectiveness anal-

ysis results (including total cost and QALYs) were weighted by their respective probabilities (based on stage prevalence and likelihood of negative AUS), and integrated into a population-level model to simulate real-world outcomes. For $j=1, \dots, 6$

$$P(\text{stage}_j|\text{AUS-}) = \frac{P(\text{stage}_j) \times P(\text{AUS-}|\text{stage}_j)}{\sum_{j=1}^6 P(\text{stage}_j) \times P(\text{AUS-}|\text{stage}_j)}$$

where stage1 = T1aN0, stage2 = T1aN1, stage3 = T1aN2, stage4 = T1b-T2N0, stage5 = T1b-T2N1, and stage6 = T1b-T2N2. SLNB Sentinel lymph node biopsy, AUS Axillary ultrasound, ODX Oncotype Dx test, RS Oncotype DX Recurrence Score, ALND axillary lymph node dissection

Cost-effectiveness analyses

Subpopulation analyses

Cost-effectiveness analyses were conducted in each of the six models to compare observation to SLNB after negative AUS. Based on the baseline probabilities, costs, and utilities, expected values were computed as the model outputs,

including total cost and quality-adjusted life years (QALYs). A half-cycle correction was applied to the Markov models. Future costs were discounted to the present value at an annual rate of 3%. Cost-effectiveness was evaluated by comparing net monetary benefit (NMB), calculated as $(\text{QALYs} \times \text{willingness-to-pay threshold}) - \text{cost}$, between observation and SLNB. NMB was used, as opposed to the incremental cost-effectiveness ratio (ICER), because NMB

Table 1 Key input parameters

Variable type	Variable description	Value	Range used in sensitivity analyses
Probability	False-negative SLNB	0.07 ⁶⁵	0.01–0.10
Probability	Lymphedema after SLNB	0.05 ^{10,15}	0.005–0.10
Probability	Surgical site infection after SLNB	0.11 ¹⁰	0.005–0.20
Probability	Lymphedema after ALND	0.15 ¹⁰	0.005–0.20
Probability	Surgical site infection after ALND	0.15 ¹⁰	0.005–0.20
Probability	AUS true-negative result given N0 disease	0.87 ³⁶	0.5–1.0
Probability	AUS false-negative result given N1 disease (1–2LNs)	0.59 ³⁶	0.1–0.8
Probability	AUS false-negative result given N2 + disease (3 + LNs)	0.25 ³⁶	0.1–0.6
Cost	ALND	\$7,367 ⁵⁴	\$1,500–\$46,546
Cost	SLNB	\$6,430 ⁵⁴	\$13–\$96,593
Cost	Oncotype Dx	\$3,912 ⁵⁴	\$1–\$4481
Cost	AUS	\$164 ⁵⁴	–
Utility	Health (post-breast cancer)	0.88 ^{66–69}	0.5–1.0
Utility	Local recurrence	0.71 ^{70,71}	0.2–0.9
Utility	Regional recurrence	0.60 ⁷⁰	0.2–0.9
Utility	Metastatic recurrence	0.57 ^{65,71,72}	0.2–0.9
Utility	Death	0**	–
Utility	Lymphedema	0.82 ⁷³	0.4–0.99
Utility	Surgical site infection	0.52 ^{72, 74, 75}	0.4–0.99
Probability	Stage T1a N0 within cohort of T1–T2 patients with negative AUS	0.084 ^{35,36}	0–0.2
Probability	Stage T1a N1 within cohort of T1–T2 patients with negative AUS	0.003 ^{35,36}	0–0.15
Probability	Stage T1a N2 within cohort of T1–T2 patients with negative AUS	0.004 ^{35,36}	0–0.15
Probability	Stage T1b–T2 N0 within cohort of T1–T2 patients with negative AUS	0.720 ^{35,36}	0.5–0.99
Probability	Stage T1b–T2 N1 within cohort of T1–T2 patients with negative AUS	0.144 ^{35,36}	0.05–0.25
Probability	Stage T1b–T2 N2 within cohort of T1–T2 patients with negative AUS	0.045 ^{35,36}	0–0.15
Annual Probability	Regional recurrence	0.003–0.005 ^{*62,63}	0.001–0.20
Annual Probability	Metastatic recurrence	0.008–0.044 ^{*4,9,62}	0.001–0.20
Annual Probability	Metastatic progression after regional recurrence	0.13 ^{55, 57, 58}	0.001–0.20
Annual Probability	Death after regional recurrence	0.08 ^{56, 57}	0.001 – 0.20
Multiplier for probability	Regional recurrence in patients with unrecognized N1 disease	1 ^{1, 38, 46, 47}	1–20
Multiplier for probability	Regional recurrence in patients with unrecognized N2 + disease	5 ^{38, 39, 46, 47}	1–20
Multiplier for probability	Metastatic recurrence in patients with unrecognized N1 disease	1 ^{1, 38, 47}	1–20
Multiplier for probability	Metastatic recurrence in patients with unrecognized N2 + disease	5 ^{38, 39, 47}	1–20

* Assumption

** Stage-specific values were used from the stated range of values

SLNB sentinel lymph node biopsy, ALND axillary lymph node dissection, AUS axillary ultrasound, LNs lymph nodes, \$ US dollars

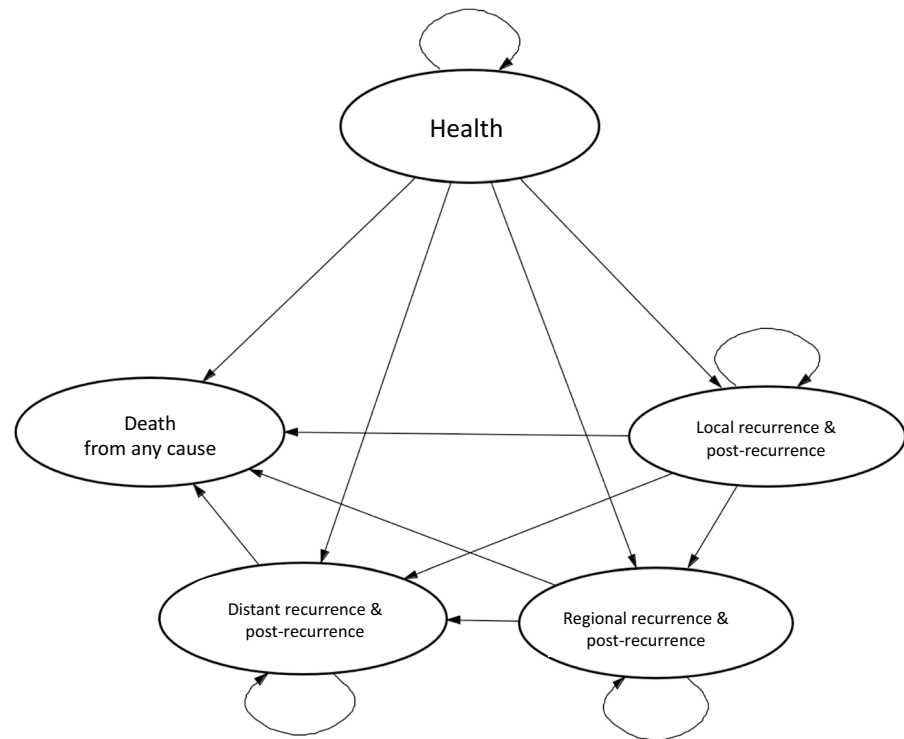
allows for assessment of interventions which are less costly and more effective [45, 46]. Willingness-to-pay threshold of \$100,000/QALY was used (\$50,000–\$150,000 in sensitivity analyses) [47]. The strategy with higher NMB was the superior option.

Population-level analysis

Given that a patient's pathologic nodal stage is not known at presentation, we combined the outputs from the six

subpopulations using Bayes' theorem based on (1) the prevalence of each stage (derived from the 2011–2016 SEER Cancer Registry from patients with T1–T2 HR⁺/HER2⁻ breast cancer [35], S–V); and (2) AUS performance (derived via systematic review of the literature and meta-analysis [35, 40]).

Fig. 3 Markov Model State Transition Diagram. Recurrence states include diagnosis of recurrence, recurrence treatment, and subsequent surveillance. Simultaneous recurrence types were classified based on the most severe type (i.e., concurrent local and distant recurrences were considered a distant recurrence)



Sensitivity analyses

Multiple one-way sensitivity analyses were performed to evaluate the effect of uncertainty from the following variables on our model conclusion, including false-negative rate of AUS, false-negative rate of SLNB, probability and cost of complications from SLNB/ALND, stage prevalence, probability of disease outcomes (recurrence, death) especially given unrecognized nodal disease, and willingness-to-pay thresholds. See Table 1 for the ranges used for these parameters.

Results

Subpopulation analyses

Over the 10-year time horizon, N0 and N1 patients in the observation arm incurred lower costs and higher QALYs than SLNB patients. N2+ patients incurred higher cost but higher QALYs with SLNB (Table 2). Using a willingness-to-pay threshold of \$100,000, NMB (calculated using both cost and quality-of-life measures) for observation was larger than that for SLNB. Thus, observation was superior in N0 and N1 patients. However, in N2+ patients, NMB for observation was smaller than NMB for SLNB, and thus SLNB was superior.

Population-level analysis

Our systematic review of the AUS literature resulted in a pooled false-negative rate of 59% for low axillary burden (N1 or 1–2 positive LNs), and 25% for high axillary burden (N2 or ≥ 3 positive LNs) [48]. T1b–T2 N0 was the largest subpopulation based on prevalence data (~60% of the target population) [35]. Observation after negative AUS was the optimal strategy for patients with N0 and N1 disease, representing approximately 95% of the study population (Table 2). Therefore, combining the prevalence of the subpopulations with the probabilities of false-negative AUS (Fig. 2), observation resulted in lower cost (observation \$120,403 versus SLNB \$131,721), higher QALYs (observation 7.76 versus SLNB 7.73), and higher NMB (observation \$655,659 versus SLNB \$641,778). As a result, observation was favored over SLNB.

Sensitivity analyses

For patients with N0 and N1 disease, observation was the superior strategy despite significant variation across input variables tested via sensitivity analyses (Table 3). Only the N2+ models consistently favored SLNB, despite wide variation in input parameters.

The node-positive models demonstrated sensitivity to variation in the multiplier we used to estimate the recurrence risk in the setting of unrecognized nodal disease. For example,

Table 2 Results of cost-effectiveness analyses: subpopulation- and population-level

T-stage	N-stage	Axillary staging strategy	Cost (US\$)	QALYs	NMB	Favored strategy	Calculated % of target population
T1a	N0	Observation	\$108,660	8.07	\$698,153	Observation	8.4%
T1a	N0	SLNB	\$115,931	7.97	\$681,270		
T1a	N1	Observation	\$111,807	7.70	\$657,991	Observation	0.3%
T1a	N1	SLNB	\$136,921	7.61	\$623,625		
T1a	N2	Observation	\$136,538	4.92	\$349,014	SLNB	0.4%
T1a	N2	SLNB	\$232,668	6.88	\$447,057		
T1b-T2	N0	Observation	\$113,069	8.03	\$689,782	Observation	72.0%
T1b-T2	N0	SLNB	\$120,295	7.93	\$672,973		
T1b-T2	N1	Observation	\$131,345	7.07	\$576,124	Observation	14.4%
T1b-T2	N1	SLNB	\$138,569	6.99	\$560,412		
T1b-T2	N2	Observation	\$149,068	5.35	\$385,576	SLNB	4.5%
T1b-T2	N2	SLNB	\$234,282	6.65	\$431,145		
All stages (Population-level model)		Observation	\$120,403	7.76	\$655,659	Observation	
		SLNB	\$131,721	7.73	\$641,778		

Cost-effectiveness was assessed by comparing the net monetary benefit (NMB) between strategies which was calculated by (QALYs gained x willingness-to-pay threshold) – cost. The strategy with higher NMB is the superior option (WTP=\$100,000). Axillary observation was favored over SLNB in the N0 and N1 stage-specific models (representing >95% of the target population), and in the aggregate model. SLNB sentinel lymph node biopsy, AUS axillary ultrasound, QALY quality-adjusted life-year

Table 3 Results of key one-way sensitivity analyses

Variable Description	Superior strategy	T1a N0	T1a N1	T1a N2	T1b-T2 N0	T1b-T2 N1	T1b-T2 N2	Population-level model
Cost of SLNB	Observation SLNB	\$13-\$96,593	\$13-\$96,593	\$13-\$96,593	\$13-\$96,593	\$13-\$96,593	\$52,100-\$96,593	NA ² NA ²
Probability of lymphedema after SLNB	Observation SLNB	0.005-0.10	0.005-0.10	0.005-0.10	0.005-0.10	0.005-0.10	0.005-0.10	NA ² NA ²
Utility of lymphedema	Observation SLNB	0.4-0.99	0.4-0.99	0.4-0.99	0.4-0.99	0.4-0.99	0.4-0.5	NA ² NA ²
Probability: regional recurrence	Observation SLNB	0.001 – 0.20	0.001 – 0.20	0.001 – 0.20	0.001 – 0.20	0.001 – 0.20	0.001 – 0.20	NA ² NA ²
Multiplier for probability of regional recurrence in patients with unrecognized nodal disease	Observation SLNB	NA ¹	1-5.9	1-20	NA ¹	1-4.3	1-7.6	NA ² NA ²
Multiplier for probability of distant recurrence in patients with unrecognized nodal disease	Observation SLNB	NA ¹	1-1.6	1-2.8	NA ¹	1-1.3	1-2.3	NA ² NA ²
Utility of regional recurrence	Observation SLNB	0.2-0.9	0.2-0.9	0.2-0.9	0.2-0.9	0.2-0.9	0.2-0.9	NA ² NA ²
Utility of metastatic recurrence	Observation SLNB	0.2-0.9	0.2-0.9	0.2-0.9	0.2-0.9	0.2-0.9	0.2-0.9	NA ² NA ²
False negative rate AUS for N1 disease	Observation SLNB	NA ³ NA ³	NA ³ NA ³	NA ³ NA ³	NA ³ NA ³	NA ³ NA ³	NA ³ NA ³	0.1-0.8
False negative rate AUS for N2+ disease	Observation SLNB	NA ³ NA ³	NA ³ NA ³	NA ³ NA ³	NA ³ NA ³	NA ³ NA ³	NA ³ NA ³	0.1-0.6
Willingness-to-pay threshold	Observation SLNB	\$50,000-\$150,000	\$50,000-\$150,000	<\$50,000 \$50,000-\$150,000	\$50,000-\$150,000	\$50,000-\$150,000	\$50,000-\$65,000 \$65,000-\$150,000	\$50,000-\$150,000

■ NMB Observation > NMB SLNB (observation was superior) for the range of values listed
 ■ NMB Observation < NMB SLNB (SLNB was superior) for the range of values listed

for T1b-T2 N2 + patients with unrecognized nodal disease, SLNB was favored if the annual risk of distant recurrence was multiplied by a factor of ≥ 2.3 (resulting annual probability ≥ 0.1012). When a lower willingness-to-pay threshold was used (\$50,000), the qualitative results did not change, except within N2 + subpopulations. In the population-level model,

significant variation in the sensitivity of AUS did not result in a qualitative change of conclusion. Observation was superior even when the AUS false-negative rate for N2 + disease was increased to 50%, and for N1 disease to 80%.

Discussion

This study compared the cost-effectiveness of observation versus SLNB after negative AUS in postmenopausal women with clinical T1-T2 N0, HR⁺/HER2⁻ breast cancer. We found that in patients with N0 and N1 disease, observation was associated with lower costs and greater QALYs. This finding aligns with clinical intuition and NCCN recommendations as there is no therapeutic benefit associated with surgery, and biomarker and gene expression profile drive clinical decision-making in these patients. The low prevalence of AUS-negative patients with N2 + disease and the fact that observation was clearly the superior strategy for patients with N0 and N1 disease lead to the conclusion that observation is the superior strategy for the entire patient population.

Sensitivity analyses were performed for many input parameters, including two variables of particular interest: (1) the false-negative rate of AUS for the detection of high versus low nodal burden, and (2) the regional and distant recurrence rates in the setting of unrecognized nodal disease. To determine the false-negative rate of AUS, we combined high quality evidence from multiple sources in a robust systematic review, and derived a reliable estimate of AUS performance for the exclusion of high and low nodal burden. The results of this systematic review confirmed that AUS is highly sensitive for the detection of N2 + disease. To account for AUS variability (for example, from operator dependence), our sensitivity analysis evaluated the impact of a very wide range of false-negative rates on cost-effectiveness: 10–80% for N1 disease and 10–60% for N2 + disease. The conclusion that AUS is superior to SLNB was remarkably robust, even with false-negative rate of 80% for N1 disease and 60% for N2 + disease. To assess the risk of recurrence in the setting of unrecognized disease, we used a combination of relevant literature and expert opinion to estimate a risk multiplier for regional and distant recurrence. This multiplier allowed us to use known values of recurrence risk in the setting of accurately diagnosed nodal disease, and measure the effect of variation in this risk due to potential undertreatment of unrecognized nodal disease. We took into consideration risk reduction estimates for disease progression related to both systemic therapy and extended field radiation therapy. Current guidelines and a study of clinical practice suggest that physicians strongly consider gene expression profile, rather than nodal burden, when selecting systemic therapies [38, 49]. We also considered that extended field radiation therapy might be omitted for patients with unrecognized nodal disease [38, 41, 42, 50, 51]. For example, in a randomized trial by Whelan et al., nodal irradiation marginally benefitted N1 patients (small decrease in regional

recurrence, but no overall survival benefit). However, subset analysis demonstrated no benefit for patients with HR⁺ disease [41, 52]. Therefore, a multiplier of 1.0 for regional and/or distant recurrence in AUS false-negative cN0/pN1 patients within our target population of relatively low-risk breast cancer is justified. To account for uncertainty in these variables, we used a wide range of values in our sensitivity analyses, and the conclusion remained consistent: AUS is superior to SLNB in this population.

This study provides a new perspective on the benefit of observation/non-invasive axillary staging in the context of mounting literature supporting more judicious application of surgical staging. Z0011 was not the first study in breast oncology to generate evidence that surgical axillary clearance is not always associated with survival benefit [53]. One of the key practice changes from Z0011 was omitting ALND for patients with < 3 positive nodes. Our study demonstrates the survival, quality of life, and financial cost benefits of using a negative AUS to identify patients who can forego axillary surgery. The presence of undetected nodal disease in 27% of Z0011 patients, without survival decrement, underscores the potential that systemic therapy is effective in treating some nodal disease. This critical result suggests that, in the 5% of patients who may have unrecognized N2 + disease, the impact of undertreatment may be mitigated by the fact that all patients are treated with systemic therapy.

A considerable body of evidence suggests that complications and costs associated with SLNB significantly impact patients' quality of life [54]. Out-of-pocket costs and productivity losses contribute to a heavy burden for breast cancer survivors who suffer from lymphedema which is most often iatrogenic from axillary surgery [31]. Avoidance of unnecessary surgery will decrease the financial burden and eliminate potentially long-term physical, psychological, and emotional challenges presented by surgery itself and surgical complications such as lymphedema [55]. Although the psychological and emotional effects of lymphedema are not easily quantified in a cost-effectiveness analysis, they are critically important to consider when weighing the costs and benefits of axillary staging procedures with individual patients, and are avoidable when axillary observation is an appropriate alternative.

This study has several strengths. We utilized cost estimates from novel cost analyses for diagnostic procedures and complications related to lymphedema. Costs which we did not derive were taken from sources which used the same or very similar source data [56, 57]. The consistency of cost data sources enhances the validity of this study. Furthermore, we conducted extensive literature reviews related to SLNB performance and complications, Oncotype DX testing, ALND complications, health state utilities, as well as long-term recurrence and survival outcomes. When sufficient published data were available, e.g., AUS performance

by nodal burden, we conducted a meta-analysis to synthesize the data. These reviews provided evidence for the values of our base models, a reference range to ensure adequate sensitivity analyses, and contributed to the formation of a realistic and reproducible model.

Of note, our model design did not include the cost, effectiveness, and complications related to bisphosphonate therapy or endocrine therapy. This is appropriate because we do not expect that the use of bisphosphonate and/or endocrine therapies differs between our two modeled strategies. Our model also did not include the potential complications and disutility associated with chemotherapy or radiotherapy. SLNB would likely result in more chemotherapy and radiotherapy use (given the recognition of nodal disease). Therefore, including these complications would only emphasize observation as the superior strategy. Similarly, we only modeled SLNB and ALND complications related to lymphedema and surgical site infection. Doing so allowed us to account for both acute and chronic complications, although we did not include all potential complications. In literature review, we found that lymphedema and surgical site infections were well documented in large trials and data sets which generated reliable probabilities. In contrast, the costs associated with dye reactions, seroma, paresthesias, and range of motion deficits were less reliable/available. Importantly, inclusion of these additional complications would only emphasize observation as the superior strategy.

A limitation of our study is the fact that only a subset of breast cancer patients (postmenopausal, HR⁺/HER2⁻) were included. However, the selected population represents the majority of breast cancer patients: HR⁺/HER2⁻ subtype represents approximately 73% of breast cancer cases in the US, 90% of HR⁺/HER2⁻ patients have T1-T2 tumors, and 81% of HR⁺/HER2⁻ patients are > 50 years old [36]. Another limitation is that we assumed patients were managed with standard regimens based on clinical guidelines, which included Oncotype DX testing for T1b-T2N0 and N1 patients. In real-world practice, there is variation in management given patient preference and providers' clinical judgment. However, our models were based on NCCN guidelines, and informed by studies which have demonstrated increasing use of recurrence scores to guide treatment decisions [49]. The proposed approach may be particularly well suited for low-income countries in which surgery and optimal therapy for complications are even less accessible. Observation after negative AUS would not require any changes in standard-of-care surveillance as recommended by NCCN guidelines. Therefore, we would expect no difference in patient adherence to follow-up between the two examined strategies: observation after negative AUS versus SLNB.

The concern related to observation versus SLNB is that some patients may be undertreated. Patients with unrecognized nodal disease may not receive appropriate

therapy such as chemotherapy and/or extended field radiation. There are important counterpoints to consider. First, SLNB is associated with false-negative rates ranging from 5 to 22.9% [17]. Second, observation includes appropriate therapy for the primary tumor, including surgery, radiation therapy, and systemic endocrine therapy. It is likely that systemic therapy contributes to control of nodal disease, although this is an area that requires further investigation. Third, unrecognized nodal disease would likely be identified during surveillance and successfully treated at the time of discovery, suggesting that observation may only delay definitive therapy. Current paradigms in cancer biology suggest that lymph node disease is unlikely to spread to other organs. Fourth, using SEER data and AUS performance statistics, we calculated that approximately 5% of patients in our study population would have unrecognized N2+ disease, and most of those patients would receive Oncotype DX testing and appropriate systemic therapy. The ethical implications of potential undertreatment versus decreased quality of life from potential surgical complications must be considered. In our analysis, observation is clearly supported by the ethical principle of "first, do no harm."

In conclusion, for postmenopausal woman with cT1-T2 N0, HR⁺/HER2⁻ breast cancer, observation after negative AUS results in lower costs and higher QALYs compared to SLNB. Our study provides unique and reassuring evidence for observation in low-risk, postmenopausal women with cT1-T2, HR⁺/HER⁻ breast cancer after negative axillary ultrasound and avoid unnecessary surgery. Cost and quality-of-life outcomes will be important complements to the data generated by ongoing randomized clinical trials (SOUND, INSEMA) and, altogether, will provide evidence for future guidelines. Our study clearly demonstrates that observation is a reasonable alternative to SLNB in an important subset of breast cancer patients where adjuvant therapy decision-making is less dependent on axillary staging.

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Compliance with ethical standards

Conflict of interest All authors (Aubriana McEvoy, Steven Poplack, Katelin Nickel, Margaret Olsen, Foluso Ademuyiwa, Imran Zoberi, Elizabeth Odom, Jennifer Yu, Su-Hsin Chang, and William Gillanders) have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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