HHS Public Access

Author manuscript

Ann Surg Oncol. Author manuscript; available in PMC 2025 October 01.

Published in final edited form as:

Ann Surg Oncol. 2024 October ; 31(11): 7621–7633. doi:10.1245/s10434-024-15812-w.

Utility of Axillary Staging in Older Patients with HER2-Positive Breast Cancer

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Abstract

Background: The utility of sentinel lymph node biopsy (SLNB) in older patients remains controversial. Advancements in HER2-directed therapy have revolutionized disease response rates and prognosis, supporting efforts to reevaluate the utility of SLNB. We aimed to assess the differences in treatment and overall survival (OS) in older patients with HER2-positive breast cancer based on SLNB.

Methods: Using the National Cancer Database (2010-2020), patients ≥70y diagnosed with cT1-2/cN0/M0, HER2-positive breast cancer were identified. Logistic regression assessed associations with SLNB, systemic therapy, and radiation. Cox proportional hazards models were

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DISCLOSURES

- The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.
- Dr. Plichta was the recipient of research funding from the Color Foundation (2017-2018; PI: Plichta) and Earlier.org (2023-2024; PI: Plichta). She is a member of Editorial Committee for the American Joint Committee on Cancer (AJCC), the Breast Panel for the AJCC, and the National Comprehensive Cancer Network (NCCN) Breast Cancer Diagnosis and Screening Committee. She is an editorial board member for the Annals of Surgical Oncology.
- Dr. E.S. Hwang serves on the National Cancer Institute (NCI) Breast Cancer Steering Committee and the NCCN Breast Cancer Prevention Committee. She is an Associate Editor for the Annals of Surgical Oncology.
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- S. Thomas is a member of the Evidence-Based Medicine Committee for the AJCC, the Breast Panel for the AJCC, and the Neuroendocrine Tumors Panel for the AJCC.
- The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health (NIH).

Presentation: Parts of this work were presented as a poster at the ASBrS Annual Meeting in April 2024 and the Academic Surgical Congress in February 2024.

used to identify factors associated with OS. Analyses were stratified by treatment sequence: 1) upfront surgery, or 2) neoadjuvant therapy (NAT) followed by surgery.

Results: Of the 17,609 patients included, 94% underwent upfront surgery (n=16,492), and the remaining had NAT (n=1,117). Those who underwent SLNB were more likely to receive adjuvant therapy, irrespective of nodal status [upfront surgery/systemic therapy (OR 2.82; 95% CI, 2.17-3.67); upfront surgery/radiation (OR, 3.97; 95% CI, 3.03-5.21); NAT/radiation (OR, 5.69; 95% CI, 1.83-17.69)]. Breast pCR rate was highest among the HR-negative/HER2-positive subtype (50.0%), of which none were found to be ypN+. Comorbidity burden was associated with significantly lower rates of adjuvant systemic therapy and worse OS.

Conclusions: Patients who underwent SLNB, regardless of pN status, were more likely to receive adjuvant therapy. Nodal positivity is exceedingly rare for patients with a breast pCR following NAT, especially among the HR-negative/HER2-postitive subtype. It is reasonable to consider omission of SLNB in select subgroups of older patients with HER2-positive breast cancer.

Keywords

breast cancer; elderly; HER2-positive; survival; sentinel lymph node; neoadjuvant; pathologic complete response

INTRODUCTION

One of the most significant risk factors for the development of breast cancer is age, with about one-third of breast cancers diagnosed in women over 70 years old.[1] The population of individuals over 70 is growing, as is the number of breast cancers diagnosed in this group. However, older women with breast cancer represent a diverse group with varying levels of physical activity, comorbidities, and life expectancy. This variation in baseline health status at this age complicates the management of breast cancer and makes establishing treatment guidelines especially challenging.

Despite this, there are specific treatment guidelines for older patients with hormone receptor (HR)-positive breast cancer driven by the CALGB 9343 study.[2] In a secondary analysis, it was demonstrated that women over 70 years old with small (cT1-2), clinically node negative (cN0), HR-positive, human-epidermal-growth-factor-receptor-2 (HER2)-negative breast cancer who take adjuvant endocrine therapy exhibit similar survival outcomes regardless of whether they undergo axillary surgery. These results, as well as other trials,[3,4] led to the creation of the *Choosing Wisely* guidelines that recommend omission of routine sentinel lymph node biopsy (SLNB) in clinically node-negative women over 70 years of age with HR-positive/HER2-negative breast cancer. This is especially clinically relevant given that a fair majority of older patients are diagnosed with this breast cancer subtype.[5]

In comparison, approximately 10% of older patients are diagnosed with HER2-positive breast cancer.[5,6] Moreover, HER2-positive breast cancer has been associated with a higher clinical aggressiveness,[7,8] and toxicity concerns[9,10] related to treatment may lead to further exclusion of older patients from clinical trials out of fear of fragility. As a result, unlike for patients with HR-positive/HER2-negative breast cancer, there are no national

recommendations to tailor or potentially de-escalate surgical approaches for some of the more vulnerable older patients with early-stage HER2-positive breast cancer. Currently, treatment of patients with HER2-positive breast cancer is largely “one-size-fits-all” strategy without respect to patient age, comorbidities, or tumor response to systemic therapies. However, advancements in HER2-directed therapy have revolutionized patient prognosis, as demonstrated with the use of trastuzumab and other targeted therapies, resulting in improved disease-free survival, lower rates of recurrence, and higher rates of pathologic complete response (pCR).[11-13] These dramatic improvements in patient outcomes suggest that tumor biology may now be a more significant driver of treatment decisions than the previously dominant anatomic characteristics of a breast cancer diagnosis, such as nodal status. As such, the aim of this study was to assess the differences in treatment decisions and overall survival (OS) based on SLNB receipt/result in older patients with cT1-T2/cN0, HER2-positive breast cancer.

METHODS

Study Population

Using the National Cancer Database (NCDB), patients aged ≥70 years old diagnosed with HER2-positive, cT1-2/cN0/M0 breast cancer between 2010-2020 were retrospectively identified. Patients who met the inclusion criteria were stratified by treatment sequence: 1) upfront surgery, or 2) neoadjuvant therapy (NAT) followed by surgery. Patients with cT3-4, cN1-3, cM1, or pT3-4, or pM1 disease were excluded. Patients with missing data, those who received neoadjuvant radiation, or those who did not have breast surgery (i.e., lumpectomy or mastectomy) were also excluded. Sentinel lymph node biopsy was defined as the retrieval of 5 or fewer lymph nodes (LNs), which has been utilized in prior studies.[14-16] Notably, the NCDB did not have a specific variable differentiating SLNB from axillary lymph node dissection until 2012, and the details of SLNB were not routinely recorded until 2018. Patients who had more than 5 LNs removed were excluded. Based on SLNB receipt/result, patients were grouped for sub-analyses based on the following characteristics: 1) No SLNB (no LNs removed; pNx), 2) SLNB-negative (1-5 LNs removed with 0 positive LNs; pN0), and (3) SLNB-positive (1-5 LNs removed with at least 1 positive LN; pN+). In the NCDB, immunotherapy is defined as biological or chemical agents that alter the immune system or change the host’s response to tumor cells.[17] Importantly, HER2-targeted therapy, such as trastuzumab, was initially included with the chemotherapy variable in the NCDB until 2013, at which time it was then included with the immunotherapy variable.

Statistical Analysis

Patient characteristics were summarized as N (%) for categorical variables and as median (interquartile range [IQR]) for continuous variables. Mann-Whitney and Chi-Square or Fisher’s Exact tests were used to assess intergroup differences for continuous and categorical variables, respectively. Analysis of variance (ANOVA) or Kruskal-Wallis test was used to assess differences between SLNB result, depending on the normality of the data. Logistic regression models were used to identify factors associated with (1) SLNB receipt (yes/no), (2) SLNB result (pN+/pN0), (3) adjuvant systemic therapy (yes/no), and (4) adjuvant radiation therapy (yes/no); odds ratios (ORs) and 95% confidence intervals (CIs)

are reported. Logistic regression models were adjusted for several covariates including age, sex, race/ethnicity, patient insurance type, Charlson/Deyo comorbidity score, education level of the community, income level of the community, community type, facility type, facility location, clinical T-category, pathologic T/N-category, tumor grade, and breast surgery type. Logistic regression models were built in the generalized estimating equations framework and included a compound symmetry covariance structure to account for the correlation of patients treated at the same facility.

OS was defined as the time from diagnosis to death or last follow-up. The reverse Kaplan-Meier method was used to estimate follow-up time. The Kaplan-Meier method was used to estimate unadjusted OS, and log-rank tests were used to assess for differences in survival between groups. A Cox Proportional Hazards model was used to identify factors associated with OS after adjustment for available covariates; hazard ratios (HRs) and 95% CIs are reported. The adjusted survival model included a sandwich covariance estimator to account for the correlation of patients treated at the same facility. Due to NCDB administrative censoring, patients diagnosed in 2020 were excluded from all survival analyses.

Only patients with available data for all variables were included in each regression model and/or figure. Statistical significance was determined using a threshold of $P < 0.05$. No adjustments were made for multiple comparisons. All statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC) or R Studio (Version 4.2.2, Vienna, Austria). This study was deemed exempt by our Institutional Review Board due to the use of de-identified, publicly available data.

RESULTS

Patient Characteristics

A total of 17,609 patients were included with a median follow-up of 62.6 months (IQR 61.7-63.4) (Supplemental Figure 1). The median age was 75.0 years old (IQR 72.0-80.0). Of the 17,051 patients who received a SLNB (96.8%), 1,686 had pathologically positive nodes (9.9% pN+), most of whom were pN1 (98.7%, n=1,664). Additional clinicopathologic features for patients who underwent upfront surgery and those who received NAT are recorded in Table 1.

Upfront Surgery Cohort

Of the overall cohort, 93.7% received surgery first (n=16,492). Approximately 73.2% (n=12,086) of these patients were ER-positive/HER2-positive and the remaining 27.8% (n=4,406) were ER-negative/HER2-positive (Table 2). The median age at diagnosis was 75.0 years old (IQR 72.0-80.0). Most patients who underwent upfront surgery also underwent SLNB (96.8%, n=15,971), of which 10.1% were pN+ (n=1,615). Of those who were pN+, the majority were pN1 (98.7%, n=1,594). Patients who did not undergo SLNB, compared to those who did, were older [age 70-74, REF vs 80-84, OR 0.30 (95% CI 0.23-0.41) vs 85+, OR 0.09 (95% CI 0.07-0.11); p<0.001] and had a lower tumor grade [grade 1, REF vs grade 2, OR 1.87 (95% CI 1.34-2.62) vs grade 3, OR 2.08 (95% CI 1.48-2.93); p=0.004). There

was no significant association between SLNB receipt and Charlson/Deyo comorbidity score or clinical T-category (both p>0.05) (Table 3).

Adjuvant Systemic Therapy: A significant difference in systemic therapy receipt was found in patients who *did* vs those who *did not* undergo SLNB, regardless of nodal status. SLNB receipt was associated with higher rates of adjuvant systemic therapy [OR 2.82 (95% CI 2.17-3.67), p<0.001]. Positive nodal status was also associated with an increased likelihood of adjuvant systemic therapy, compared to those with negative nodes [pN0, REF vs pN+, OR 2.16 (95% CI 1.90-2.46); p<0.001] (Table 4). Patients who did not have a SLNB were less likely to receive adjuvant systemic therapy, compared to those with negative nodes [pN0, REF vs pNx, OR 0.39 (95% CI 0.30-0.50), p<0.001]. Older age was associated with a decreased likelihood of receiving adjuvant systemic therapy [70-74y, REF vs 75-79y, OR 0.57 (95% CI 0.53-0.62) vs 80-84y, OR 0.26 (95% CI 0.23-0.29), vs 85y+, OR 0.10 (95% CI 0.08-0.12), p<0.001] (Table 4).

Adjuvant Radiation: Similar to adjuvant systemic therapy, SLNB receipt was associated with a higher likelihood of radiation, regardless of nodal status [No SLNB, REF vs Yes SLNB, OR 3.97 (95% CI 3.03-5.21), p<0.001]. Compared to those with negative nodes, nodal positivity was associated with a higher likelihood of radiation [pN0, REF vs pN+, OR 2.4 (95% CI 1.90-3.02), p<0.001] (Table 4). However, negative nodal status was also associated with a higher likelihood of radiation compared to patients who did not have a SLNB [pN0, REF vs pNx, OR 0.27 (95% CI 0.21-0.36), p<0.001]. Older age [70-74y, REF vs 75-79y, OR 0.70 (95% CI 0.63-0.78) vs 80-84y, OR 0.45 (95% CI 0.39-0.51), vs 85y+, OR 0.28 (95% CI 0.23-0.33), p<0.001] was associated with a decreased likelihood of receiving radiation (Table 4).

Neoadjuvant Therapy (NAT) Cohort

Of the overall cohort, 6.3% received NAT (n=1,117). The median age at diagnosis was 73.0 years old (IQR 71.0-77.0). Of the 96.7% (n=1,080) who underwent a SLNB, 6.6% were ypN+ (n=71), most of whom were ypN1 (98.6%, n=70) (Table 1). A breast pCR was found in 35.6% of patients (n=398). Of those with a breast pCR who underwent SLNB (n=386), only a *single* patient (0.3%) was ypN+ (Table 5). Of the 514 patients classified as ypT1 following NAT and received SLNB, 8.8% (n=45) were ypN+. Of the 180 patients classified as ypT2 following NAT and received SLNB, 15.0% (n=27) were ypN+. Due to limited observations, potential variables associated with SLNB receipt, such as comorbidity score, clinical T-category, and tumor grade, were not assessed.

Hormone Receptor Status: Approximately 58.4% (n=653) of patients were ER-positive/HER2-positive and the remaining 41.6% (n=464) were ER-negative/HER2-positive (Table 2). Half (n=232) of the patients with HR-negative/HER2-positive breast cancer had a breast pCR, and all were ypN0. In contrast, only 25.4% (n=166) of patients with HR-positive/HER2-positive breast cancer achieved a breast pCR, with a nodal positivity rate of 0.6%. The overall rate of nodal positivity in patients who had residual breast disease was 7.8% for HR-negative/HER2-positive and 11.1% for HR-positive/HER2-positive.

Adjuvant Radiation: SLNB following NAT was associated with increased adjuvant radiation receipt, compared to those who did not undergo SLNB [OR 5.69 (95% CI 1.83-17.69), p=0.02]. Furthermore, positive nodal status was associated with a higher likelihood of receiving radiation, compared to those with negative nodes [pN0, REF vs pN+, OR 3.77 (95% CI 1.47-9.66), p=0.01] (Table 4). However, negative nodal status was also associated with a higher likelihood of receiving radiation, compared to those who did not undergo SLNB [pN0, REF vs pNX, OR 0.17 (95% CI 0.05-0.55), p=0.003]. Adjuvant radiation receipt was not associated with clinical T-category, tumor grade, or Charlson/Deyo comorbidity score (all p>0.05) (Table 4).

Survival Analyses

On unadjusted analyses, patients in both the upfront surgery and NAT cohorts, who were either node-positive or did not undergo SLNB, exhibited worse survival outcomes than those with negative nodes (Figure 1). Even in this older population, the receipt of systemic therapy was associated with better survival, regardless of performance of SLNB or nodal status. After adjustment, similar findings were noted in OS for patients who underwent upfront surgery and had positives nodes or no SLNB [pNx, REF vs pN+, HR 1.09 (95% CI 0.89-1.33), p=0.41] (Table 6). Conversely, in the NAT cohort, patients who were pathologically node negative and those who did not undergo SLNB demonstrated similar OS [pN0, REF vs pNx, HR 1.38 (95% CI 0.58-3.29), p=0.47].

DISCUSSION

Our findings demonstrate low rates of nodal positivity in a cohort of older patients with HER2-positive, clinically node-negative breast cancer with approximately 10% pN+ in the upfront surgery subgroup and <7% in the NAT subgroup. Furthermore, the vast majority appeared to have limited nodal burden. Among the 398 patients who underwent NAT and had a breast pCR, only a *single* patient was found to have pathologically positive nodes. When further stratified by hormone receptor status, half of patients with HR-negative/HER2-positive breast cancer had a breast pCR, and among those, all were node negative. These findings support prior work that has demonstrated similar rates of breast pCR[9,18-21] and its association with a remarkably low incidence of nodal positivity following NAT.[18,21-23] As such, a SLNB in select patients may offer limited value, and suggests this cohort represents a subgroup in whom omission of SLNB may be considered.

When identifying subgroups of patients that could be considered for omission of SLNB, our cohort is particularly relevant for several reasons. As previously mentioned, among patients with HER2-positive breast cancer, there is a high rate of breast pCR and low rate of nodal positivity following treatment with neoadjuvant HER2-directed therapy.[18-21] Prior studies have consistently shown that the rate of breast pCR is higher in patients with HER2-postitive and triple-negative breast cancer, in comparison to those with the the HR-positive/HER2-negative subtype.[20,22,24-26] In addition, breast pCR in HER2-positive breast cancer has been demonstrated to be an accurate predictor of excellent prognosis and an appropriate surrogate end point, which may be particularly relevant in a cohort of older women.[27] Second, our study has provided further evidence to the existing literature that even

those with pathologically positive nodes exhibit very low disease burden, with nearly 99% of patients classified as pN1 (vs. pN2-3).[22] Finally, a consideration unique to our cohort of older women is the comorbidity burden associated with increasing age that oftentimes has a greater impact on survival than cancer itself.[10] Our findings reveal that for all patients, regardless of treatment, a higher comorbidity status was associated with worse outcomes.

Nevertheless, we acknowledge there may be relevant information gained from SLNB to guide adjuvant therapy in healthy older women. As described in the APHINITY trial[28], higher-risk breast cancer patients, such as those without prior neoadjuvant therapy who are found to have positive nodes at the time of surgery, may derive benefit from adjuvant treatments. However, those with node-negative breast cancer may not necessitate such additional therapy, and SLNB may allow for omission of potentially more toxic chemotherapeutic regimens. In our study, approximately 10% of patients initially treated with surgery were found to have positive nodes, highlighting the utility of SLNB in guiding a more individualized treatment approach for this subgroup. Similarly, patients who received NAT may also derive benefit from additional systemic therapy if a SLNB were to reveal residual nodal disease. The KATHERINE trial[29] demonstrated that adjuvant treatment with trastuzumab emtansine (T-DM1) in this setting decreases the risk of recurrence by 50% compared to treatment with trastuzumab alone. However, in both the APHINITY trial[28] and the KATHERINE trial[29], only 13% and fewer than 10% were ≥ 65 years old, respectively, indicating the importance of assessing for appropriate indications prior to proceeding with SLNB.

Furthermore, we found that most older patients with early stage HER2-positive breast cancer underwent upfront surgery. This may be in part due to the uncertainty of optimal treatments in this population.[18,30,31] Moreover, according to the American Society of Clinical Oncology (ASCO) guidelines[32], patients with clinically T2 disease, which represents approximately a quarter of our cohort, are candidates for NAT. In addition, there is an increasing trend to use NAT, due to the opportunity to adjust therapies in the adjuvant setting depending on disease response.[30,31] NAT also provides an opportunity to achieve pCR and downstage the breast and axilla, which could facilitate de-escalation of surgery. However, whether a breast pCR is achieved is not known prior to surgery, and there have been efforts to find alternative methods for establishing pCR. Thus far, imaging and vacuum-assisted biopsy (VAB) when used independently following NAT have not proven to be acceptably accurate methods due to either a high false negative rate (ultrasound, mammography, and VAB) or a high false positive rate (MRI).[33-35] However, the use of a machine learning algorithm that incorporates numerous variables related to tumor response following NAT has been shown to reliably identify patients with a pCR before surgery and demonstrated the lowest false negative rate (0.0%) in an external validation set when compared to imaging alone, VAB alone, or the combination of the two.[36] Although based on a different study population, the SOUND (Sentinel Node vs Observation After Axillary Ultra-Sound) trial recently demonstrated acceptable outcomes for patients with a negative axillary ultrasound who did and did not undergo axillary surgery.[37] Notably, omitting SLNB upfront and returning to the operating room in a second surgery for only a few select patients when necessary could prove to be cost effective.[14] These approaches and considerations warrant further investigation.

Of our patients who received NAT, nodal status specifically impacted rates of adjuvant radiation therapy, but this was not found to be associated with improved OS. While radiation therapy is generally well tolerated, even in older women, it may provide less benefit in this population where the absolute risk of local recurrence is lower (likely due in part to shorter life expectancy) and continues to decrease with age.[38,39] Furthermore, evidence from prior studies suggest that treatment with HER2-directed therapy drives a large proportion of local-regional recurrence reduction, compared to post-mastectomy radiation therapy.[40-42] Guidelines for patients with early-stage breast cancer who achieve a pCR in the axilla following NAT recommend an individualized approach to nodal radiation based on risk stratification.[43] While there are prospective observational data showing axillary radiation could be safely avoided in low-risk HER2-positive early-stage breast cancer[43-45], ongoing randomized trials such as NSABP B51[46] will further refine this recommendation and the role of a SLNB in radiation treatment planning.

Among patients who underwent upfront surgery, the prevalence of positive lymph nodes was relatively modest at 10.1% in our study. However, irrespective of nodal status, those who had a SLNB were more likely to receive adjuvant treatment compared to those without a SLNB, even among those with negative nodes. Additionally, the nodal burden of disease was predominantly low, with the majority classified as pN1. Notably, among these patients who did not receive adjuvant treatment, their survival outcomes were similar when compared to those who neither underwent SLNB nor received adjuvant therapy. These outcomes could potentially be attributed to the escalating impact that comorbidity burden has on mortality, regardless of nodal status.[10,47,48] Our findings support this as well, with higher comorbidity burden exhibiting worse survival outcomes across all patient groups. Similarly, a recent study found that, after adjusting for tumor characteristics and guideline concordant treatment, patients older than 70 with severe comorbidities were the only subgroup to exhibit worse survival outcomes.[10] There are several possible reasons that guideline concordant therapy may be attenuated, including poor baseline status, vulnerability to toxicity, and/or polypharmacy interacting with breast cancer-related therapy.[10] While this may be more relevant in a case-by-case basis rather than establishing guidelines, it has a potentially significant impact on outcomes that should be reflected in multidisciplinary discussions.

Limitations

While utilizing the NCDB contributes to the strengths in this study, such as the ability to narrow our investigation to a specific subgroup but still maintain a large sample size, it also results in several limitations. The NCDB relies on data reported by participating cancer programs across the US, which inherently can impact the completeness and quality. Unfortunately, there is some missingness in the NCDB, which has been shown to be associated with outcomes.[49] Furthermore, the NCDB does not include information about recurrence or cancer-specific survival. However, in our older patient population, all-cause mortality is likely a meaningful endpoint. Finally, as with all retrospective studies, causal relationships cannot be established, and all results should be interpreted cautiously in the context of treatment bias in which patients deemed more fit receive more treatment.

Conclusion

Among older patients with cT1-2/N0, HER2-positive breast cancer, there are subgroups for whom a SLNB may provide limited utility, such as those with HR-negative/HER2-postitive disease or those who appear to have a pCR following NAT. Additionally, a patient centered approach should be an important focus among older women for whom individual comorbidities may outweigh the ability to derive benefits from adjuvant treatment, therefore making SLNB unnecessary. However, adjuvant treatment decisions are oftentimes made under the guidance of nodal status, which may lead to omission of toxic chemotherapy agents and/or prolonged survival with adjunctive therapies. Additional research is warranted to further clarify the ongoing role of a SLNB in this unique, heterogenous population with highly effective systemic therapy options.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

The National Cancer Data Base (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC's NCDB are the source of the de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

FUNDING SOURCES

- This work was supported by the National Institutes of Health [grant numbers P30CA014236, K12AR084231].

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SYNOPSIS:

For select patients ≥70y with cT1-2/cN0 HER2-positive breast cancer, including those who achieve a breast pCR following NAT or who present with significant comorbidities, the utility of a SLNB may be limited and omission of axillary assessment could be considered.

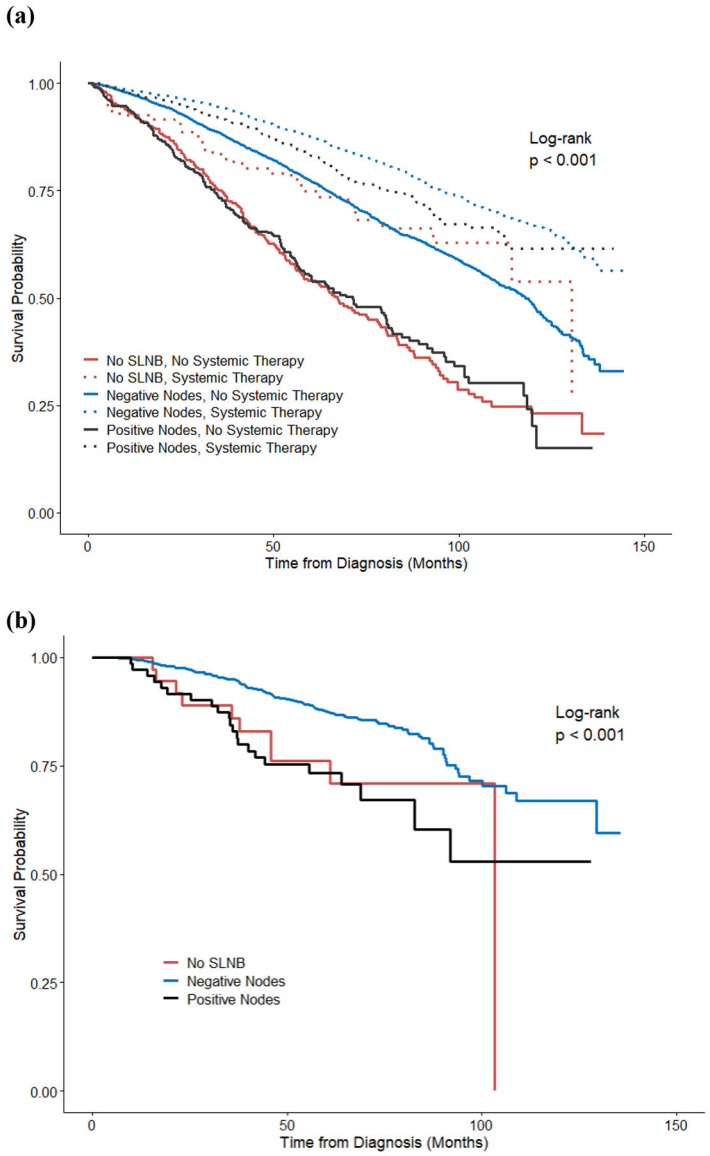

Figure 1. Unadjusted survival stratified by SLNB receipt and result, and systemic therapy receipt for patients that received (a) upfront surgery and (b) NAT.

Abbreviations: SLNB=sentinel lymph node biopsy.

Table 1.

Patient characteristics of those aged ≥70y with cT1/cT2, cN0, M0, HER2-positive breast cancer diagnosed 2010-2020 in the National Cancer Database who were treated with upfront surgery or neoadjuvant therapy (NAT), stratified by SLNB receipt/result.

	Upfront Surgery					Neoadjuvant Therapy (NAT)			
			SLNB					SLNB	
	All Patients N=16492 (%)	No SLNB N=521 (%)	Negative SLNB N=14321 (%)	Positive SLNB N=1650 (%)	P-Value	All Patients N=1117 (%)	No SLNB N= 37 (%)	Negative SLNB N=1007 (%)	Positive SLNB N=73 (%)
Age (Years)					<0.001				
70-74	7151 (43.4)	103 (19.8)	6369 (44.5)	679 (41.2)		678 (60.7%)	18 (48.6%)	617 (61.3%)	43 (58.9%)
75-79	4795 (29.1)	74 (14.2)	4255 (29.7)	466 (28.2)		312 (27.9)	12 (32.4%)	276 (27.4%)	24 (32.9%)
80-84	2847 (17.3)	114 (21.9)	2419 (16.9)	314 (19.0)		87 (7.79)	3 (8.11%)	79 (7.85%)	5 (6.85%)
85+	1699 (10.3)	230 (44.1)	1278 (8.92)	191 (11.6)		40 (3.58)	4 (10.8%)	35 (3.48%)	1 (1.37%)
Median [IQR]	75.0 [72.0;80.0]	83.0 [77.0;88.0]	75.0 [72.0;80.0]	76.0 [72.0;81.0]	<0.001	73.0 [71.0;77.0]	75.0 [72.0;78.0]	73.0 [71.0;76.0]	74.0 [71.0;77.0]
Sex					0.005				
Female	16328 (99.0)	519 (99.6)	14187 (99.1)	1622 (98.3)		1111 (99.5)	37 (100)	1002 (99.5%)	72 (98.6%)
Male	164 (0.99)	2 (0.38)	134 (0.94)	28 (1.70)		6 (0.54)	0 (0.00)	5 (0.50%)	1 (1.37%)
Race/Ethnicity					0.77				
Hispanic	563 (3.41)	13 (2.50)	498 (3.48)	52 (3.15)		55 (4.92%)	1 (2.70%)	52 (5.16%)	2 (2.74%)
Non-Hispanic Asian	392 (2.38)	13 (2.50)	341 (2.38)	38 (2.30)		35 (3.13%)	0 (0.00%)	32 (3.18%)	3 (4.11%)
Non-Hispanic Black	1263 (7.66)	36 (6.91)	1095 (7.65)	132 (8.0)		91 (8.15%)	3 (8.11%)	82 (8.14%)	6 (8.22%)
Non-Hispanic White	13730 (83.3)	444 (85.2)	11899 (83.1)	1387 (84.1)		904 (80.9%)	30 (81.1%)	813 (80.7%)	61 (83.6%)
Other	112 (0.68)	1 (0.19)	101 (0.71)	10 (0.61)		8 (0.72%)	0 (0.00%)	8 (0.79%)	0 (0.00%)
Insurance					0.89				
Government	14754 (89.5%)	458 (87.9%)	12807 (89.4%)	1489 (90.2%)		971 (86.9%)	34 (91.9%)	868 (86.2%)	69 (94.5%)
None	33 (0.20%)	1 (0.19%)	28 (0.20%)	4 (0.24%)		3 (0.27%)	0 (0.00%)	3 (0.30%)	0 (0.00%)
Private	1550 (9.40%)	53 (10.2%)	1350 (9.43%)	147 (8.91%)		132 (11.8%)	3 (8.11%)	125 (12.4%)	4 (5.48%)
Charlson/Deyo Comorbidity Score					0.002				
0	12272 (74.4%)	381 (73.1%)	10685 (74.6%)	1206 (73.1%)		873 (78.2%)	30 (81.1%)	789 (78.4%)	54 (74.0%)
1	2919 (17.7%)	85 (16.3%)	2554 (17.8%)	280 (17.0%)		158 (14.1%)	3 (8.11%)	145 (14.4%)	10 (13.7%)

	Upfront Surgery					Neoadjuvant Therapy (NAT)			
	All Patients N=16492 (%)	No SLNB N=521 (%)	SLNB		P-Value	All Patients N=1117 (%)	No SLNB N= 37 (%)	SLNB	
			Negative SLNB N=14321 (%)	Positive SLNB N=1650 (%)				Negative SLNB N=1007 (%)	Positive SLNB N=73 (%)
≥2	1301 (7.89%)	55 (10.6%)	1082 (7.56%)	164 (9.94%)		86 (7.70%)	4 (10.8%)	73 (7.25%)	9 (12.3%)
Grade					<0.001				
1	1174 (7.12%)	60 (11.5%)	1041 (7.27%)	73 (4.42%)		41 (3.67%)	3 (8.11%)	34 (3.38%)	4 (5.48%)
2	6793 (41.2%)	212 (40.7%)	5906 (41.2%)	675 (40.9%)		438 (39.2%)	15 (40.5%)	393 (39.0%)	30 (41.1%)
3	8525 (51.7%)	249 (47.8%)	7374 (51.5%)	902 (54.7%)		638 (57.1%)	19 (51.4%)	580 (57.6%)	39 (53.4%)
Clinical T-Category					<0.001				
cT1	12893 (78.2%)	377 (72.4%)	11428 (79.8%)	1088 (65.9%)		361 (32.3%)	15 (40.5%)	318 (31.6%)	28 (38.4%)
cT2	3599 (21.8%)	144 (27.6%)	2893 (20.2%)	562 (34.1%)		756 (67.7%)	22 (59.5%)	689 (68.4%)	45 (61.6%)
Pathologic T-Category					<0.001				
pT0/pTis	45 (0.27%)	1 (0.19%)	42 (0.29%)	2 (0.12%)		398 (35.6%)	12 (32.4%)	385 (38.2%)	1 (1.37%)
pT1	12122 (73.5%)	361 (69.3%)	10866 (75.9%)	895 (54.2%)		528 (47.3%)	14 (37.8%)	469 (46.6%)	45 (61.6%)
pT2	4325 (26.2%)	159 (30.5%)	3413 (23.8%)	753 (45.6%)		191 (17.1%)	11 (29.7%)	153 (15.2%)	27 (37.0%)
Pathologic N-Category					<0.001				
pN0	14863 (90.1%)	519 (99.6%)	14309 (99.9%)	35 (2.12%)		1044 (93.5%)	36 (97.3%)	1006 (99.9%)	2 (2.74%)
pN1	1608 (9.75%)	2 (0.38%)	12 (0.08%)	1594 (96.6%)		72 (6.45%)	1 (2.70%)	1 (0.10%)	70 (95.9%)
pN2	19 (0.12%)	0 (0.00%)	0 (0.00%)	19 (1.15%)		1 (0.09%)	0 (0.00%)	0 (0.00%)	1 (1.37%)
pN3	2 (0.01%)	0 (0.00%)	0 (0.00%)	2 (0.12%)		0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Surgery Type					0.007				
Lumpectomy	11472 (69.6%)	377 (72.4%)	9999 (69.8%)	1096 (66.4%)		757 (67.8%)	29 (78.4%)	680 (67.5%)	48 (65.8%)
Mastectomy	5020 (30.4%)	144 (27.6%)	4322 (30.2%)	554 (33.6%)		360 (32.2%)	8 (21.6%)	327 (32.5%)	25 (34.2%)
Treatment with Radiation					<0.001				
No	7755 (47.0%)	394 (75.6%)	6718 (46.9%)	643 (39.0%)		483 (43.2%)	22 (59.5%)	440 (43.7%)	21 (28.8%)
Yes	8737 (53.0%)	127 (24.4%)	7603 (53.1%)	1007 (61.0%)		634 (56.8%)	15 (40.5%)	567 (56.3%)	52 (71.2%)
Treatment with Chemotherapy					<0.001				

	Upfront Surgery					Neoadjuvant Therapy (NAT)			
	All Patients N=16492 (%)	No SLNB N=521 (%)	SLNB		P-Value	All Patients N=1117 (%)	No SLNB N= 37 (%)	SLNB	
			Negative SLNB N=14321 (%)	Positive SLNB N=1650 (%)				Negative SLNB N=1007 (%)	Positive SLNB N=73 (%)
No	9155 (71.9%)	427 (82.0%)	7421 (51.8%)	630 (38.2%)		27 (2.42%)	2 (5.41%)	24 (2.38%)	1 (1.37%)
Yes	3572 (28.1%)	94 (18.0%)	6900 (48.2%)	1020 (61.8%)		1090 (97.6%)	35 (94.6%)	983 (97.6%)	72 (98.6%)
Treatment with immunotherapy					<0.001				
No	9505 (57.6%)	444 (85.2%)	8330 (58.2%)	731 (44.3)		192 (17.2%)	8 (21.6%)	163 (16.2%)	21 (28.8%)
Yes	6987 (42.4%)	77 (14.8%)	5991 (41.8%)	919 (55.7)		925 (82.8%)	29 (78.4%)	844 (83.8%)	52 (71.2%)

Abbreviations: CI=confidence interval, IQR=interquartile range, SLNB=sentinel lymph node biopsy.

Percentages may not add up to 100 due to rounding or missing values

P values were not calculated for NAT due to small observations between groups

Table 2.

Patient characteristics of those aged ≥70y with cT1/cT2, cN0, M0, HER2-positive breast cancer diagnosed 2010-2020 in the National Cancer Database who were treated with upfront surgery and neoadjuvant therapy (NAT), stratified by Hormone Receptor (HR) status.

	Upfront surgery				Neoadjuvant therapy (NAT)			
	All Patients N=16492 (%)	Hormone Receptor Status		P-Value	All Patients N=1117 (%)	Hormone Receptor Status		P-Value
		ER-negative N= 4,406 (%)	ER-positive N= 12,086 (%)			ER-negative N= 464 (%)	ER-positive N= 653 (%)	
SLNB Receipt				0.975				1.000
No	521 (3.16%)	140 (3.18%)	381 (3.15%)		37 (3.31%)	15 (3.23%)	22 (3.37%)	
Yes	15971 (96.8%)	4266 (96.8%)	11705 (96.8%)		1080 (96.7%)	449 (96.8%)	631 (96.6%)	
SLNB Outcome				0.003				0.010
0 Nodes Removed	521 (3.16%)	140 (3.18%)	381 (3.15%)		37 (3.31%)	15 (3.23%)	22 (3.37%)	
Negative SLNB	14321 (86.8%)	3884 (88.2%)	10437 (86.4%)		1007 (90.2%)	431 (92.9%)	576 (88.2%)	
Positive SLNB	1650 (10.0%)	382 (8.67%)	1268 (10.5%)		73 (6.54%)	18 (3.88%)	55 (8.42%)	
Pathologic T-Category				<0.001				<0.001
pT0/pTis	45 (0.27%)	13 (0.30%)	32 (0.26%)		398 (35.6%)	232 (50.0%)	166 (25.4%)	
pT1	12122 (73.5%)	3054 (69.3%)	9068 (75.0%)		528 (47.3%)	177 (38.1%)	351 (53.8%)	
pT2	4325 (26.2%)	1339 (30.4%)	2986 (24.7%)		191 (17.1%)	55 (11.9%)	136 (20.8%)	
Pathologic N-Category				0.004				0.001
pN0	14863 (90.1%)	4026 (91.4%)	10837 (89.7%)		1044 (93.5%)	446 (96.1%)	598 (91.6%)	
pN1	1608 (9.75%)	374 (8.49%)	1234 (10.2%)		72 (6.45%)	17 (3.66%)	55 (8.42%)	
pN2	19 (0.12%)	5 (0.11%)	14 (0.12%)		1 (0.09%)	1 (0.22%)	0 (0.00%)	
pN3	2 (0.01%)	1 (0.02%)	1 (0.01%)		0 (0.00%)	0 (0.00%)	0 (0.00%)	
Nodal Positivity				0.001				0.004
pN0	14863 (90.1%)	4026 (91.4%)	10837 (89.7%)		1044 (93.5%)	446 (96.1%)	598 (91.6%)	
pN1- pN3	1629 (9.88%)	380 (8.62%)	1249 (10.3%)		73 (6.54%)	18 (3.88%)	55 (8.42%)	

Abbreviations: SLNB=sentinel lymph node biopsy.

Percentages may not add up to 100 due to rounding or missing values

Table 3.

Adjusted logistic regression model for SLNB receipt for patients aged ≥70y with cT1-2/pT1-2/cN0/M0, HER2-positive breast cancer diagnosed 2010-2020 in the National Cancer Database who were treated with upfront surgery.

In addition to the variables listed, the models were also adjusted for sex, race/ethnicity, patient insurance, zip code education level, zip code income level, community type, facility type, facility location, tumor grade, and breast surgery type.

	Odds Ratio (95% CI)	P-Value	Overall P-Value
Age (Years)			<0.001
70-74	REF		
75-79	0.97 (0.69-1.35)	0.85	
80-84	0.3 (0.23-0.41)	<0.001	
85+	0.09 (0.07-0.11)	<0.001	
Charlson/Deyo Comorbidity Score			0.31
0	REF		
1	1 (0.76-1.32)	0.98	
≥2	0.77 (0.57-1.05)	0.10	
Clinical T-Category			0.49
cT1	REF		
cT2	0.93 (0.75-1.14)	0.49	
Grade			0.004
1	REF		
2	1.87 (1.34-2.62)	<0.001	
3	2.08 (1.48-2.93)	<0.001	

Abbreviations: CI=confidence interval, SLNB=sentinel lymph node biopsy.

Table 4.

Adjusted logistic regression model for adjuvant systemic therapy and radiation therapy for patients aged ≥70y with cT1-2/pT1-2/cN0/M0, HER2-positive breast cancer diagnosed 2010-2020 in the National Cancer Database who received upfront surgery or neoadjuvant therapy (NAT).

In addition to the variables listed, the models were also adjusted for sex, race/ethnicity, patient insurance, zip code education level, zip code income level, community type, facility type, facility location, and breast surgery type.

	Upfront Surgery						Neoadjuvant Therapy (NAT)		
	Association with systemic therapy			Association with radiation therapy			Association with radiation therapy		
	Odds Ratio (95% CI)	P-Value	Overall P-value	Odds Ratio (95% CI)	P-Value	Overall P-Value	Odds Ratio (95% CI)	P-Value	Overall P-Value
SLNB Result			<0.001			<0.001			0.001
Negative SLNB	REF			REF			REF		
No SLNB	0.39 (0.3-0.5)	<0.001		0.27 (0.21-0.36)	<0.001		0.17 (0.05-0.55)	0.003	
Positive SLNB	2.16 (1.9-2.46)	<0.001		2.4 (1.9-3.02)	<0.001		3.77 (1.47-9.66)	0.01	
Age Group			<0.001			<0.001			0.06
70-74	REF						REF		
75-79	0.57 (0.53-0.62)	<0.001		0.7 (0.63-0.78)	<0.001		0.83 (0.54-1.29)	0.41	
80-84	0.26 (0.23-0.29)	<0.001		0.45 (0.39-0.51)	<0.001		0.75 (0.36-1.55)	0.44	
85+	0.1 (0.08-0.12)	<0.001		0.28 (0.23-0.33)	<0.001		0.18 (0.07-0.46)	<0.001	
Charlson/Deyo Comorbidity Score			0.003			0.20			0.90
0	REF			REF			REF		
1	0.97 (0.88-1.07)	0.53		0.97 (0.86-1.09)	0.59		0.91 (0.5-1.66)	0.76	
≥2	0.79 (0.69-0.9)	0.0006		0.85 (0.71-1.02)	0.07		0.87 (0.44-1.7)	0.69	
Clinical T-Category			<0.001			0.02			0.76
cT1	REF			REF			REF		
cT2	1.22 (1.11-1.34)	<0.001		0.86 (0.77-0.97)	0.01		0.94 (0.62-1.43)	0.76	
Grade			<0.001			<0.001			0.10
1	REF			REF					
2	2.37 (2.03-2.78)	<0.001		1.37 (1.16-1.63)	<0.001		0.59 (0.22-1.6)	0.29	
3	4.23 (3.59-4.98)	<0.001		1.57 (1.32-1.87)	<0.001		0.86 (0.32-2.33)	0.76	

Abbreviations: OR=odds ratio, CI=confidence interval, SLNB=sentinel lymph node biopsy.

Table 5.

Breast pCR of those aged ≥70y with cT1/cT2, cN0, M0, HER2-positive breast cancer diagnosed 2010-2020 in the National Cancer Database who were treated with neoadjuvant therapy (NAT), stratified by Estrogen Receptor (ER) status.

	ER-positive/HER2-positive					ER-negative/HER2-positive				
	All patients	**pN0**	**pN1**	**pN2**	**pN3**	**All patients**	**pN0**	**pN1**	**pN2**	**pN3**
Pathologic T-Category	***N=653***	***N=598***	***N=55***	***N = 0***	***N = 0***	***N=464***	***N=446***	***N=17***	***N=1***	***N = 0***
pT0/pTis	166 (25.4%)	165 (27.6%)	1 (1.82%)	0 (0.00%)	0 (0.00%)	232 (50.0%)	232 (52.0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
pT1	351 (53.8%)	316 (52.8%)	35 (63.6%)	0 (0.00%)	0 (0.00%)	177 (38.1%)	167 (37.4%)	10 (58.8%)	0 (0.00%)	0 (0.00%)
pT2	136 (20.8%)	117 (19.6%)	19 (34.5%)	0 (0.00%)	0 (0.00%)	55 (11.9%)	47 (10.5%)	7 (41.2%)	1 (100%)	0 (0.00%)

Table 6.

Multivariable adjusted overall survival model for patients aged ≥70y with cT1-2/pT1-2/cN0/M0, HER2-positive breast cancer diagnosed 2010-2019 in the National Cancer Database stratified by treatment with (A) upfront surgery and (B) neoadjuvant systemic therapy (NAT).

In addition to the variables listed, the models were also adjusted for sex, race/ethnicity, patient insurance type, zip code education level, zip code income level, community type, facility type, facility location, tumor grade, tumor size, and breast surgery type. Abbreviations: CI=confidence interval, SLNB=sentinel lymph node biopsy.*Grade not included in NAT due to small cell counts

	Upfront Surgery			Neoadjuvant therapy (NAT)		
	Hazard Ratio (95% CI)	**P-Value**	**Overall P-Value**	**Hazard Ratio (95% CI)**	**P-Value**	**Overall P-Value**
SLNB Result			<0.001			0.004
Negative SLNB	REF			REF		
No SLNB	1.34 (1.14-1.57)	<0.001		1.38 (0.58-3.29)	0.47	
Positive SLNB	1.46 (1.28-1.66)	<0.001		2.41 (1.43-4.09)	0.001	
SLNB Result			<0.001			0.003
0 Nodes Removed	REF			REF		
Negative SLNB	0.75 (0.64-0.87)	<0.001		0.72 (0.31-1.69)	0.45	
Positive SLNB	1.09 (0.89-1.33)	0.41		1.77 (0.68-4.62)	0.24	
Age Group			<0.001			0.002
70-74	REF			REF		
75-79	1.48 (1.33-1.64)	<0.001		1.27 (0.85-1.9)	0.24	
80-84	2.2 (1.97-2.45)	<0.001		2.39 (1.37-4.16)	0.002	
85+	3.44 (3.04-3.89)	<0.001		2.93 (1.59-5.39)	<0.001	
Charlson/Deyo Comorbidity Score			<0.001			0.004
0	REF			REF		
1	1.28 (1.16-1.4)	<0.001		1.13 (0.7-1.81)	0.62	
≥2	1.95 (1.71-2.22)	<0.001		2.41 (1.43-4.06)	0.001	
Clinical T-Category			<0.001			0.42
cT1	REF			REF		
cT2	1.55 (1.43-1.69)	<0.001		1.16 (0.81-1.68)	0.42	
Treatment with radiation therapy			<0.001			0.20
No	REF			REF		
Yes	0.64 (0.58-0.71)	<0.001		0.74 (0.47-1.17)	0.20	
Treatment with systemic therapy			<0.001			0.11
No	REF			REF		
Yes	0.67 (0.61-0.74)	<0.001		0.7 (0.45-1.08)	0.11	
Grade*			<0.001			
1	REF					
2	1.23 (1.05-1.45)	0.01				

	Upfront Surgery			Neoadjuvant therapy (NAT)		
	Hazard Ratio (95% CI)	**P-Value**	**Overall P-Value**	**Hazard Ratio (95% CI)**	**P-Value**	**Overall P-Value**
3	1.42 (1.2-1.67)	<0.001				

Abbreviations: CI=confidence interval, SLNB=sentinel lymph node biopsy.