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Nodal Response and Survival After Neoadjuvant Endocrine Therapy in Hormone Receptor-Positive Breast Cancer: 20 Year Experience from A Single Institution

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Abstract

Introduction: Axillary response to neoadjuvant endocrine therapy (NET) in the treatment of hormone receptor-positive breast cancer (HR+ BC) is not well-described. We aimed to characterize nodal response after NET.

Methods: Patients receiving NET followed by curative intent surgery at a comprehensive cancer center from 1998–2022 in a prospectively collected registry were included. Patients with distant metastasis were excluded. Primary outcome was nodal pathologic complete response (pCR). Downstaging was defined as post-NET decrease in category.

Results: We included 123 patients; the majority were cT2 (n=59) or cT3 (n=35), and cN0 (n=81). Median age was 70.0 years (interquartile range 62.1, 76.0). Forty-two patients (34.1%) were clinically node positive. After NET, 73 (59.8%) underwent breast conserving surgery. All patients underwent sentinel lymph node biopsy and 12 (9.8%) underwent completion axillary lymph node dissection. In-breast downstaging was achieved in 51 (41.5%) patients, 1 (0.8%) had breast pCR, and 14 (11.4%) had breast upstaging. Axillary downstaging was achieved in 10 (23.8%), 6 patients (14.3%) had nodal pCR, and 14 (33.3%) had axillary upstaging. At 10-year follow-up, local recurrence was 1% and distant recurrence was 14%, while disease-free survival was 82%. After adjusting for demographic and clinical factors, age was the only characteristic associated with mortality (hazard ratio 1.07, 95% confidence interval 1.01–1.13).

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Conclusion: In HR+ BC treated with NET, long-term disease-free survival is good, although nodal pCR is uncommon for cN+ patients. Future studies are needed to elucidate optimal neoadjuvant systemic therapy and delineate oncologically safe strategies to de-escalate axillary management for residual microscopic disease.

Keywords

endocrine therapy; neoadjuvant; breast cancer; axilla; node

Introduction

Treatment for non-metastatic hormone receptor positive (HR+) breast cancer (BC) includes surgery, radiotherapy, and systemic therapies such as chemotherapy and endocrine therapy. Systemic therapies can be delivered in neoadjuvant, adjuvant, or both settings. In recent years, the use of neoadjuvant systemic therapy has increased for locally advanced BC.[1] The advantages of this approach include assessing tumor response for prognosis, decreasing tumor size to increase eligibility for breast-conserving therapy (BCT), and clearing axillary disease to reduce the need for axillary lymph node dissection (ALND).[2] However, HR+/HER2− tumors have lower response rates to neoadjuvant chemotherapy (NCT) as measured by conversion to pathologic complete response (pCR) and clearance of axillary disease.[3] Additionally, unlike patients with HER2+ or triple negative breast cancer (TNBC), adjuvant therapy decisions for HR+/HER2− patients treated with NCT are not based on the presence or absence of residual disease, making response to NCT a less actionable variable for these patients.

In comparison, endocrine therapy (ET) has traditionally been used in the adjuvant setting for HR+ BC as well as for frail patients with more advanced locoregional disease.[4] More recently, several national trials have further investigated ET in the neoadjuvant setting for tumor response and downstaging to BCT. In the American College of Surgeons Oncology Group (ACOSOG) Z1031 trial, 1% of patients had pCR.[5] After neoadjuvant endocrine therapy (NET), 67.2% of patients had BCT, and 50% of patients who were previously candidates for mastectomy were downstaged to allow BCT. In addition to Z1031, the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) and the Pre-operative Arimidex Compared to Tamoxifen (PROACT) trials also found comparable results in post-menopausal women with clinical stage II and III HR+ BC.[6,7]

However, assessment of tumor burden after therapy is an evolving area. The Z1031, IMPACT, and PROACT trials were based on the then-current Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, which included criteria for imaging modality used in evaluating tumor burden but did not include determination of nodal response to therapy. The most recent version of RECIST guidelines have incorporated additional criteria for the measurement and assessment of nodal response.[8] Few studies have followed to examine nodal response to NET in HR+ BC, with one recent review finding a range of 8.1–13.3% for nodal pCR.[9] Thus, there is a critical gap in the literature and unclear guidelines for NET in this patient population.

An important goal of neoadjuvant systemic therapy is the reduction of surgical morbidity via axillary disease clearance. Given the low response rates to NCT in HR+ BC, the efficacy of NET in downstaging in-breast tumor burden, and tolerability of NET relative to NCT, interest in NET has increased as an alternative regimen to NCT in HR+ BC. Additionally, the possibility of de-escalating axillary surgery for patients with residual nodal disease by use of adjuvant radiotherapy – a novel concept termed “tailored axillary surgery” – is under active investigation.[10] In this context, information from recently published series on long-term response to NET for HR+ BC with a focus on nodal response to therapy is especially important but currently lacking. Therefore, we aimed to characterize long term outcomes and, in node-positive patients, effects on nodal response in a patient cohort with HR+ BC from a National Comprehensive Cancer Network (NCCN)-designated treatment center.

Methods

Study Cohort

This study was based on a longitudinal cohort of patients at the University of North Carolina Lineberger Comprehensive Cancer Center. We included adult women 18 years of age and older diagnosed with non-metastatic HR+ and HER2− BC who received NET and surgery from 1998 to 2022. Follow up began at the initiation of endocrine therapy. Duration of neoadjuvant endocrine therapy was determined at the discretion of the treating physicians. Final data abstraction was performed on September 15, 2022. We excluded patients who received neoadjuvant radiation, NCT, and immunotherapy.

Statistical Analysis

In this study, nodal pCR was the primary outcome of interest. Secondary outcome of interest was long-term disease free and overall survival in this cohort. Using the AJCC TNM staging system, downstaging was defined as post-neoadjuvant therapy decrease in T category (i.e. clinical tumor category > pathologic tumor category) and nodal burden (i.e. clinical nodal category > pathologic nodal category).[11]

Patient demographics, clinical characteristics, and treatment were reported using descriptive statistics of median and interquartile ranges (IQRs) for continuous variables, and number and percentages (n, %) for binary and categorical variables. To assess characteristics associated with overall survival, we used unadjusted (one characteristic and outcome) and adjusted (all relevant characteristics and outcome) logistic regression to identify characteristics associated with mortality. Results were presented as odds ratios (ORs) and 95% confidence intervals (CIs). Lastly, we conducted a Cox proportional hazards analysis to assess for the association between nodal pCR and each of the following covariates: age, race, tumor grade, clinical tumor category, and clinical nodal category. Survival analyses using the Kaplan-Meier (KM) estimator were used to determine locoregional recurrence, distant recurrence, disease-free survival, and overall survival.

All analyses were conducted using SAS Version 9.4 (SAS Inc., Cary, North Carolina). The study was approved, including waiver of consent, by the Institutional Review Board at the University of North Carolina at Chapel Hill (IRB #01–1154).

Results

Patient and Treatment Characteristics

A total of 123 patients were included, of which 101 (82.1%) were White and 17 (13.8%) were Black (Table 1). Twenty-one patients were (17.1%) anatomic clinical stage I, 70 (56.9%) were clinical stage II, and 32 (26.0%) were clinical stage III. One (0.8%) patient had clinical T (cT) category 0 (occult primary with nodal disease). Eighty-one (65.9%) patients were clinically node negative (cN0), while 42 (34.1%) were clinically node positive. Median length of endocrine therapy was 169 days (IQR 138–211). Median age was 70 years (IQR 62.1–76.0). Four patients (3.3%) were pre-menopausal. One hundred and four (84.6%) patients had ER positivity ≥ 90%. Most neoadjuvant endocrine therapy was given as aromatase inhibitors: 133 regimens involving aromatase inhibitors, 20 regimens involving fulvestrant, 16 regimens involving tamoxifen, and 5 regimens involving other endocrine therapy.

After NET, 73 (59.8%) underwent BCT and 49 (40.2%) underwent mastectomy (Table 2). Axillary surgery included sentinel lymph node biopsy for 123 (100%) and completion ALND for 12 (9.8%). Forty-four (36.1%) patients received adjuvant chemotherapy and 92 (75.4%) received adjuvant radiotherapy.

Primary Tumor Response to NET

After excluding the patient with occult breast primary, tumor downstaging was achieved in 51 (41.8%) of patients. Only 1 patient (initially cT1) had breast pCR (Figure 1). Patients with higher cT category were more likely to have in breast downstaging with 23 (39.0%) of cT2, 20 (57.1%) of cT3, and 6 (60.0%) of cT4 were downstaged in the breast with NET.

Long-Term Survival Outcomes

Two (1.6%) locoregional recurrence events and 10 (8.1%) distant recurrence events occurred over the study period (Figure 2). The 10-year survival rate of non-metastatic HR+ patients with locoregional recurrence after NET is 99%, while the 10-year survival rate with distant recurrence after NET is 86%. The 10-year disease-free survival rate is 82%. The 10-year all-cause overall survival rate is 62% (Figure 3). Patients with cN0 disease had a 10-year disease free survival rate of 95.1% compared to 85.7% in cN+ patients, and 10-year OS was 85.2% in cN0 patients and 76.2% in cN+ patients.

In the entire cohort, after adjusting for demographic and clinical factors including race, tumor grade, and clinical T and N categories, age was the only characteristic associated with overall mortality (hazard ratio 1.07, 95% confidence interval [CI] 1.01–1.13, Table 4).

Targeted Analysis of Nodal Response in cN+ Patients

Forty-two (34.1%) were clinically node positive. Of these cN+ patients, axillary downstaging was achieved in 10 (23.8%), and 6 (14.3%) achieved nodal pCR. Approximately one third of patients had nodal upstaging (cN0 to pN+: 24; cN1 to pN2+: 13; cN2 to pN3: 1). A majority of patients who experienced nodal upstaging had clinically positive nodes at diagnosis (Figure 1). Ten-year disease-free survival was 85.7% and ten-year OS was 76.2% in this group.

Unadjusted analyses demonstrated that higher grade (grade 3 versus 1, OR 0.29, 95% CI 0.09–0.98), higher tumor category (cT3 versus cT1, OR 0.20, 95% CI 0.06–0.68; cT4 versus cT1, OR 0.06, 95% CI 0.01–0.55), and higher clinical nodal category (cN2 versus cN1, OR 0.12, 95% CI 0.05–0.29; cN3 versus cN1, OR 0.04, 95% CI 0.01–0.37) are associated with nodal residual disease (Table 3). Due to sample size limitations, adjusted analysis was not conducted for this association.

Discussion

Neoadjuvant chemotherapy for locally advanced breast cancer has several advantages, including assessment of response to tailor adjuvant therapy and decreasing the morbidity of surgery in the breast and axilla. However, these outcomes are less likely in ER+/HER2− patients, where response rates are lower and adjuvant therapy decisions are not made based on response. Some centers have utilized neoadjuvant endocrine therapy for patients with ER+/HER2− breast cancer, though the optimal strategy remains unclear. We found in this single-institution study that 41.8% of patients achieved downstaging in the breast and 23.8% achieved downstaging in the axilla, though only 14.3% of clinically node positive patients achieved nodal pCR. At 10-year follow-up, all-cause overall survival was 62%, while locoregional recurrence rate was 1% and distant recurrence rate was 14%, suggesting that mortality in this cohort is often due to non-breast cancer causes.

Historically, NET was associated with lower response rates compared to NCT in terms of both in-breast and nodal pCR.[12,13] However, more recent randomized studies have demonstrated similar outcomes between NET and NCT.[14] In our cohort of mixed NET regimens, nodal pCR of 14% was similar to the nodal pCR range of 4.8% to 14.5% found in previous studies.[15,16] In addition, approximately one in four patients who presented with clinically positive nodes had axillary downstaging, but only 1 in 7 had nodal pCR. However, for patients who fail to have a complete nodal response, even if downstaged, the American Society of Breast Surgeons (ASBRS) guidelines continue to recommend ALND, although it should be noted that NCCN guidelines do not specifically state how these patients should be managed.[17,18] Therefore, according to ASBRS guidelines, the receipt of neoadjuvant systemic therapy obligates ALND as standard treatment for residual nodal disease, which may have been avoidable with an upfront surgery approach.[19]

Currently, patients with nodal clearance can de-escalate axillary surgery, which ultimately leads to fewer complications such as lymphedema and improved quality of life. One goal of this study was to inform which patients may be more likely to achieve axillary clearance with NET. However, in our cohort, only 6 (14.3%) had nodal pCR. While we identified

age as the only characteristic associated with pN0 for the overall cohort, we were not able to identify factors that were associated with nodal pCR after NET in the subgroup of patients with cN+ given small cohort size. This may be because these clinical factors are not associated with response, or a consequence of the low nodal response rate and lack of statistical power. Further study is needed to inform features that could guide patient selection for NET to maximize the probability of nodal clearance.

Prior work has demonstrated no difference in overall survival between those receiving NET and those receiving surgery upfront.[20] For patients with cN0 disease receiving NET and found to have nodal disease at time of surgery, overall survival was similar between those receiving SLNB and ALND.[21] Additionally, NET patients with minimal residual nodal disease were less likely to undergo ALND.[22] We also found excellent disease-free survival and recurrence rates in our cohort, with 9.8% of patients undergoing completion ALND. These findings continue to support the idea that ALND for minimal residual nodal disease may not drive outcomes. Indeed, ongoing trials are assessing whether de-escalation of axillary surgery is safe for this patient population. For example, the TAXIS trial aims to investigate the safety of ALND omission in selected patients whose nodal burden can be downstaged and managed with radiotherapy.[23]

Recurrence events were rare, and in our cohort the risk of death from other causes was higher than recurrence. Importantly, our cohort was enriched for older women with a median age of 70. These findings suggest that strategies prioritizing locoregional treatments may have limited opportunities to improve outcomes, given the competing risks for survival. With low pCR and nodal clearance rates after both NCT and NET, in addition to stratification of responders and non-responders, more efficacious tumor clearing systemic therapies and improved understanding of recurrence after residual disease are necessary. In addition, one in three patients did receive adjuvant chemotherapy, which demonstrates that some oncologic risk was identified in our cohort, and the administration of adjuvant chemotherapy may have improved recurrence rate. Taken together, our findings must be interpreted in light of the demographic and clinical characteristics of our cohort, and may not address outcomes after NET in younger patients or patients with more advanced disease.

In the context of the relatively good disease-free survival of HR+ patients undergoing NET, the significantly fewer toxicities of NET, and the relative unresponsiveness of HR+ BC to NCT, identifying patients who may respond better to NET is critical to optimize patient selection. Recent advances in genomic assays offer a promising approach in providing risk stratification for ER+/HER2− breast cancer patients. Three commercially available assays, Prosigna, Oncotype Dx, and MammaPrint, can be used to estimate distant-recurrence free survival.[24,25,26] Studies are increasingly using these assays to define populations that do and do not benefit from chemotherapy. While this approach has not been widely applied prospectively to preoperative systemic therapy decisions, a recent trial found that patients with low- and intermediate-risk Oncotype Dx categories compared to those in the high-risk category were more likely to respond to NET.[27] This finding has been confirmed in a recent systematic review.[28] These initial results highlight the potential utility of genomic assays in guiding NET, but this remains an area requiring further research. Eventually,

biomarker-driven targeted therapies tailored to each patient's unique profile may be possible to improve disease clearance while de-escalating therapy and maintaining quality of life.[29]

This single-institution study provides information regarding long-term outcomes of a cohort receiving NET with little missing data. However, our study has several limitations. The relatively small size of the cohort and the relative rarity of nodal pCR limit the ability to compare between patients with nodal pCR and residual disease. In addition, this cohort of patients were most likely selected for NET due to patient-specific factors such as older age, comorbidities, or more indolent disease, and may not represent all patients with HR+/HER2− BC. Furthermore, details regarding comorbidities and frailty were not available as part of this analysis. Therefore, the excellent disease-free survival seen here may have limited generalizability to broader HR+ BC patient population, and conclusions regarding nodal clearance should be interpreted with these limitations. Furthermore, given the relatively small number of patients who achieved nodal pCR, estimates of the association between patient characteristics and nodal pCR are imprecise. Nevertheless, this study provides important information regarding nodal response to and long-term outcomes in patients receiving NET.

Conclusions

For patients with hormone-receptor positive breast cancer, nodal pathologic complete response following neoadjuvant endocrine therapy was uncommon, but recurrences were low. Future studies are needed to elucidate optimal patient selection for neoadjuvant chemotherapy versus NET to achieve nodal clearance, and to delineate oncologically safe strategies to de-escalate axillary management for residual microscopic disease.

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Synopsis

After neoadjuvant endocrine therapy, 14.3% of patients with node positive hormone receptor-positive breast cancer achieved nodal pathologic complete response. Locoregional and distant recurrence rates at 10 years of follow up were 1% and 14%, respectively, and mortality was low.

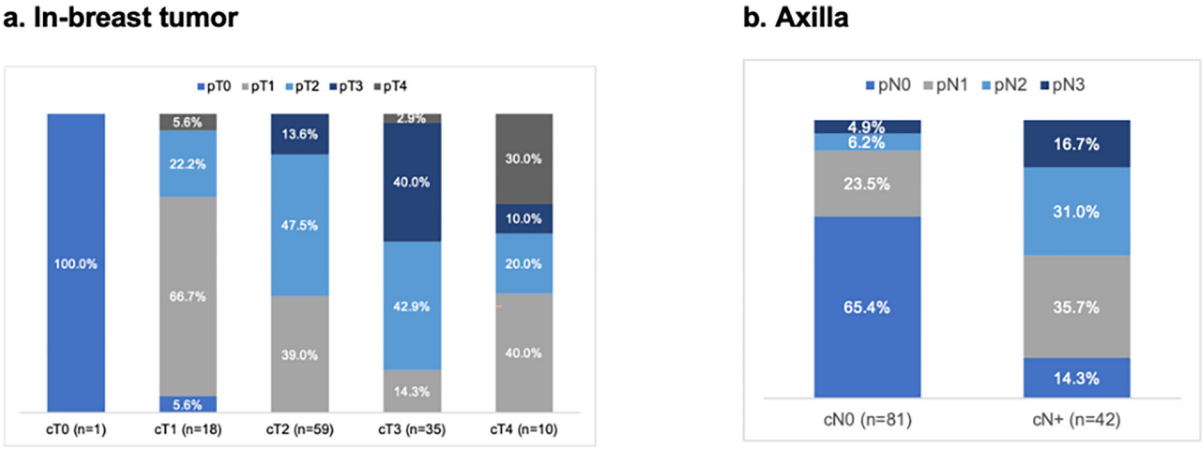

Figure 1.

Response after neoadjuvant endocrine therapy (NET) for patients with non-metastatic ER+ breast cancer, by clinical tumor (cT) category and clinical nodal (cN) category, at the University of North Carolina Lineberger Comprehensive Cancer Center, 1998–2022

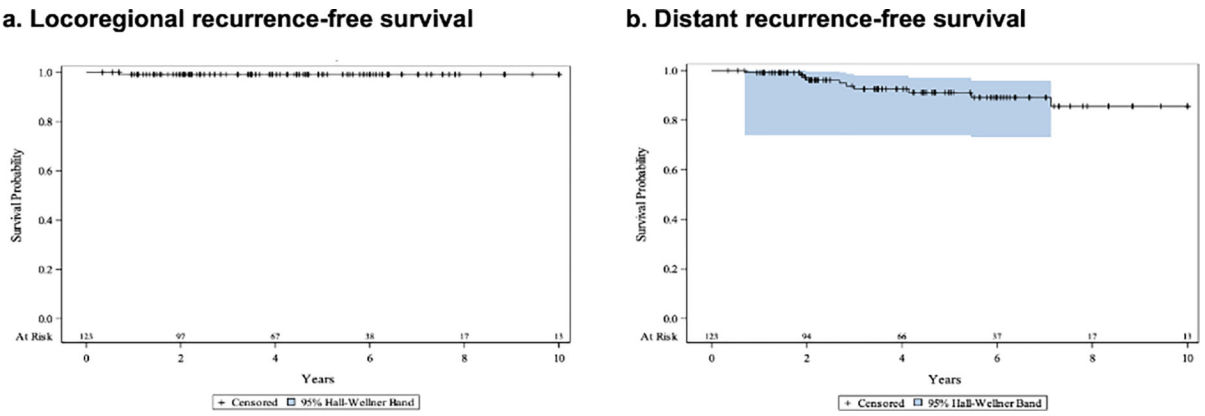

Figure 2.

10-year outcomes for non-metastatic ER+ breast cancer patients following neoadjuvant endocrine therapy (NET), locoregional recurrence-free survival and distant recurrence-free survival, at the University of North Carolina Lineberger Comprehensive Cancer Center, 1998–2022

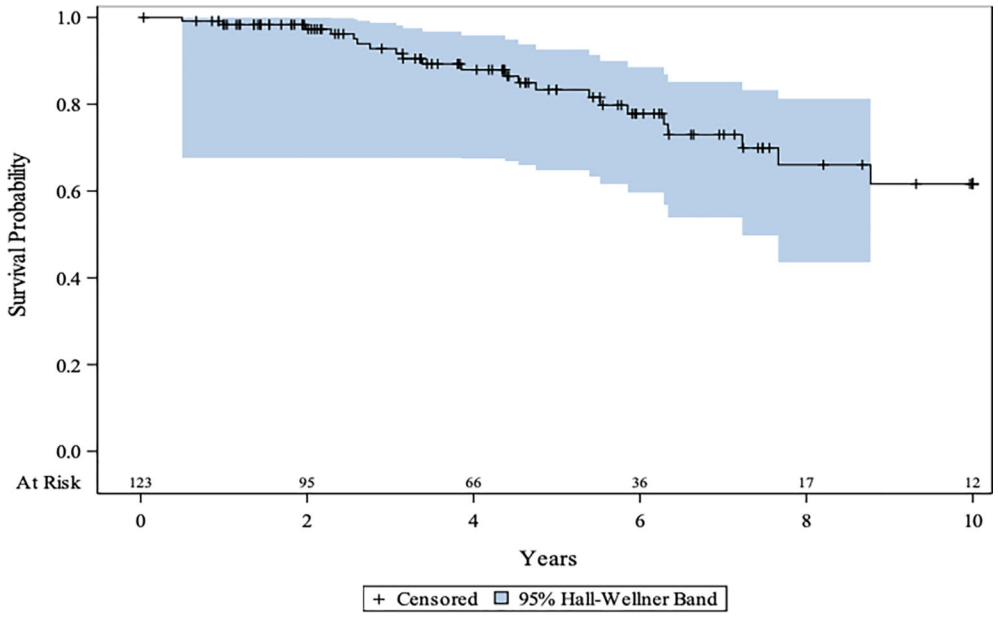

Figure 3.

10-year overall survival of patients with non-metastatic ER+ breast cancer receiving neoadjuvant endocrine therapy (NET), at the University of North Carolina Lineberger Comprehensive Cancer Center, 1998–2022

Table 1.

Baseline characteristics of patients with non-metastatic ER+ breast cancer receiving neoadjuvant endocrine therapy (NET), at the University of North Carolina Lineberger Comprehensive Cancer Center, 1998–2022

	cN0 n=81	cN+ n=42	Total n=123
Age, in years, median (interquartile range)	69.1 (60.1, 74.1)	71.5 (64.1, 78.0)	70.0 (62.1, 76.0)
Race, no (%)			
White	71 (87.7%)	30 (71.4%)	101 (82.1%)
Black	7 (8.6%)	10 (23.8%)	17 (13.8%)
American Indian	0 (0.0%)	1 (2.4%)	1 (0.8%)
Other	3 (3.7%)	1 (2.4%)	4 (3.3%)
Menopausal status, no (%)			
Pre	3 (3.7%)	1 (2.4%)	4 (3.3%)
Post	78 (96.3%)	41 (97.6%)	119 (96.7%)
Focality of tumor, no (%)			
Unifocal	69 (85.2%)	28 (66.7%)	97 (78.9%)
Multifocal	11 (13.6%)	7 (16.7%)	18 (14.6%)
Multicentric	1 (1.2%)	5 (11.9%)	6 (4.9%)
Bilateral	0 (0.0%)	2 (4.8%)	2 (1.6%)
Clinical tumor category, no (%)			
0	0 (0.0%)	1 (2.4%)	1 (0.8%)
1	16 (19.8%)	2 (4.8%)	18 (14.6%)
2	42 (51.9%)	17 (40.5%)	59 (48.0%)
3	17 (21.0%)	18 (42.9%)	35 (28.5%)
4	6 (7.4%)	4 (9.5%)	10 (8.1%)
Clinical nodal category, no (%)			
0	81 (100.0%)	0 (0.0%)	81 (65.9%)
1	0 (0.0%)	31 (73.8%)	31 (25.2%)
2	0 (0.0%)	9 (21.4%)	9 (7.3%)
3	0 (0.0%)	2 (4.8%)	2 (1.6%)
Histology, no (%)			
Ductal	57 (70.4%)	32 (76.2%)	89 (72.4%)
Lobular	19 (23.5%)	6 (14.3%)	25 (20.3%)
Other	5 (6.2%)	4 (9.5%)	9 (7.3%)
Grade, no (%)[a,b]			
Well differentiated	26 (34.2%)	5 (12.2%)	31 (26.5%)
Moderately differentiated	43 (56.6%)	24 (58.5%)	67 (57.3%)
Poorly or undifferentiated	7 (9.2%)	12 (29.3%)	19 (16.2%)

	cN0 n=81	cN+ n=42	Total n=123
Estrogen receptor positivity, no (%)			
50% to <90%	14 (17.3%)	5 (11.9%)	19 (15.4%)
≥ 90%	67 (82.7%)	37 (88.1%)	104 (84.6%)
Progesterone receptor positivity, no (%)[b,c]			
< 50%	23 (34.8%)	13 (36.1%)	35 (34.3%)
50% to <90%	19 (28.8%)	16 (44.4%)	36 (35.3%)
≥ 90%	24 (36.4%)	7 (19.4%)	31 (30.4%)
HER 2 status, no (%)[b,d]			
Positive	0 (0.0%)	0 (0.0%)	0 (0%)
Negative	16 (19.8%)	19 (46.3%)	87 (71.3%)
Equivocal	65 (80.2%)	22 (53.7%)	35 (28.7%)

[a] Missing data from 1 cN0 and 5 cN+ patients

[b] Percentages did not incorporate missing data

[c] Missing data from 6 cN0 and 15 cN+ patients

[d] Missing data from 1 cN0 patient

Table 2.

Treatment for patients with non-metastatic ER+ breast cancer receiving neoadjuvant endocrine therapy (NET), at the University of North Carolina Lineberger Comprehensive Cancer Center, 1998–2022

	cN0 n=81	cN+ n=42	NET[a] n=123
Type of breast surgery, no (%)[b]			
Breast conserving therapy	57 (70.4%)	16 (38.1%)	73 (59.8%)
Mastectomy	24 (29.6%)	25 (59.5%)	49 (40.2%)
Type of axillary surgery, no (%)			
SLNB[c] only	77 (95.1%)	34 (81.0%)	111 (90.2%)
SLNB and ALND[d]	4 (4.9%)	8 (19.0%)	12 (9.8%)
Radiotherapy: yes	2 (50.0%)	8 (100.0%)	10 (83.3%)
Adjuvant chemotherapy, no (%)[e]			
Yes	23 (28.4%)	21 (50.0%)	44 (36.1%)
No	57 (70.4%)	21 (50.0%)	78 (63.9%)
Adjuvant radiotherapy, no (%)[f]			
Yes	55 (67.9%)	37 (88.1%)	92 (75.4%)
Breast conserving therapy	43 (78.2%)	14 (37.8%)[b]	57 (62.0)
Mastectomy	12 (21.8%)	22 (59.5%)[b]	34 (37.0%)
No	25 (30.9%)	5 (11.9%)	30 (24.6%)

[a] NET neoadjuvant endocrine therapy

[b] One cN+ patient had axillary lymph node dissection without breast surgery

[c] SLNB Sentinel lymph node biopsy

[d] ALND axillary lymph node dissection

[e] Missing data from one cN+ patient

[f] Missing data from one cN+ patient

Table 3.

Unadjusted analysis of factors associated with pN0 among patients with nonmetastatic ER+ breast cancer receiving neoadjuvant endocrine therapy (NET), at the University of North Carolina Lineberger Comprehensive Cancer Center, 1998–2022

	OR[a]	(95% CI[b])	P value
Age (years)	1.00	(0.96, 1.03)	0.86
Race (ref = White)			
Black	0.38	(0.13, 1.17)	0.09
Other	0.62	(0.1, 3.8)	0.60
Grade (ref = 1)			
2	0.53	(0.22, 1.26)	0.15
3	0.29	(0.09, 0.98)	0.05
ER+ percentage (ref = 50–90%)			
>90%	1.05	(0.39, 2.79)	0.92
PR+ percentage (ref = 50–90%)			
<50%	0.71	(0.28, 1.82)	0.47
>90%	1.15	(0.44, 3.02)	0.78
Clinical tumor category (ref = cT1)[c]			
cT2	0.82	(0.27, 2.49)	0.72
cT3	0.20	(0.06, 0.68)	0.01
cT4	0.06	(0.01, 0.55)	0.01
Clinical nodal category (ref = cN1)[c]			
cN2	0.12	(0.05, 0.29)	<0.01
cN3	0.04	(0.01, 0.37)	<0.01

[a] Odds ratio

[b] Confidence intervals

[c] Estimates have wide confidence intervals due to small number of patients within each category.

Table 4.

Cox proportional hazard model of mortality among patients with non-metastatic ER+ breast cancer receiving neoadjuvant endocrine therapy (NET), at the University of North Carolina Lineberger Comprehensive Cancer Center, 1998–2022

	HR[a]	(95% CI[b])	P value
Age (years)	1.07	(1.01, 1.13)	0.02
Race (ref = White)			
Black	2.23	(0.79, 6.29)	0.13
Other	0.77	(0.07, 8.12)	0.83
Grade (ref = 1)			
2	0.68	(0.22, 2.08)	0.49
3	1.44	(0.36, 5.78)	0.60
Clinical tumor category (ref = cT1)			
cT2	0.93	(0.19, 4.64)	0.93
cT3	1.08	(0.20, 5.75)	0.93
cT4	1.90	(0.25, 14.56)	0.54
Clinical nodal category (ref = cN0)			
cN+	1.42	(0.48, 4.21)	0.53

[a]Hazard ratio of the overall survival is adjusted for age, race, tumor grade, clinical tumor category, and clinical nodal category. This model is for non-missing observations of all variables included in the model.

[b]Confidence intervals