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EPIDEMIOLOGY

Utilization, duration, and outcomes of neoadjuvant endocrine therapy in the United States

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Abstract

Purpose To evaluate if real-world utilization of neoadjuvant endocrine therapy (NET) is associated with similar rates of response and breast conservation surgery (BCS) compared to neoadjuvant chemotherapy (NAC).

Methods Our population-based assessment used the National Cancer Data Base to identify women diagnosed with stage II–III, hormone receptor (HR)-positive BC who underwent surgery and received endocrine therapy from 2004 to 2014. Women were categorized by receipt of NET, NAC or no neoadjuvant therapy. We used logistic regression to assess differences in outcomes between therapies using inverse propensity score weighting to adjust for potential selection bias.

Results In our sample of 211,986 women, 6584 received NET, 52,310 received NAC, and 153,092 did not receive any neoadjuvant therapy. After adjusting for multiple relevant covariates and cofounders, there was no significant difference between NET and NAC with regard to BCS [odds ratio (OR) 0.91; 95% confidence interval (CI) (0.82–1.01)]; however, women who received NET were significantly less likely to achieve pCR [OR 0.34; 95% CI (0.23–0.51)] or a decrease in T stage [OR 0.39; CI (0.34–0.44)] compared to women treated with NAC. Patients who received NET for ≥ 3 months had higher odds of BCS (OR 1.59; 95% CI 1.46–1.73) and downstaging (OR 1.79; 95% CI 1.63–1.97) compared to patients who did not receive neoadjuvant therapy.

Conclusions Women who received NET had similar rates of BCS compared to women who received NAC. Those who received NET for longer treatment durations had increased odds of BCS and downstaging compared to women who did not receive neoadjuvant therapy.

Keywords Neoadjuvant endocrine therapy · Neoadjuvant chemotherapy · Breast conservation therapy · Hormone positive breast cancer

Background

Neoadjuvant therapy was first evaluated as a treatment strategy starting in the late 1980s [1]. Initially, studies focused on neoadjuvant chemotherapy (NAC) for the treatment of inoperable breast cancer to reduce tumor burden and to allow for surgical resection [2]. Subsequent trials demonstrated that patients who underwent pre-operative chemotherapy were significantly more likely to receive breast conservation surgery (BCS) compared to those who received adjuvant chemotherapy [3]. This led to increased use of NAC; however, additional neoadjuvant studies demonstrated decreased response rates to chemotherapy among hormone receptor (HR; estrogen and/or progesterone receptor) positive tumors compared to HR-negative tumors [3–7]. The results of these trials led to increased interest in using neoadjuvant endocrine therapy (NET) in HR-positive patients.

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Data for NET in patients with HR positive breast cancer has demonstrated overall response rates ranging from 25 to 36% for tamoxifen and 35–72% for aromatase inhibitors (AI). [4, 7–12] In clinical trials, rates of BCS after NET range from 25 to 56% with higher rates of BCS in patients treated with AIs compared to those treated with tamoxifen [4, 5, 7–9, 11, 13, 14]. Less is known about clinical response and BCS rates among premenopausal women, as far fewer studies have evaluated NET in this population [8, 14]. Small clinical trials have demonstrated that for select patients, NET is associated with similar rates of overall response and BCS compared to neoadjuvant chemotherapy (NAC) [10, 11, 15].

Also demonstrated in these small studies were differences in expected side effect profiles between NET and NAC. As expected, NAC had higher rates of cytopenias, febrile neutropenia, alopecia, GI toxicity, and cardiotoxicity that were statistically significant, and NET had higher rates of hot flashes and arthralgias [8, 11]. For patients who receive NAC regimens containing either alkylating agents or topoisomerase II inhibitors, there is a small but significant risk of myelodysplasia and development of a secondary malignancy, but this risk was not demonstrated in these small studies [8, 11].

Less is known about the optimal length of NET. Clinical trials comparing NET to NAC as well as those comparing neoadjuvant AI to neoadjuvant tamoxifen have used varying lengths of treatment, ranging from 3 to 6 months [4, 7, 8, 11, 13, 14]. For some patients, treatment beyond 4 months led to increased rates of tumor regression and increased proportions of patients eligible for BCS [16–18]. In a phase IV trial, 8 months of NET was sufficient for most patients to achieve adequate tumor regression for BCS; however, this and similar trials evaluating extended NET therapy lengths have been limited by small sample sizes and slow accrual [16–18].

A recent report using the National Cancer Data Base (NCDB) provided a snapshot of the use of NET among postmenopausal women with stage II–III HR positive tumors [19]. The authors found a small but significant increase in the use of NET after the publication of the Z1031 study in 2011, in which fifty-one percent of women undergoing NET with an AI who were initially candidates only for mastectomy underwent BCS [5]. This recent analysis also confirmed higher rates of BCS in women undergoing NET compared to no neoadjuvant therapy; however, women who received NAC were excluded.

The present study is the first to utilize a comprehensive national database such as the NCDB to compare clinical outcomes of NET and NAC and to evaluate the associations between length of NET and receipt of BCS. Our descriptive analysis of NET usage is the first to evaluate the full decade from 2004 to 2014. It highlights the potential benefits of NET therapy as well as the ongoing need to better identify the population of women with HR-positive breast cancer most likely to benefit from this therapy.

Methods

Data source

The NCDB is a joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons. The American College of Surgeons has executed a Business Associate Agreement that includes a data use agreement with each of its Commission on Cancer accredited hospitals. The NCDB, established in 1989, is a nationwide, facility-based, comprehensive clinical surveillance resource oncology data set that currently captures 70% of all newly diagnosed malignancies in the US annually. We identified women diagnosed with stage II–III, HR-positive breast cancer during 2004–2014 who underwent surgery and who received endocrine therapy. Stages were based on AJCC staging 6th edition for women diagnosed prior to 2010 and AJCC staging 7th edition for women diagnosed after 2010. We excluded women who met the following criteria: had any prior cancer diagnosis; had non-invasive disease; did not receive definitive surgery; were documented to have HR-negative disease; had clinical evidence of distant metastases at the time of initial staging; had unknown sequence of surgery, hormone therapy, and chemotherapy (if given). We further excluded women who started hormone therapy > 2 years before surgery to exclude women who had extended delays to surgery. Women who received both neoadjuvant hormone therapy and neoadjuvant chemotherapy were excluded. We also excluded women who started systemic hormone therapy > 1 year after surgery to exclude patients who were initially diagnosed as localized disease but received endocrine therapy for metastatic disease. Clinical stage at diagnosis was used when available; however, when clinical staging information was missing, pathologic stage (determined at the time of surgery) was used to determine stage.

Construction of variables

We first categorized women according to the type of neoadjuvant therapy received (neoadjuvant chemotherapy (NAC), neoadjuvant endocrine (NET), or none), and type of adjuvant therapy received (adjuvant chemotherapy + adjuvant endocrine therapy, adjuvant endocrine therapy alone). Sequence of therapy was determined by comparing the number of days from diagnosis to start of endocrine therapy (for NET) or chemotherapy (for NAC) to the number of days from diagnosis to receipt of definitive surgery. If the number of days from diagnosis to definitive surgery was longer than the number of days from diagnosis to the start of hormone therapy or chemotherapy, the patient was categorized as having received NET or NAC, respectively. Women whose time to chemotherapy and time to hormone therapy were both shorter than time to surgery were excluded. Women were classified as having received adjuvant therapy if the time to definitive surgery was shorter than the time to hormone therapy or chemotherapy. Among those women who received NET, we classified patients by duration of NET, determined by the length of time between hormone therapy start and definitive surgery.

Outcomes assessed included change in stage, receipt of breast-conserving surgery (BCS), and pathologic complete response (pCR). Change in stage was determined by comparing the clinical stage to the pathologic stage among patients with non-missing clinical and pathologic stage. Downstaging was defined as pathologic stage lower than clinical stage and upstaging as pathologic stage higher than clinical stage. Receipt of BCS was based on the surgical procedure performed to the primary site, as recorded in the NCDB dataset. Achievement of a pCR was determined by the NCDB site-specific factor (SSF-21) variable.

Sociodemographic characteristics included in our analysis were age at diagnosis, race, ethnicity, median household income at the zip code level, type of insurance, population size of the patient's area of residence (e.g. metropolitan, urban, and rural), and number of comorbid conditions. Clinical characteristics included overall stage, tumor (T) and nodal (N) stage, histologic grade, and year of diagnosis. HER2 information was not included in our initial analysis due to a large amount of missing data (49.9% of the sample did not have HER2 data). A separate sensitivity analysis accounting for HER2 status among those with non-missing data was performed. Facility characteristics included facility type (academic center, comprehensive community cancer center, community practice) and location by US geographic region (Table 1).

Statistical analyses

We used χ^2 tests to determine whether receipt of NET or NAC was associated with each of the covariates among the entire sample. First, we examined the impact of NET duration (categorized into five groups) on likelihood of (1) receiving BCS versus mastectomy and (2) downstaging, using logistic regression models adjusted for sociodemographic and clinical characteristics. In this analysis, we compared patients who received NET to patients who did not receive neoadjuvant therapy. We created additional logistic regression models to assess the association between neoadjuvant treatment (NET or NAC) and our outcomes (change in stage, BCS, and pCR), with inverse probability of treatment weighting (IPTW) using the propensity score to balance covariates between the two different treatment groups and adjust for potential selection bias. To evaluate for potential confounding of HER2 status, we performed a sensitivity analysis including patients with known HER2 negative disease to assess the association between neoadjuvant treatment (NET or NAC) and our outcomes (change in stage, BCS, and pCR). The propensity scores were estimated using potential confounders identified in bivariate analyses. We assessed balance diagnostics in the sample weighted by inverse probability of treatment using absolute standardized differences [20], with differences less than 10% suggesting balance in baseline covariates [21]. Model discrimination was measured by evaluating the c-statistic or area under the Receiver Operating Curve (ROC) [22]. Standardized differences after weighting were all less than 10% and the c-statistic was 0.86 for our propensity score model.

All analyses were performed using SAS version 9.4. The Yale Human Investigations Committee determined that this study did not constitute human subjects research.

Results

We identified 211,986 women with stage II–III HR-positive breast cancer who underwent surgery and received endocrine therapy; of these, 6584 (3.1%) received NET and 52,310 (24.7%) received NAC. A higher percentage of women older than 60 received NET compared to women under 60 (5.1 vs. 1.5%, $p < 0.001$). Additionally, a higher percentage of women with stage III disease received NET compared to stage II disease (4.8% vs. 2.7%, $p < 0.001$). The percentage of women receiving NET increased steadily as T stage increased from T1 to T4 (1.6% to 8.1%, $p < 0.001$). Notably, although the percentage of women receiving NET remained low overall, the percentage of women receiving NET increased steadily over time, from 2.3% in 2004 to 3.5% in 2014, with greatest increase from 2010 to 2011 (Fig. 1). Receipt of NET also differed by treatment setting, with a greater percentage of women receiving NET at academic centers compared to community cancer centers (4.1% vs. 2.7%, $p < 0.001$).

The duration of NET was variable, with the greatest percentage of patients (41.0%) receiving between 3 and 6 months of therapy; however, treatment durations ranged from less than 3 months to 24 months. Compared to patients who received neither NET nor NAC neoadjuvant therapy, patients who received NET had increased rates of both BCS and smaller tumor size at time of surgery. Additionally, there was a dose response relationship between duration of endocrine therapy and odds of BCS, with long duration of therapy being associated with higher odds of BCS: OR 0.69 (95% CI 0.62–0.77) for 1–3 months duration; OR 1.59 (95% CI 1.46–1.73) for 3–6 months of therapy; OR 1.85 (CI 95% 1.67–2.05) for 6–12 months;

Table 1 Distribution of sample and receipt of neo-adjuvant endocrine therapy (NET) and neoadjuvant chemotherapy (NAC)

	N	%	% received NET	*p* value* (NET vs. no neo)	% received NAC	*p* value* (NAC vs. no neo)	*p* value* (NET vs. NAC)	% received no neoadjuvant therapy
Overall	211,986		3.1		24.7			72.2
Age at diagnosis				< 0.001		< 0.001	< 0.001	
< 60	118,167	55.7	1.5		33.5			65.0
≥ 60	93,819	44.3	5.1		13.6			81.3
Race				< 0.001		< 0.001	< 0.001	
Caucasian	176,045	83.1	3.1		23.5			73.4
African-American	24,553	11.6	3.3		31.7			65.0
Other	11,388	5.4	2.8		28.5			68.7
Ethnicity				0.167		< 0.001	< 0.001	
Non-Hispanic	188,965	89.1	3.1		24.3			72.6
Hispanic	12,112	5.7	3.0		33.1			63.9
Unknown	10,909	5.2	3.0		22.6			74.4
Median household income				0.013		< 0.001	< 0.001	
< $30 K (bottom quartile)	23,527	11.1	3.4		24.5			72.1
$30 K–$34,999	33,487	15.8	3.3		23.2			73.5
$35 K–$45,999	56,081	26.5	3.1		24.1			72.8
$46 K+ (top quartile)	91,771	43.3	3.0		25.5			71.5
Unknown	7120	3.4	2.7		25.8			71.5
Insurance				< 0.001		< 0.001	< 0.001	
Private	5963	2.8	3.3		38.2			58.5
Uninsured	120,172	56.7	1.8		29.4			68.8
Medicaid	17,453	8.2	2.8		35.2			62.0
Medicare	63,369	29.9	5.7		11.5			82.8
Military	2135	1.0	2.6		28.3			69.1
Unknown	2894	1.4	4.1		24.6			71.3
Community type (population)				< 0.001		< 0.001	0.114	
Metro	173,088	81.7	3.2		25.3			71.5
Urban	29,123	13.7	2.7		21.2			76.1
Rural	3735	1.8	3.0		20.5			76.5
Unknown	6040	2.9	2.9		27.5			69.6
Comorbid conditions				< 0.001		< 0.001	< 0.001	
0	178,591	84.3	2.9		26.1			71.0
1	27,369	12.9	3.9		17.8			78.3
≥ 2	6026	2.8	5.5		13.1			81.4
Stage				< 0.001		< 0.001	< 0.001	
II	171,532	80.9	2.7		18.1			79.2
III	40,454	19.1	4.8		52.3			42.9
Clinical T stage				< 0.001		< 0.001	< 0.001	
T0	546	0.3	3.1		35.0			61.9
T1	26,132	12.3	1.6		16.8			81.6
T2	143,757	67.8	2.7		18.2			79.1
T3	26,048	12.3	4.7		49.2			46.1
T4	12,951	6.1	8.1		64.8			27.1
Unknown	2552	1.2	2.2		16.4			81.4
Clinical N stage				< 0.001		< 0.001	< 0.001	
N0	117,030	55.2	3.2		13.9			82.9
N1	69,402	32.7	3		38.4			58.6
N2	13,061	6.2	3.3		41.5			55.2

OR 2.37 (95% CI 1.86–3.02) for 12–24 months of therapy. Similarly, downstaging at the time of surgery was more common in patients who received longer durations of NET (Fig. 2).

Of the women who received neoadjuvant therapy ($n = 52{,}310$), 88.8% received NAC. Women who received NET were older than those who received NAC. While 27% of patients who received NET were younger than 60, 75% of

Table 1 (continued)

	N	%	% received NET	*p* value* (NET vs. no neo)	% received NAC	*p* value* (NAC vs. no neo)	*p* value* (NET vs. NAC)	% received no neoadjuvant therapy
N3	5500	2.6	3.2		47.4			49.4
Unknown	6993	3.3	2.7		18.7			78.6
Grade				< 0.001		< 0.001	< 0.001	
1	28,221	13.3	5.0		13.4			81.6
2	98,858	46.6	3.3		21.5			75.2
3	72,211	34.1	1.9		31.2			66.9
Unknown	12,696	6.0	4.1		37.4			58.5

*p value is for χ^2 test of the association between each covariate and receipt of neo-adjuvant therapy

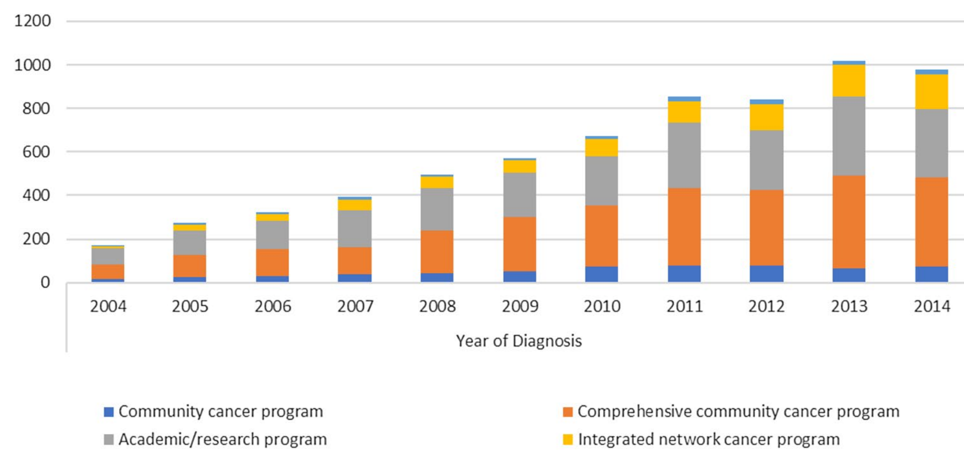

Fig. 1 Neoadjuvant therapy (NET) usage by facility type from 2004 to 2014

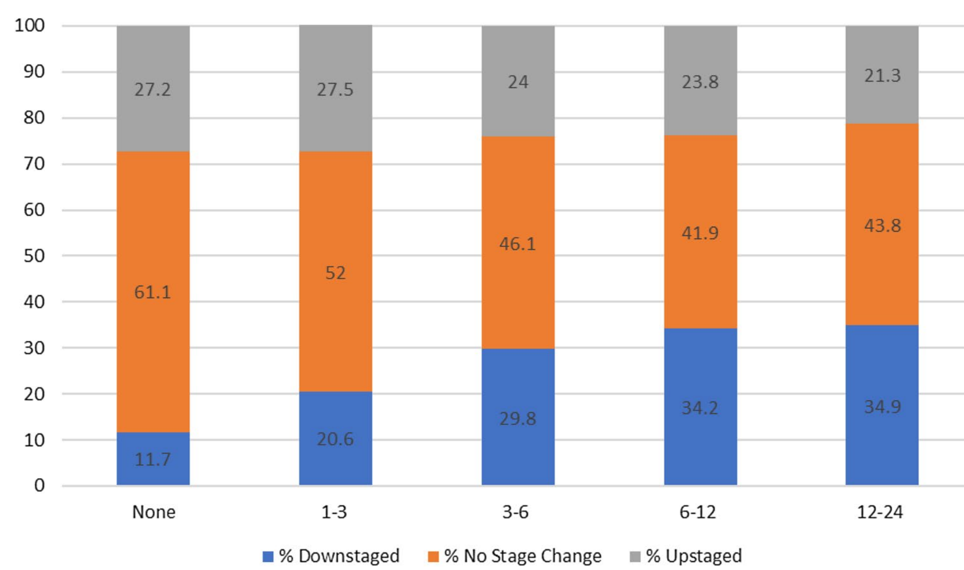

Fig. 2 Effect of neoadjuvant endocrine therapy (NET) duration on change of stage

women who received NAC were younger than 60. Women who received NET had more comorbidities (1 or more) compared to women who received NAC (21% vs 11%). Additionally, tumor grade was lower for women receiving NET than NAC: grade 1 tumor (23% vs 8%); grade 2 tumor (54% vs 45%); grade 3 tumor (23% vs 47%).

Forty-three percent ($n=2820$) of patients who received NET underwent BCS; in comparison, 30% ($n=15{,}804$) of patients who received NAC underwent BCS. On multivariate regression modeling, there was no significant difference with regards to BCS between women who underwent NET versus NAC [OR 0.91; 95% CI (0.82–1.01)].

Fewer patients who received NET achieved pCR or were downstaged compared to those receiving NAC (Fig. 3). Twenty-eight percent ($n=1632$) of patients who received NET were downstaged at the time of surgery compared to 46% ($n=18{,}826$) of patients who received NAC. The finding persisted after adjusting for potential confounders [odds ratio (OR) of downstaging for patients receiving NET compared to NAC 0.47, (95% confidence interval (CI) 0.41–0.54)]. When excluding patients with either HER2 positive or unknown HER2 status, OR of downstaging remained lower for NET patients: OR 0.61 (95% CI 0.51–0.74); however, the rate decreased to 45.1% ($n=8373$) for patients who received NAC, while the percentage increased to 30.1% ($n=1051$) for those who received NET. There was no difference in likelihood of upstaging between NET and NAC [OR 1.02 (95% CI 0.88–1.17)]. After excluding patients for whom pCR status was missing, 4.8% ($n=117$) of patients achieved pCR with NET compared to 22.8% ($n=5457$) of patients who received NAC. The weighted OR for pCR was 0.34 (95% CI 0.23–0.51) for patients who received NET compared to NAC. Sensitivity analysis including only patients with known HER2-negative disease resulted in similar OR for pCR of 0.38 (95% CI 0.23–0.62); however, a decrease in pCR rate was noted with 4.1% ($n=88$) of patients receiving NET and 15.6% ($n=2332$) of patients who received NAC achieving a pCR.

Discussion

Although NET is uncommonly utilized in the United States, this study supports its use and potential benefit in a subset of HR positive patients. We found that the likelihood of BCS was equivalent for NET and NAC and this clinically important endpoint was similar in the two groups even though patients who underwent NAC had higher rates of downstaging and pCR compared to those who underwent NET. Importantly, a positive correlation between length of NET and both BCS and downstaging was identified.

Although previously published prospective trials found similar rates of clinical response (complete response and partial response) with NET and NAC, our research demonstrates that patients who receive NET are significantly less likely to achieve either pCR or downstaging. There are several potential explanations for the difference between these trials and our results. First, the trials used a composite endpoint of clinical PR and CR. The rates of CR in these trials were low, ranging from 3 to 6% for NET and 6 to 13% for NAC [8, 11]. Furthermore, response rates in these trials were determined by clinical palpation or radiologic findings, as opposed to pathologic stage. Low rates of pCR in our study are expected given low pCR rates seen for hormone positive

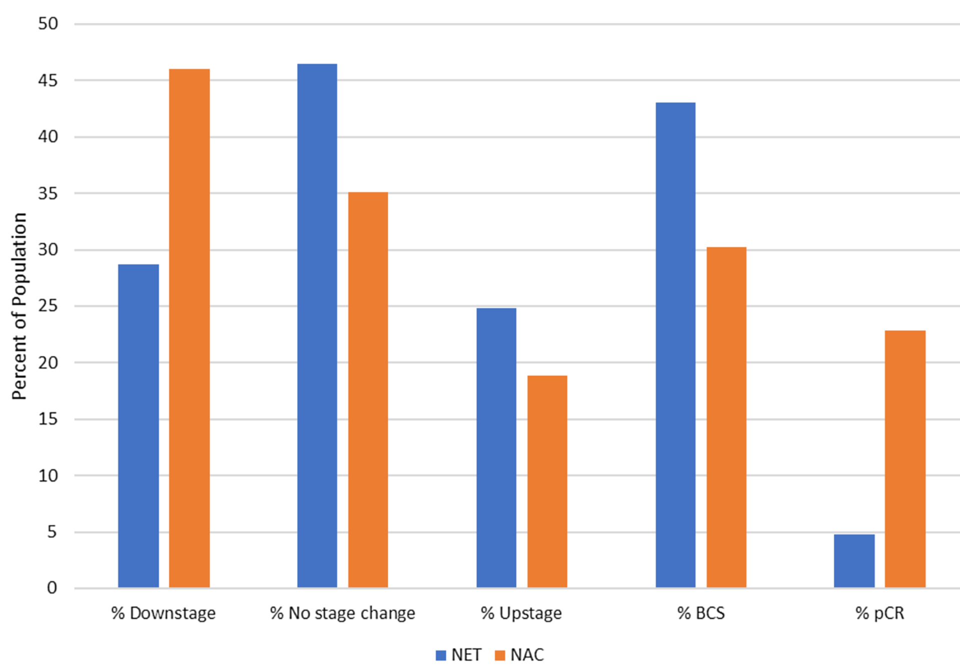

Fig. 3 Unadjusted frequency of stage change, BCS, and pCR for patients who received neoadjuvant chemotherapy (NAC) and neoadjuvant endocrine therapy (NET). *BCS* breast-conserving surgery, *pCR* pathologic complete response

tumors in previous neoadjuvant and adjuvant chemotherapy trials [23]. The association between the extent of pathologic response to NAC and survival is weakest in HR-positive cancers, particularly in grade 1 cancers, demonstrated by the fact that many HR-positive patients with extensive residual disease have excellent long-term survival, and likely reflects the better prognosis and survival benefit of adjuvant endocrine therapy [23–25].

Prospective data evaluating NET's effects on downstaging, pCR, and rates of BCS are limited. Only three small prospective trials have compared the efficacy of NET and NAC [8, 11, 15]. Additional trials have evaluated the efficacy of aromatase inhibitors compared to tamoxifen or to each other; however, all these trials are small with population sizes ranging from 95 to 451 patients [4, 5, 7, 13, 14]. The ALTERNATE trial, which is still undergoing accrual, will evaluate neoadjuvant anastrozole, fulvestrant, or the combination in postmenopausal women with HR positive breast cancer; this study utilizes both change in Ki-67 expression and the PEPI score, developed and validated in these earlier studies, to evaluate response to NET and select patients for longer treatment [5, 8, 11, 26]. This phase III trial is the largest prospective trial to evaluate NET and the first to incorporate a biomarker into evaluation of treatment [27].

With regards to the trials discussed above, the length of NET duration was variable and ranged from 3 to 6 months [7, 11, 15]. Several trials have attempted to determine optimal length of NET duration; however, the length of NET duration varied from 4 to over 24 months and these studies were limited due to small size and difficulty with accrual [16–18, 28]. Our analysis is the largest and the first to use real-world data from a comprehensive, national cancer database to evaluate for associations between length of NET and clinical outcomes. We have found that duration of NET administration is highly variable in national practice. Although 3–6 months of NET is the most common treatment duration, a significant percentage of patients (> 26%) received NET for fewer than 3 months. We found an association between longer duration of treatment and higher likelihood of both downstaging and breast conservation among women who received NET, raising two plausible hypotheses to explain this association. The first is that some women who received NET did not achieve maximal benefit from the therapy due to inadequate duration of treatment. The second and more probable hypothesis is that women who were responding to NET therapy were more likely to continue, and thus had both longer durations of therapy as well as improved likelihoods of both BCS and downstaging.

Use of the NCDB afforded us the opportunity to evaluate practice patterns among large numbers of patients across multiple treatment settings and geographic regions, which was not possible in single institution retrospective analyses. Our analysis revealed that women who receive NET were more likely to be older than 60, have stage III disease, and have lower grade tumors. Additionally, a higher percentage of women received NET at academic centers (4.1%) compared to community cancer centers (2.1%). Lastly, NET usage has increased from 2004 to 2014 likely reflecting the publication of phase I and II data from multiple small trials comparing either NET to NAC or comparing different NET regimens. [15]

There are several limitations to the use of this data, however. The NCDB has substantial missing data regarding hormone status as well as clinical endpoints, most notably pCR and HER2 status. [25] Furthermore, type of systemic treatment received as well as adherence to treatment is unavailable. The data is based on coding done by certified tumor registrars, extracted from routine medical records at participating institutions with no confirmation of the accuracy of the data. Additionally, the data do not account for patients who were deemed eligible for BCS but elected to undergo mastectomy instead. Finally, the NCDB lags several years due to complexity of data entry.

Missing HER2 data is a noteworthy limitation of the current study, as patients with HER2 positive disease have higher clinical and pathologic response rates to NAC compared to HER2-negative patients. [23] Higher rates of both pCR and downstaging among NAC patients in our analysis compared to previously published clinical trials suggests that HER2 positive patients were included in our sample. Notably, when patients with known HER2-positive cancers and those with HER2 unknown status were excluded from our sample the rate of pCR in the NAC group did decrease to 15.6%, which is more consistent with the literature, particularly for grade 3, HR-positive cancers. [23] The fact that odds of pCR, BCS and downstaging were similar when we ran a sensitivity analysis excluding patients with known HER2-positive disease confirms our original findings.

Our study is the largest population-based study to examine neoadjuvant endocrine therapy among women diagnosed with stage II and III HR-positive breast cancer between 2004 and 2014, irrespective of menopausal status, with evaluation of associations between type of neoadjuvant therapy received (NAC and NET) and clinical outcomes (pCR, BCS and stage change). Our results demonstrate that for a select population of women with HR-positive breast cancer, NET administration led to similar odds of BCS compared to NAC. Although NAC leads to higher rates of pCR and downstaging, the more favorable side effect profile of NET makes NET a reasonable alternative for patients seeking to avoid chemotherapy to become eligible for mastectomy. Based on the available data, it is difficult to identify the patient population who would derive the greatest benefit from NET. However, it is reasonable to assume that postmenopausal women with favorable profiles would be the most appropriate candidates. Additionally, longer durations of therapy may make NET a more successful treatment regimen for a select population of HR-positive breast cancer patients. Ultimately, more research is needed to determine the population most likely to benefit from NET administration.

Compliance with ethical standards

Disclosure Pamela R. Soulos: 21st Century Oncology

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