




Effectiveness of a Short Duration of Neoadjuvant Endocrine Therapy in Patients with HR+ Breast Cancer—An NCDB Analysis (2004–2016)

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ABSTRACT

Background. National medical/surgical organizations have recommended the use of neoadjuvant endocrine therapy (NET) to bridge surgery delay of weeks to months for patients with hormone receptor positive (HR+) breast cancer during the ongoing coronavirus disease 2019 (COVID-19) pandemic. The effects of NET of varying durations on pathologic response are unclear. Using the National Cancer Database (NCDB), we evaluated objective response to short (< 9 weeks), moderate (9–27 weeks), and long (> 27 weeks) duration of NET.

Patients and Methods. The study cohort included female patients diagnosed with nonmetastatic invasive HR+ breast cancer, stratifying by those who received NET versus no NET between 2004 and 2016. Pathologic

response was grouped into four categories (complete, downstaged, stable, upstaged) by comparing clinical and pathologic staging data. Objective response to NET included complete, downstaged, and stable pathologic response. Clinical characteristics were compared using χ^2 and analysis of variance (ANOVA) tests. Multivariable logistic regression was used to determine factors associated with NET use and objective response according to NET duration.

Results. A minority (1.2%) received NET in our cohort. Factors associated with NET use included older age, non-Black patients, more advanced clinical stage, higher comorbidity score, government insurance, and lobular histology. Objective response rate (ORR) was 56.7%, 52.1%, and 49.0% after short, moderate, and long NET duration, respectively.

Conclusion. Short NET duration did not result in an inferior ORR. Future study to evaluate the interaction between surgery delay and NET use on clinical outcome will provide insights into the safety of NET to bridge potential surgery delay in patients with HR+ breast cancer.

Macy M. Goldbach and Laura Burkbauer are co-first authors.

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Hormone receptor positive (HR+) breast cancer, defined as breast cancer that expresses estrogen (ER) and/or progesterone receptors (PR) and lacks HER-2/neu (HER2) expression, is the most common subtype of breast cancer, accounting for over 70% of all breast cancer cases.¹ Although endocrine therapy is widely used in the adjuvant setting, it is infrequently used in the neoadjuvant setting. Neoadjuvant endocrine therapy (NET) is usually

recommended for those who will not tolerate neoadjuvant chemotherapy (NAC) in the USA.² However, there has been a recent resurgence of interest in the use of NET in the setting of the coronavirus disease 2019 (COVID-19) pandemic.^{3–9} National medical and surgical organizations, including the American Society of Breast Surgeons (ASBrS), the Commission on Cancer (CoC), and the Society of Surgical Oncology (SSO), have recommended the use of NET to bridge possible surgery delays during the pandemic to allow for conservation of limited resources such as personal protective equipment and ventilators.^{3–9} In addition, during the pandemic, patients who may otherwise require NAC to downstage their disease are likely to receive NET instead, with the goal of sparing these patients from the immunosuppressive side effects of chemotherapy that may increase the risk of COVID-19 infection in this population.¹⁰

A recent meta-analysis has compared the efficacy of NET and NAC and reported similar pathologic response rates between the two neoadjuvant treatment strategies. Importantly, NET was associated with significantly lower adverse events and toxicity.¹⁰ Historically, the most common NET duration used in clinical trials and in the clinics has been reported to range from 12 to 24 weeks.^{10,11} In the context of the pandemic, the duration of NET is likely to vary, but it is anticipated to be shorter than the reported duration and will depend on both regional COVID-19 disease trends and when treatment facilities have the capacity to resume elective surgery. The impact of a shorter NET duration on disease outcomes such as objective response is, however, unclear. Furthermore, whether the use of NET may ameliorate the potential deleterious consequences of surgery delay is unknown.¹²

As an attempt to understand real-world experience of NET in the setting of its utility during the novel COVID-19 pandemic, we designed this study using data from the National Cancer Database (NCDB) to evaluate the impact of NET use on the objective response rate (ORR) as stratified by three NET durations, defined as short (< 9 weeks), moderate (9–27 weeks), and long (> 27 weeks), in patients with HR+ breast cancer. The primary outcome of this study was to determine the ORR according to short, moderate, or long NET duration, focusing on shorter NET duration, which may have been commonly employed during the COVID-19 pandemic. The secondary outcome of this study was to determine clinical factors associated with objective response to NET.

MATERIALS AND METHODS

Cohort Selection

The study cohort consisted of female patients diagnosed with nonmetastatic, invasive HR+ breast cancer between 2004 and 2016 identified in the National Cancer Database (NCDB). The NCDB is a clinical oncology database that acquires data from more than 1500 Commission on Cancer-accredited facilities with estimated capture of 75% of all new cancer diagnoses.¹³ Institutional review board approval was not required for this study since data from the NCDB are deidentified. We identified 811,802 patients who met inclusion criteria (Fig. 1). Patients with unknown or no surgery ($n = 37,121$), unknown chemotherapy ($n = 18,139$), or unknown endocrine therapy ($n = 16,615$) were excluded.

We defined patients who received preoperative therapy as those who started either chemotherapy or endocrine therapy ≥ 14 days before surgery. Time elapsed between DX_CHEMO_STARTED_DAYS or DX_HORMONE_STARTED_DAYS and DX_SURG_STARTED_DAYS was used to determine whether patients received preoperative therapy or no preoperative therapy. Patients who received both neoadjuvant chemotherapy (NAC) and neoadjuvant endocrine therapy (NET) ($n = 3,427$) or NAC only ($n = 29,735$) were excluded. Our final study cohort consisted of

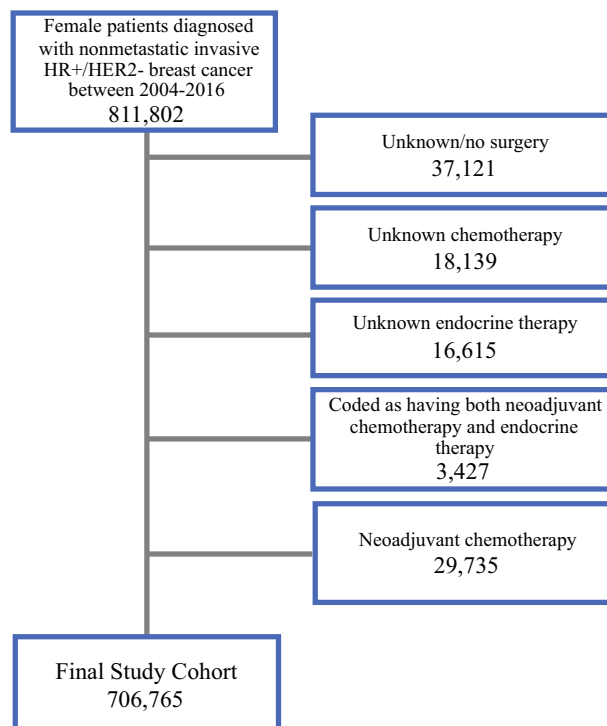


FIG. 1 Consort diagram depicting inclusion and exclusion criteria used to establish study cohort

706,765 patients, of whom 698,439 (98.8%) received no NET (surgery first) versus 8326 (1.2%) received NET. Time elapsed between DX_HORMONE_STARTED_DAYS and DX_SURG_STARTED_DAYS was also used as a proxy to determine the duration of NET. A histogram was generated to determine the frequency of NET durations in our cohort (Fig. 2). We then stratified NET duration into three intervals (short, moderate, and long) based on the first quartile (< 9 weeks), interquartile range (9–27 weeks), and fourth quartile (> 27 weeks).

Definition of Objective Response to NET

Pathologic response to NET was grouped into four categories (complete response, downstaged, stable, and upstaged disease) by comparing clinical and pathologic tumor and nodal staging data (Supplementary Table 1). Treatment response was considered to be complete when pathologic stage was stage 0. Treatment response was considered “downstaged” when pathologic stage was lower than clinical stage. Treatment response was considered stable when pathologic stage remained the same as clinical stage. Treatment response was considered “upstaged” when pathologic stage was higher than clinical stage. Overall pathologic response was the summation of treatment response in both tumor (breast) and nodes (axilla) (Supplementary Table 2). We defined objective response in this study to include those with (1) complete

pathologic response, (2) downstaged disease, and (3) stable disease after NET.

Statistical Analysis

Demographic and clinical characteristics were compared using χ^2 tests for categorical variables and ANOVA tests for continuous variables. Multivariable logistic regression was performed to determine factors associated with NET use and factors associated with objective response to NET. Poisson regression was performed to evaluate trends in the use of NET over time. All hypothesis tests were two-sided, and $p < 0.05$ was considered statistically significant. STATA 16/SE software was used to carry out all statistical analyses (StataCorp LLC, College Station, TX).

RESULTS

Cohort Characteristics

Clinical characteristics of our study cohort ($n = 706,765$) stratified by receipt of NET and no NET (surgery first) are summarized in Table 1. Overall, only a minority ($n = 8326$, or 1.2%) received NET. The two groups differed in all clinical variables included in our analysis. Patients who received NET were noted to be older, had higher Charlson–Deyo (CD) comorbidity scores, had government insurance, were more likely to be treated at academic programs,

FIG. 2 Histogram of NET duration in weeks for our study cohort

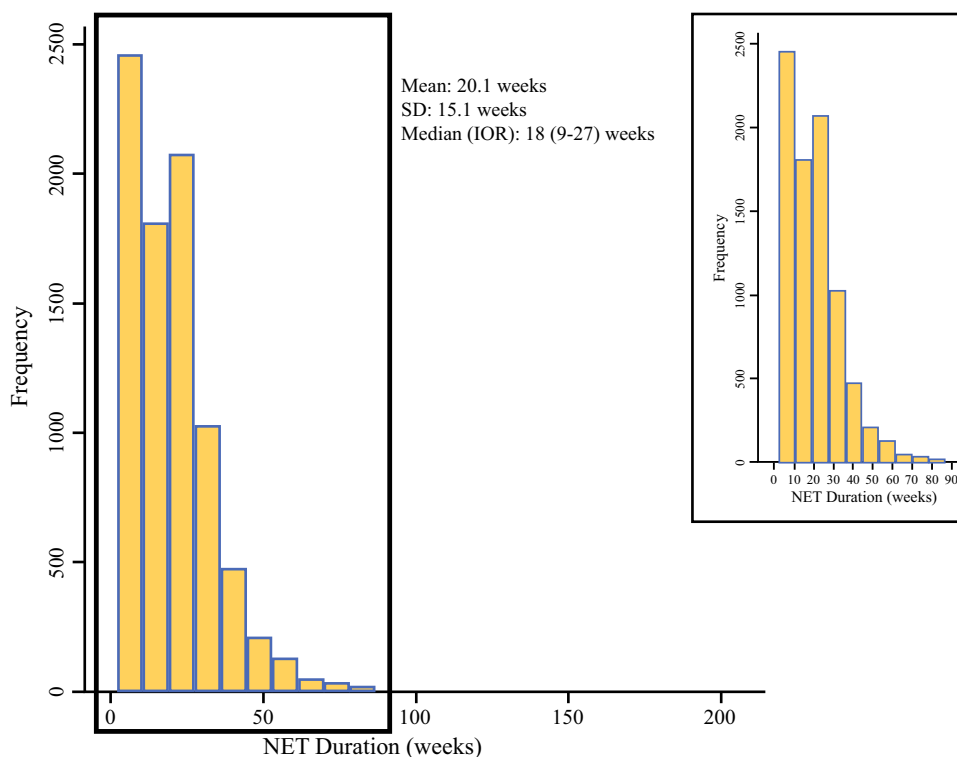


TABLE 1 Demographic and clinical characteristics of females diagnosed with nonmetastatic invasive HR+/HER2- breast cancer stratified by no preoperative therapy (surgery first) versus neoadjuvant endocrine therapy (NET)

	Overall		No NET (Surgery First)		NET		P
	N	%	N	%	N	%	
<i>n</i> = 706,765	706,765	100.0%	698,439	98.8%	8326	1.2%	
Age at Diagnosis (mean ± (SD))	62.8 ± 12.6		62.7 ± 12.6		67.7 ± 12.1		<0.001
Year of Diagnosis							
2010-2013	382,364	54.1%	378,255	54.2%	4109	49.4%	<0.001
2014-2016	324,401	45.9%	320,184	45.8%	4217	50.6%	
Race							
White	607,750	86.0%	600,642	86.0%	7108	85.4%	0.03
Black	62,112	8.8%	61,310	8.8%	802	9.6%	
Asian/PI	23,902	3.4%	23,642	3.4%	260	3.1%	
Other/Unknown	13,001	1.8%	12,845	1.8%	156	1.9%	
Comorbidity Score							
0	581,580	82.3%	575,003	82.3%	6577	79.0%	<0.001
1	98,212	13.9%	96,963	13.9%	1249	15.0%	
2	19,996	2.8%	19,646	2.8%	350	4.2%	
3+	6977	1.0%	6827	1.0%	150	1.8%	
Insurance Status							
Private Insurance	347,107	49.1%	344,238	49.3%	2869	34.5%	<0.001
Government	342,047	48.4%	336,909	48.2%	5138	61.7%	
Other/Unknown	17,611	2.5%	17,292	2.5%	319	3.8%	
Hospital Category							
Community	65,853	9.3%	65,338	9.4%	515	6.2%	<0.001
Comprehensive Community	312,008	44.1%	308,826	44.2%	3182	38.2%	
Academic	208,288	29.5%	205,169	29.4%	3119	37.5%	
Integrated Network Cancer Program	100,302	14.2%	98,881	14.2%	1421	17.1%	
Other/Unknown	20,314	2.9%	20,225	2.9%	89	1.1%	
Clinical Stage							
Overall							
1	447,180	63.3%	444,854	63.7%	2326	27.9%	<0.001
2	160,016	22.6%	155,637	22.3%	4379	52.6%	
3	19,647	2.8%	18,432	2.6%	1215	14.6%	
Unknown	79,922	11.3%	79,516	11.4%	406	4.9%	
Tumor Stage							
1	474,223	67.1%	471,644	67.5%	2579	31.0%	<0.001
2	140,017	19.8%	136,358	19.5%	3659	43.9%	
3	17,587	2.5%	16,476	2.4%	1111	13.3%	
4	5748	0.8%	5036	0.7%	712	8.6%	
Unknown	69,190	9.8%	68,925	9.9%	265	3.2%	
Nodal Stage							
0	603,034	85.3%	596,702	85.4%	6332	76.1%	<0.001
1	51,324	7.3%	49,907	7.1%	1417	17.0%	
2/3	9230	1.3%	8937	1.3%	293	3.5%	
Unknown	43,177	6.1%	42,893	6.1%	284	3.4%	
Histology							
Ductal	551,165	78.0%	545,407	78.1%	5758	69.2%	<0.001
Lobular	87,263	12.3%	85,539	12.2%	1724	20.7%	
Other/Unknown	68,337	9.7%	67,493	9.7%	844	10.1%	

TABLE 1 continued

	Overall		No NET (Surgery First)		NET		P
	N	%	N	%	N	%	
Tumor Grade							
Well Differentiated	214,714	30.4%	212,305	30.4%	2409	28.9%	<0.001
Moderately Differentiated	344,871	48.8%	340,503	48.8%	4368	52.5%	
Poorly/Undifferentiated	113,664	16.1%	112,627	16.1%	1037	12.5%	
Unknown	33,516	4.7%	33,004	4.7%	512	6.1%	
Surgery							
Primary							
Lumpectomy	438,587	62.1%	434,240	62.2%	4347	52.2%	<0.001
Mastectomy	267,642	37.9%	263,669	37.8%	3973	47.7%	
Surgery, NOS	536	0.1%	530	0.1%	6	0.1%	
Axilla (*2012 and later)							
None	33,756	4.8%	32,900	4.7%	856	10.3%	<0.001
SLN	348,296	49.3%	344,917	49.4%	3379	40.6%	
ALND	51,050	7.2%	49,966	7.2%	1084	13.0%	
SLN + ALND	90,773	12.8%	89,643	12.8%	1130	13.6%	
Other/Unknown	182,890	25.9%	181,013	25.9%	1877	22.5%	
Adjuvant Radiation							
Post-Lumpectomy Radiation							
Yes	363,915	83.0%	360,908	83.1%	3007	69.2%	<0.001
None	73,798	16.8%	72,485	16.7%	1313	30.2%	
Unknown	874	0.2%	847	0.2%	27	0.6%	
Post-Mastectomy Radiation							
Yes	66,587	24.9%	65,179	24.7%	1408	35.4%	<0.001
No	200,147	74.8%	197,603	74.9%	2544	64.0%	
Unknown	908	0.3%	887	0.3%	21	0.5%	
Treatment Duration, median(IQR) (weeks) ^a	18 (9-27)		NA		18 (9-27)		NA
Recurrence Score (Pre-TAILORX)							
<18	122,562	59.3%	121,549	59.3%	1013	57.9%	<0.001
18-30	67,536	32.7%	66,901	32.6%	635	36.3%	
>30	16,723	8.1%	16,620	8.1%	103	5.9%	
Follow-up (median (IQR)) (months) ^b	41 (24–61)		41 (24–61)		37 (23–56)		<0.001
Total Deceased ^c	51,157	7.2%	50,011	7.2%	1146	13.8%	<0.001

^aIncludes only those who received NET

^bFollow-up represents the elapsed time between diagnosis and last contact

^cVital status available for (597,151, 84.5%) patients in cohort

NET neoadjuvant endocrine therapy, SD standard deviation, PI Pacific Islander, SLN sentinel lymph node biopsy, ALND axillary lymph node dissection, IQR interquartile range, NOS not otherwise specified, NA not applicable

presented at higher clinical stage, had lobular histology, had higher tumor grade, and more often underwent mastectomy and axilla node dissection procedures. Unexpectedly, patients in the NET group were less likely to have a recurrence score > 30 ($p < 0.001$). Length of follow-up was shorter in the NET group (37 months versus 41 months, $p < 0.001$). Despite shorter median follow-up time, patients in the NET group had a higher unadjusted

death rate than the surgery-first group (13.8% versus 7.2%, $p < 0.001$).

Clinical Characteristics Associated with NET Use

Multivariable logistic regression analysis was performed to identify clinical factors associated with NET use. Results are presented in Table 2. Older age (≥ 50), more

recent diagnosis (2014–2016), CD comorbidity score ≥ 2 , government insurance, treatment at a setting other than community hospital, higher clinical tumor and nodal stage, and lobular histology were significantly associated with NET use. Patients with clinical T4 (locally advanced) tumors were most likely to receive NET [odds ratio (OR) 25.54, $p < 0.001$]. Of note, compared with their white

counterparts, NET was less likely to be used in Black patients (OR 0.91, $p = 0.01$).

Objective Response Associated with NET Duration

To examine the effect of NET duration on treatment response, we first evaluated if the varying NET duration in our cohort followed a bell-shaped curve distribution. As

TABLE 2 Multivariable logistic regression of factors associated with NET use

	OR	(95% CI)			<i>p</i>
<i>Age at diagnosis</i>					
< 50	1.00	–	to	–	–
50+	2.29	2.09	to	2.52	< 0.001
<i>Year of diagnosis</i>					
2010–2013	1.00	–	to	–	–
2014–2016	1.25	1.20	to	1.31	< 0.001
<i>Race</i>					
White	1.00	–	to	–	–
Black	0.91	0.84	to	0.98	0.01
Asian/PI	0.97	0.85	to	1.11	0.65
Other/Unknown	0.96	0.81	to	1.14	0.67
<i>Charlson–Deyo comorbidity score</i>					
0	1.00	–	to	–	–
1	0.96	0.90	to	1.03	0.24
2	1.21	1.08	to	1.36	0.001
3+	1.31	1.10	to	1.55	0.002
<i>Insurance status</i>					
Private insurance	1.00	–	to	–	–
Government	1.58	1.51	to	1.67	< 0.001
Other/unknown	1.91	1.69	to	2.17	< 0.001
<i>Hospital category</i>					
Community	1.00	–	to	–	–
Comprehensive community	1.41	1.28	to	1.56	< 0.001
Academic	2.22	2.01	to	2.45	< 0.001
Integrated network cancer program	2.02	1.82	to	2.25	< 0.001
<i>Clinical tumor stage</i>					
1	1.00	–	to	–	–
2	5.14	4.88	to	5.42	< 0.001
3	12.68	11.71	to	13.73	< 0.001
4	25.54	23.22	to	28.09	< 0.001
<i>Clinical nodal stage</i>					
0	1.00	–	to	–	–
1	1.12	1.05	to	1.19	0.001
2/3	0.87	0.76	to	0.98	0.03
<i>Histology</i>					
Ductal	1.00	–	to	–	–
Lobular	1.32	1.25	to	1.40	< 0.001
Other/unknown	1.01	0.94	to	1.09	0.72

Patients with available information for all variables included in multivariable model ($n = 608,873$)

shown in the histogram depicted in Figure 2, a bimodal distribution was noted. The most common NET duration was ≤ 9 weeks, followed by NET duration ~ 24 weeks. The mean NET duration was 20.1 ± 15.1 weeks. We then stratified NET duration into three intervals: short, moderate, and long or < 9 , $9\text{--}27$, and > 27 weeks, respectively.

The primary outcome of this study was to determine the objective response to NET according to duration of use. Overall, the objective response rate (ORR) was 56.7%, 52.1%, and 49.0%, while the proportion of patients with upstaged disease was 25.9%, 23.4%, and 19.0%, after short, moderate, and long NET duration, respectively (Table 3). Clinical characteristics of the three NET duration groups were compared (Table 3). As expected, patient characteristics differed significantly across the three groups, except for CD comorbidity score ($p = 0.51$), tumor grade ($p = 0.50$), and length of follow-up ($p = 0.22$). Patients who received moderate and long NET duration were more likely to present with higher clinical stage ($p < 0.001$).

A secondary outcome of this study was to determine clinical factors associated with objective response to NET. A multivariable logistic regression analysis was performed, and results are depicted in a forest plot (Fig. 3). Objective response was similar between short and moderate (OR 1.00, $p = 0.90$) or long duration (OR 1.13, $p = 0.17$) of NET use (Fig. 3). Patients who were older (≥ 50 years; OR 1.42, $p < 0.01$), of Asian/Pacific Islander descent (OR 1.44, $p = 0.04$), or with clinical T4 (OR 1.72, $p < 0.01$) or N2/3 disease (OR 3.34, $p < 0.01$) were more likely to have an objective response to NET. Patients with a CD comorbidity score of 2 (but not 3) were less likely to have an objective response to NET (OR 0.64, $p < 0.01$). Unexpectedly, tumors with lobular histology (OR 0.56, $p < 0.01$) and higher tumor grade (poorly/undifferentiated, OR 0.59, $p < 0.01$; moderately differentiated, OR 0.70, $p < 0.01$) were less likely to have an objective response to NET.

To further improve the applicability of our results for the COVID-19 pandemic, we performed a subset analysis of patients with clinical stage I and II disease ($n = 6705$) whose disease stage is probably similar to those recommended to receive NET during the pandemic. Clinical factors associated with NET use and factors associated with objective response to NET use are summarized in Supplementary Table 3 and Supplementary Figure 1. Results were similar to those reported above for the entire cohort. The ORR was 60.5%, 54.9%, and 50.8%, while the proportion of patients with upstaged disease was 28.3%, 25.9%, and 21.4%, after short, moderate, and long NET duration, respectively. Objective response was similar between short and moderate (OR 1.00, $p = 0.95$) or long NET duration (OR 1.12, $p = 0.22$).

Changes in NET Practice Pattern Trend between 2010 and 2016

NET was not commonly used in the USA during the study period. As described earlier, between 2010 and 2016, only 1.2% of patients received NET prior to surgery. However, we noted a small but significant rise in the use of NET from 1% in 2010 to 1.3% in 2016 [incidence rate ratio (IRR) = 1.10, $p < 0.001$] (Supplementary Figure 2). The median NET duration lengthened from 16.0 weeks to 20.2 weeks between 2010 and 2016. We also observed a lengthening of mean NET duration from 19.2 weeks in 2010 to 20.2 weeks in 2016 ($p = 0.01$) (Supplementary Figure 3).

DISCUSSION

Although historically underutilized, NET is now gaining a foothold in the management of early-stage HR+ breast cancers, propelled in part by an unprecedented need to delay surgeries, minimize clinic visits, and conserve limited resources in the wake of the current pandemic.^{2,5} In this study, we report that the ORR was 56.7%, 52.1%, and 49.0% after short, moderate, and long NET duration, respectively. A short NET duration did not result in an inferior objective response. Our findings were comparable to prior studies, albeit of much smaller sample size, which have reported ORR ranging from 20% to 76%.¹⁴ We also showed a small proportion of patients, 25.9%, 23.4%, and 19.0%, with disease upstaged after short, moderate, and long NET duration, respectively. These results were also consistent with previous findings.⁸

Previous studies, including multiple prospective trials, have evaluated the effects of NET over periods of 12–24 weeks, with some extending as long as a year.^{10,11,14} Given the recommendations by major surgical and oncologic associations to use NET as a bridge to surgery during the ongoing pandemic,^{3–9} we anticipate shorter NET durations than those used in formal studies. Our analysis of the NCDB data shows that shorter durations of NET use are already in effect in real-world practice, with 25% of patients receiving < 9 weeks of NET. Furthermore, ORR was actually highest in those patients receiving short duration of NET (56.7%), highlighting the utility of NET as a bridge to surgery when surgical delays are expected. Objective response in this group continued to be high (60.5%) when we restricted our analysis to patients with clinical stage I and II disease, who are most likely to receive NET during the pandemic. As disease upstaging can also occur over this time frame in a sizable minority of patients, we advise interval clinical exam +/- imaging to determine which patients have poor response to NET and may require accelerated surgical intervention.

TABLE 3 Demographic and clinical characteristics of patients who received NET stratified by duration of NET (weeks)

	NET Duration						P
	<9 weeks		9-27 weeks		>27 weeks		
	N	%	N	%	n	%	
n=8326	2045	24.6%	4294	51.6%	1987	23.9%	
Age at Diagnosis (mean ± (SD))	64.8 ± 12.9		68.0 ± 11.8		69.7 ± 11.5		<0.001
Year of Diagnosis							
2010-2013	1101	53.8%	2068	48.2%	940	47.3%	<0.001
2014-2016	944	46.2%	2226	51.8%	1047	52.7%	
Race							
White	1750	85.6%	3706	86.3%	1652	83.1%	0.001
Black	185	9.0%	374	8.7%	243	12.2%	
Asian/PI	65	3.2%	131	3.1%	64	3.2%	
Other/Unknown	45	2.2%	83	1.9%	28	1.4%	
Comorbidity Score							
0	1622	79.3%	3380	78.7%	1575	79.3%	0.51
1	311	15.2%	637	14.8%	301	15.1%	
2	76	3.7%	201	4.7%	73	3.7%	
3+	36	1.8%	76	1.8%	38	1.9%	
Insurance Status							
Private Insurance	881	43.1%	1410	32.8%	578	29.1%	<0.001
Government	1109	54.2%	2705	63.0%	1324	66.6%	
Other/Unknown	55	2.7%	179	4.2%	85	4.3%	
Hospital Category							
Community	104	5.1%	285	6.6%	126	6.3%	<0.001
Comprehensive Community	812	39.7%	1661	38.7%	709	35.7%	
Academic	683	33.4%	1621	37.8%	815	41.0%	
Integrated Network Cancer Program	404	19.8%	691	16.1%	326	16.4%	
Other/Unknown	42	2.1%	36	0.8%	11	0.6%	
Clinical Stage							
Overall							
1	957	46.8%	1002	23.3%	367	18.5%	<0.001
2	815	39.9%	2434	56.7%	1130	56.9%	
3	149	7.3%	657	15.3%	409	20.6%	
Unknown	124	6.1%	201	4.7%	81	4.1%	
Tumor Stage							
1	1031	50.4%	1142	26.6%	406	20.4%	<0.001
2	699	34.2%	2,043	47.6%	917	46.1%	
3	142	6.9%	598	13.9%	371	18.7%	
4	71	3.5%	395	9.2%	246	12.4%	
Unknown	102	5.0%	116	2.7%	47	2.4%	
Nodal Stage							
0	1667	81.5%	3234	75.3%	1431	72.0%	<0.001
1	254	12.4%	757	17.6%	406	20.4%	
2/3	53	2.6%	151	3.5%	89	4.5%	
Unknown	71	3.5%	152	3.5%	61	3.1%	
Histology							
Ductal	1479	72.3%	2946	68.6%	1333	67.1%	0.001
Lobular	361	17.7%	916	21.3%	447	22.5%	
Other/Unknown	205	10.0%	432	10.1%	207	10.4%	

TABLE 3 continued

	NET Duration						<i>P</i>
	<9 weeks		9-27 weeks		>27 weeks		
	<i>N</i>	%	<i>N</i>	%	<i>n</i>	%	
Pathologic Stage							
Overall							
0/IS	16	0.8%	47	1.1%	43	2.2%	<0.001
1	790	38.6%	1093	25.5%	407	20.5%	
2	751	36.7%	1777	41.4%	768	38.7%	
3	319	15.6%	829	19.3%	384	19.3%	
Unknown	169	8.3%	548	12.8%	385	19.4%	
Tumor Stage							
0/IS	23	1.1%	67	1.6%	56	2.8%	<0.001
1	1096	53.6%	1718	40.0%	722	36.3%	
2	663	32.4%	1669	38.9%	740	37.2%	
3	149	7.3%	477	11.1%	223	11.2%	
4	66	3.2%	186	4.3%	106	5.3%	
Unknown	48	2.3%	177	4.1%	140	7.0%	
Nodal Stage							
0	1171	57.3%	2044	47.6%	860	43.3%	<0.001
1	484	23.7%	1120	26.1%	493	24.8%	
2	153	7.5%	376	8.8%	168	8.5%	
3	81	4.0%	226	5.3%	99	5.0%	
Unknown	156	7.6%	528	12.3%	367	18.5%	
Tumor Grade							
Well Differentiated	612	29.9%	1253	29.2%	544	27.4%	0.50
Moderately Differentiated	1057	51.7%	2263	52.7%	1048	52.7%	
Poorly/Undifferentiated	270	13.2%	533	12.4%	234	11.8%	
Unknown	106	5.2%	245	5.7%	161	8.1%	
Surgery							
Primary							
Lumpectomy	929	45.4%	2267	52.8%	1151	57.9%	<0.001
Mastectomy	1115	54.5%	2024	47.1%	834	42.0%	
Surgery, NOS	1	0.0%	3	0.1%	2	0.1%	
Axilla (*2012 and later)							
None	127	6.2%	428	10.0%	301	15.1%	<0.001
SLN	887	43.4%	1737	40.5%	755	38.0%	
ALND	209	10.2%	592	13.8%	283	14.2%	
SLN + ALND	305	14.9%	588	13.7%	237	11.9%	
Other/Unknown	517	25.3%	949	22.1%	411	20.7%	
Adjuvant Radiation							
Post-Lumpectomy Radiation							
Yes	705	75.9%	1605	70.8%	697	60.6%	<0.001
No	221	23.8%	647	28.5%	445	38.7%	
Unknown	3	0.3%	15	0.7%	9	0.8%	
Post-Mastectomy Radiation							
Yes	320	28.7%	754	37.3%	334	40.0%	<0.001
No	791	70.9%	1256	62.1%	497	59.6%	
Unknown	4	0.4%	14	0.7%	3	0.4%	

TABLE 3 continued

	NET Duration						<i>P</i>
	<9 weeks		9-27 weeks		>27 weeks		
	<i>N</i>	%	<i>N</i>	%	<i>n</i>	%	
Pathologic Response to NET							
Pathologic Tumor Response							
Complete	18	0.9%	67	1.6%	55	2.8%	<0.001
Downstaged	255	12.5%	1222	28.5%	662	33.3%	
Stable	1429	69.9%	2358	54.9%	941	47.4%	
Upstaged	200	9.8%	362	8.4%	145	7.3%	
Unknown	143	7.0%	285	6.6%	184	9.3%	
Pathologic Nodal Response							
Complete	27	1.3%	102	2.4%	61	3.1%	<0.001
Downstaged	9	0.4%	31	0.7%	24	1.2%	
Stable	1276	62.4%	2316	53.9%	983	49.5%	
Upstaged	515	25.2%	1187	27.6%	502	25.3%	
Unknown	218	10.7%	658	15.3%	417	21.0%	
Overall							
Complete	0	0.0%	5	0.1%	1	0.1%	<0.001
Downstaged	204	10.0%	894	20.8%	478	24.1%	
Stable	956	46.7%	1340	31.2%	495	24.9%	
Upstaged	530	25.9%	1003	23.4%	378	19.0%	
Unknown	355	17.4%	1052	24.5%	635	32.0%	
Objective Response							
Objective Response ^a Rate (ORR)	1160	56.7%	2239	52.1%	974	49.0%	0.08
Upstaged	530	25.9%	1003	23.4%	378	19.0%	
Unknown	355	17.4%	1052	24.5%	635	32.0%	
Recurrence Score (Pre-TAILORX)							
<18	307	52.8%	499	59.7%	207	62.0%	0.03
18-30	234	40.3%	287	34.3%	114	34.1%	
>30	40	6.9%	50	6.0%	13	3.9%	
Follow-up (Median (IQR)) (months) ^b	38 (22-59)		36 (22-56)		37 (24-55)		0.22
Total Deceased ^c	242	11.8%	614	14.3%	290	14.6%	0.001

^aObjective response is defined as complete, downstaged, or stable pathologic response.

^bFollow-up represents the elapsed time between diagnosis and last contact

^cVital status available for (6,850, 82.3%) of NET patients

NET neoadjuvant endocrine therapy, SD standard deviation, PI Pacific Islander, SLN sentinel lymph node biopsy, ALND axillary lymph node dissection, IQR interquartile range, NOS not otherwise specified, NA not applicable

There were several other notable findings in this study. First, the unadjusted death rate was significantly higher in patients in the NET group (13.8%) versus the surgery-first group (7.2%). This is likely due to the inherent differences in patient characteristics in these two groups. Patients in the NET group were older at time of diagnosis, with higher Charlson–Deyo comorbidity scores, more advanced tumor stage, and less likely to receive adjuvant radiotherapy. This higher unadjusted death rate is not expected in patients treated with NET during the pandemic since these patients

are more likely to present with earlier-stage disease and to receive standard adjuvant therapy after their delayed surgery. The possible adverse effects due to surgery delay of cancer patients during the pandemic will be examined using data collected by regional and national medical/surgical organizations (Rachel Jankowitz, MD, personal communication, September 2020).

Second, patients with invasive lobular carcinoma (ILC) were more likely to have disease upstaged after NET. This is unexpected given the higher rate of hormone receptor

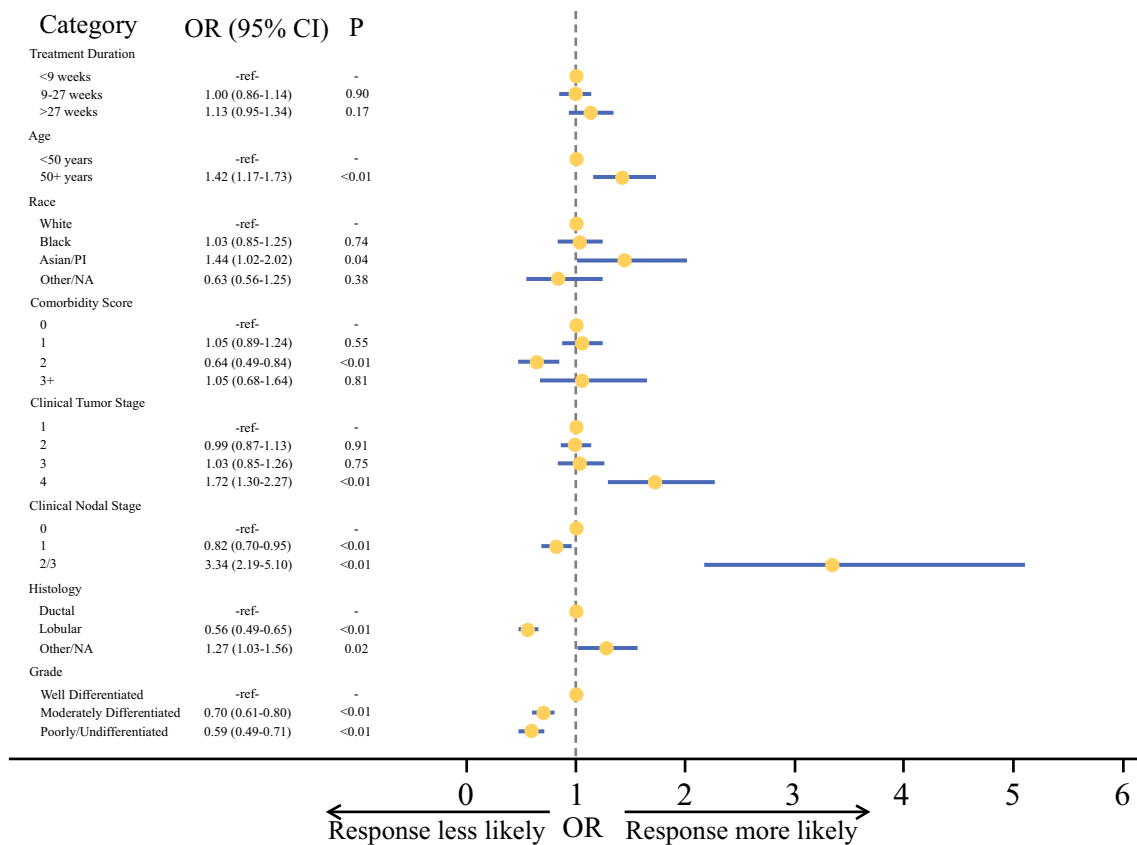


FIG. 3 Forest plot displaying the odds ratio (OR) of response to NET on multivariable logistic regression of entire study cohort ($n = 8326$)

positivity (> 95%) in this histologic subtype.¹⁵ A likely explanation is that clinical stage of ILC may often underestimate the pathologic stage. Specifically, clinical breast examination and breast imaging studies including mammography and ultrasonography often underestimate ILC disease extent.^{16,17} Histologically, ILC tends to be diffusely infiltrating, with invasion of stroma by neoplastic cells in single-cell fashion and often with minimal desmoplastic reaction contributing to the lack of discrete clinical breast examination findings.¹⁶ The reported sensitivity of mammogram for detecting ILC is only 57–79%, with up to 30% not visualized at all.¹⁷ As the treatment response of ILC is often underestimated by conventional methods, other methods, to accurately assess clinical response, such as measuring the change in % nuclear positivity for Ki67 using immunohistochemistry,^{18,19} may be more appropriate. However, these data are not available in the NCDB. The effect of NET on clinical outcomes in ILC will await results from an ongoing multicenter study (NCT02206984).²⁰

Third, our study showed that Black women were less likely to receive NET compared with their white counterparts. These results highlight the need for health care providers to remain mindful and vigilant when implementing guidelines in managing surgical delays through

the COVID-19 pandemic, especially to avoid inadvertently exacerbating racial disparities in breast cancer care as described in a recent editorial.²¹ While we were somewhat reassured by the findings that there were no significant differences in response to NET between white and Black patients in our study, the need to assess NET adherence in these vulnerable populations is warranted, as Black women are reported to have lower rates of endocrine therapy initiation and adherence compared with other racial groups.²² Periodic reassessment, as recommended by national medical and surgical organizations,^{7,9} may help to identify those with early disease progression and to direct these patients to more prompt surgical intervention.

A strength of this study is that it is one of the largest studies to evaluate the objective response to NET according to NET duration. Use of NCDB data also highlights real-world practice patterns of NET use, demonstrating a broader range of NET durations than evaluated in previous studies. Weaknesses of this study, inherent to the retrospective study design, include missing data, imbalances of clinical characteristics between subgroups due to selection bias, the inability to ascertain toxicity, compliance, and effectiveness of specific endocrine therapy regimens, and the lack of disease-specific outcome data. Results from this

study, however, were reassuring and support the use of NET to bridge surgery delay during the COVID-19 pandemic.

In summary, short NET duration (< 9 weeks) did not result in an inferior objective response. Future study to evaluate the interaction between surgery delay and NET use on clinical outcome will provide insights in the safety of NET use to bridge potential surgery delay in patients with HR+ breast cancer.

DECLARATIONS

DISCLOSURE Authors have no financial relationships or conflicts of interest relevant to this article to disclose.

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