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Delays in operative management of early-stage, estrogen receptor–positive breast cancer during the COVID-19 pandemic: A multi-institutional matched historical cohort study

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ABSTRACT

Background: During the COVID-19 pandemic, guidelines recommended that breast cancer centers delay estrogen receptor–positive breast cancer surgeries with neoadjuvant endocrine therapy. We aimed to evaluate pathologic upstaging of breast cancer patients affected by these guidelines.

Methods: Female patients with stage I/II breast cancer receiving neoadjuvant endocrine therapy were prospectively identified and were matched to a historical cohort of stage I/II estrogen receptor–positive breast cancer patients treated with upfront surgery ≤ 35 days. Primary outcomes were pathologic T and N upstaging versus clinical staging.

Results: After matching, 28 neoadjuvant endocrine therapy and 48 control patients remained. Median age in each group was 65 ($P = .68$). Most patients (78.6% and 79.2%) had invasive ductal carcinoma with a clinical tumor size of 0.9 cm vs 1.7 cm ($P = .056$). Time to surgery was 68 days in the neoadjuvant endocrine therapy group and 26.5 days in the control ($P < .001$). A total of 23 neoadjuvant endocrine therapy patients (82.1%) had the same or lower pT-stage compared with 31 (64.5%) control patients ($P = .115$). Only 3 (10.7%) neoadjuvant endocrine therapy patients had increased pN-stage vs 14 (29.2%) control patients ($P = .063$).

Conclusion: Despite 2.5-times longer delays, patients with early-stage estrogen receptor–positive breast cancer receiving neoadjuvant endocrine therapy did not experience pathologic upstaging during the COVID-19 pandemic. These findings may support the use of neoadjuvant endocrine therapy in similar patients if delays to surgery are projected.

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Introduction

In March 2020, the province of Quebec, Canada, declared a public health emergency due to the SARS-CoV-2 (COVID-19) pandemic.¹ Similar to elsewhere in the world,² extraordinary measures were taken to offload hospitals and better accommodate the influx of patients suffering from COVID-19.³ One such measure was to limit elective operations to those which were most urgent or

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life-threatening and to reassign operating room staff to COVID floors and intensive care units (ICUs).⁴ As part of this effort, federal and provincial recommendations were to postpone surgeries if necessary for early-stage (stage I or II) estrogen receptor–positive (ER+), human epidermal growth factor receptor 2–negative (HER2–) breast cancers (BCs) with neoadjuvant endocrine therapy (NET) until regular operative volume could be resumed.^{5–9}

ER+ BCs continue to be the most commonly diagnosed subtype of BC, making up roughly 80% of new diagnoses.¹⁰ For early-stage ER+ BC, standard of care includes upfront surgery (partial or total mastectomy with or without axillary staging), followed by adjuvant endocrine therapy with or without adjuvant radiotherapy and chemotherapy.¹¹ Use of NET in these patients is usually reserved for patients with large or locally advanced tumors which can be converted to breast-conserving surgery with the use of NET, or as primary endocrine therapy for elderly patients or those with significant comorbidities prohibiting operative intervention.^{12–15} The

data are mixed, but most studies have demonstrated that use of NET in large or locally advanced tumors is equivalent or superior to use of neoadjuvant chemotherapy (NAC) in postmenopausal patient populations, though this remains controversial^{16,17} However, intentional use of NET in early-stage ER+ BCs was not standard of care before the pandemic and there are therefore limited data supporting its use or demonstrating its effect on pathologic upstaging in this patient population^{9,12} Given this, when the new guidelines took effect, we aimed to prospectively identify patients affected by these guidelines at 2 referral-based breast cancer centers to evaluate the impact of this treatment on their pathological staging.

Methods

Study population

Before beginning the study, institutional ethics review board approval was obtained at both institutions. Inclusion criteria were all female patients with early-stage (stage I–II), ER+ BC. Patients were prospectively identified as of 1 March 2020 from 2 large, referral-based breast cancer centers in Quebec, Canada. To ensure that no patient receiving NET during the COVID-19 pandemic was missed, all patients diagnosed with breast cancer between 1 December 2019 and 1 May 2020 at both participating institutions were also reviewed. Patients were excluded if undergoing upfront surgery, presenting with recurrent ipsilateral breast cancer, already receiving endocrine therapy at the time of diagnosis, undergoing surgery for revision of margins, or receiving NAC. Patients who had pure in situ disease or no residual disease on final pathology were also excluded as it would be impossible to determine whether this was due to pathologic complete response of the invasive tumor or rather to the entire tumor being removed during the biopsy process. Identical inclusion and exclusion criteria were used to select those who received NET due to operative delays during the pandemic.

To identify patients for the historical control group, a prospectively maintained breast cancer database from 1 of the 2 participating institutions was queried. Two-hundred patients were randomly selected from a group of patients seen in the breast center's clinic between 2010 and 2013. Patients included in the historical cohort had to have stage I–II ER+ breast cancer and undergo upfront surgery. Identical inclusion and exclusion criteria were used to select patients in the historical control group. To eliminate bias from prolonged delays to surgery in the historical control group, only patients who underwent surgery ≤ 35 days from the date of diagnosis were included in the matching process.

Outcomes and variable definitions

Electronic medical records were used to collect demographic, clinical, pathologic, and radiologic data, as well as data specific to each patient's NET treatment, if applicable. These included age at diagnosis, date of diagnosis, clinical staging information, preoperative pathologic data, operative information including date of surgery, and final pathologic data and stage. Date of diagnosis was defined as the date of first positive biopsy in both groups and date of surgery was defined as the date of the first definitive surgical intervention. Clinical tumor size was defined as the largest tumor dimension on any preoperative imaging (mammography, ultrasound, or magnetic resonance imaging [MRI]). Patients with rare tumor subtypes (tubular, mucinous, micropapillary carcinomas) were grouped with invasive ductal carcinoma (IDC). Patients' clinical and final pathologic stage in both groups was uniformized to follow the eighth edition of the American Joint Committee on

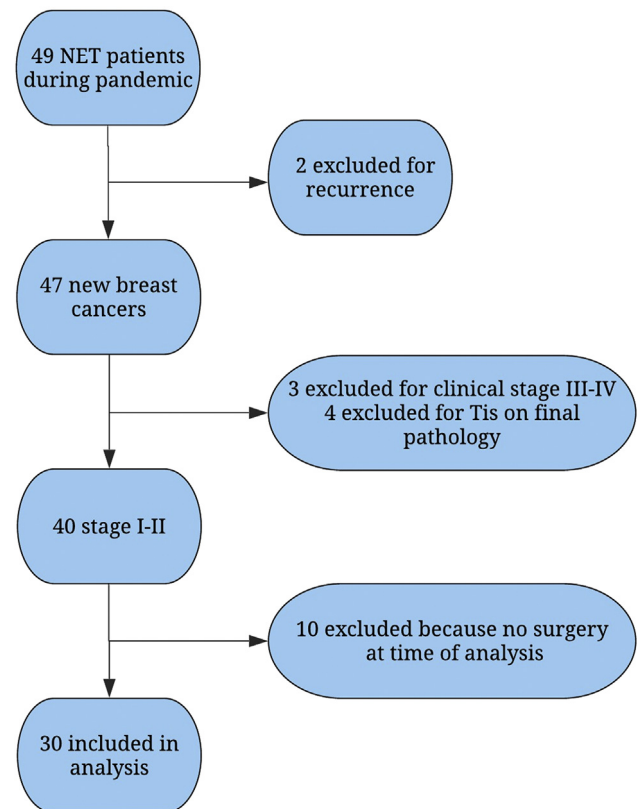


Figure 1. Flowchart of inclusion/exclusion of neoadjuvant endocrine therapy (NET) patients.

Cancer (AJCC) staging manual 2017.¹⁸ Patients who did not undergo axillary staging were considered to have N0 disease on final pathology. Luminal A subtype was defined as tumors which were ER+ and with 50% or more progesterone expression (PR+). Luminal B was defined as ER+ and <50% PR+.

The primary outcomes of interest were changes in pathologic T- and N-staging (pT and pN) compared with pretreatment clinical-radiologic T- and N-stages (cT and cN).

Statistical analysis

Statistical analysis was performed in R Version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria). Data are represented as *n* (%) for categorical variables and median (interquartile range [IQR]) for continuous variables. Univariate analyses were performed using Kruskal-Wallis one-way analysis of variance test (ANOVA) for medians of continuous variables and χ^2 test for categorical variables. To create balanced groups for comparison, exact matching was performed using preoperative pathology (IDC or invasive lobular carcinoma [ILC]), clinical grade, and clinical T-stage. Conditional multiple regression analyses were performed to identify independent predictors of changes in pathologic T- and N-stages compared with clinical stages.

Results

Patients

At both institutions, a total of 49 patients receiving NET during the study period were identified. Of these, 30 met inclusion criteria (see Figure 1). Twenty-five patients (83.3%) received a neoadjuvant

Table 1

Patient demographics and pre-operative characteristics of neoadjuvant endocrine therapy group compared with matched historical cohort of patients who underwent surgery in ≤ 35 days

Variables	Total (n = 76)	Control (n = 48)	NET (n = 28)	P value
Age (IQR)	65 (57.75–73.25)	65 (55.5–74.25)	65 (59.5–72.25)	.682
Preoperative pathology				.951
Invasive ductal carcinoma	60 (78.9%)	38 (79.2%)	22 (78.6%)	
Invasive lobular carcinoma	16 (21.1%)	10 (20.8%)	6 (21.4%)	
Preoperative subtype				.212
Luminal A	45 (59.2%)	31 (64.6%)	14 (50.0%)	
Luminal B	31 (40.8%)	17 (35.4%)	14 (50.0%)	
Preoperative grade				.221
I	19 (25.0%)	9 (18.8%)	10 (35.7%)	
II	55 (72.4%)	38 (79.2%)	17 (60.7%)	
III	2 (2.6%)	1 (2.1%)	1 (3.6%)	
Preoperative Allred score for ER				.442
7	1 (1.3%)	1 (2.1%)	0 (0.0%)	
8	75 (98.7%)	47 (97.9%)	28 (100.0%)	
Maximum size on imaging in cm (IQR)	1.5 (0.8–2.35)	1.7 (0.9–2.325)	0.9 (0.775–1.725)	.056
Imaging modality for maximum size				.287
Mammography	24 (31.6%)	18 (37.5%)	6 (21.4%)	
Ultrasound	33 (43.4%)	18 (37.5%)	15 (53.6%)	
Magnetic resonance imaging	19 (25.0%)	12 (25.0%)	7 (25.0%)	
Clinical T-stage				.073
T1a	10 (13.2%)	6 (12.5%)	4 (14.3%)	
T1b	20 (26.3%)	8 (16.7%)	12 (42.9%)	
T1c	26 (34.2%)	19 (39.6%)	7 (25.0%)	
T2	20 (26.3%)	15 (31.2%)	5 (17.9%)	
Clinical N-stage				.286
N0	70 (92.1%)	43 (89.6%)	27 (96.4%)	
N1	6 (7.9%)	5 (10.4%)	1 (3.6%)	
Clinical stage				.358
IA	61 (81.3%)	39 (83.0%)	22 (78.6%)	
IB	2 (2.7%)	2 (4.3%)	0 (0.0%)	
IIA	12 (16.0%)	6 (12.8%)	6 (21.4%)	
NET type				NA
Tamoxifen	5 (17.9%)	NA	5 (17.9%)	
Letrozole	12 (42.9%)	NA	12 (42.9%)	
Anastrozole	11 (39.3%)	NA	11 (39.3%)	
Duration of NET in days (IQR)	33.5 (19.75–57.5)	NA	33.5 (19.75–57.5)	NA

ER, estrogen receptor; IQR, Interquartile range; NET, neoadjuvant endocrine therapy.

aromatase inhibitor (letrozole or anastrozole) and 5 received tamoxifen. The median duration of NET before surgery was 34.5 days (IQR 22.0–58.5 days).

In the historical control group, 189 patients met inclusion criteria. After matching, 28 patients remained in the NET group and 48 in the historical control group (Table 1). The median age at diagnosis in both groups was 65 (IQR 59.5–72.25 in the NET group and 55.5–74.25 in the control group, $P = .682$). 22 patients (78.6%) in the NET group and 38 (79.2%) in the control group had IDC ($P = .951$), and most had grade II disease at diagnosis (60.7% in the NET group and 79.2% in the control group, $P = .221$). The median largest size on imaging in the NET group was 0.9 cm (IQR 0.78–1.73 cm) compared with 1.7 cm (IQR 0.9–2.33 cm) in the historical control group ($P = .056$). In the NET group, 82.1% of patients (23 patients) had cT1 disease compared with 68.8% (33 patients) in the control group ($P = .73$).

Pathologic staging and upstaging

In the NET group, 82.1% of patients underwent partial mastectomy and 100% underwent sentinel lymph node biopsy (SLNB) compared with 83.3% undergoing partial mastectomy and 62.5% undergoing SLNB in the control group ($P = .894$ and $P = .001$, respectively). The median time to surgery in the NET group from the day of diagnosis was 68 days (IQR 41.8–87.0 days) compared with 26.5 days in the historical control (IQR 22.8–32.0 days) ($P < .001$). In the NET group, the median tumor size on final pathology was 1.2 cm (IQR 0.79–1.50 cm) compared with 1.8 cm (IQR

1.20–2.85 cm) in the historical control group ($P = .003$). The median difference in size was significantly different between both groups during the operative period (-0.025 cm in the NET group [IQR -0.13 – -0.23 cm] vs 0.1 cm [IQR -0.53 – 0.03 cm] in the historical control group, $P = .016$) (Table II).

Looking at pathologic T-stage, 23 patients (82.1%) in the NET group had pT1 disease compared with 28 patients (58.3%) in the control group ($P = .315$). The overall change in T-stage from clinical to pathologic between the NET and the control groups was not statistically different; indeed 82.1% of patients in the NET group had the same or lower pT-stage compared with cT-stage vs 64.6% of patients in the control group ($P = .115$).

Regarding pN-stage, 85.7% of patients (24 patients) in the NET group had N0 disease; two of these had isolated tumor cells (ITCs). Of the 4 remaining patients, 1 had N1 with microinvasion (N1mi) and 3 had N1a disease. In the control group, 64.6% of patients (31 patients) had Nx or N0 disease (4 with ITCs), 4 had N1mi, and 13 had N1a and above ($P = .097$). Overall, in the NET group, 89.3% of patients had the same N-stage when comparing cN with pN vs 70.8% in the historical control group ($P = .063$).

On multivariate regression analysis evaluating independent risk factors for T- and N-upstaging, maximum size on imaging was the only variable which independently affected upstaging. Larger tumors were 0.68 times less likely to have T-upstaging (95% confidence interval [CI] 0.43–1.00), although they had a 2.4-fold increased likelihood of having N-upstaging (95% CI 1.67–3.58) for every 1-cm increase in clinical-radiologic tumor size. None of the other evaluated patient or tumor characteristics affected the risk of

Table II
Surgical details and pathological characteristics of neoadjuvant endocrine therapy group compared with matched historical cohort of patients who underwent surgery in ≤35 days

Variables	Total (n = 76)	Control (n = 48)	NET (n = 28)	P value
Time to surgery in days (IQR)	32 (25–50.25)	26.5 (22.75–32)	68 (41.75–87)	<.001
Mastectomy type				.894
Partial mastectomy	63 (82.9%)	40 (83.3%)	23 (82.1%)	
Total mastectomy	13 (17.1%)	8 (16.7%)	5 (17.9%)	
Axillary staging				.001
None	6 (7.9%)	6 (12.5%)	0 (0.0%)	
SLNB	58 (76.3%)	30 (62.5%)	28 (100.0%)	
ALND	12 (15.8%)	12 (25.0%)	0 (0.0%)	
Size on final pathology in cm (IQR)	1.5 (1–2.35)	1.8 (1.2–2.85)	1.2 (0.788–1.5)	.003
Difference in size in cm (IQR)	–0.1 (–0.4 to 0.1)	0.1 (–0.525 to 0.025)	–0.025 (–0.125 to 0.225)	.016
Pathologic T-stage				.315
T1a	4 (5.3%)	2 (4.2%)	2 (7.4%)	
T1b	16 (22.5%)	8 (17.4%)	8 (32.0%)	
T1c	30 (42.3%)	18 (39.1%)	12 (48.0%)	
T2	21 (29.6%)	17 (37.0%)	4 (16.0%)	
T3	4 (5.6%)	3 (6.5%)	1 (4.0%)	
Change in T-stage				.115
Downstaged	6 (7.9%)	2 (4.2%)	4 (14.3%)	
Unchanged	48 (63.2%)	29 (60.4%)	19 (67.9%)	
Upstaged	22 (28.9%)	17 (35.4%)	5 (17.9%)	
Pathologic N-stage				.097
Nx	6 (7.9%)	6 (12.5%)	0 (0.0%)	
N0	43 (56.6%)	21 (43.8%)	22 (78.6%)	
N0 (i+)	6 (7.9%)	4 (8.3%)	2 (7.1%)	
N1mi	5 (6.6%)	4 (8.3%)	1 (3.6%)	
N1a	13 (17.1%)	10 (20.8%)	3 (10.7%)	
N2a	2 (2.6%)	2 (4.2%)	0 (0.0%)	
N3a	1 (1.3%)	1 (2.1%)	0 (0.0%)	
Change in N-stage				.063
Downstaged	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Unchanged	59 (77.6%)	34 (70.8%)	25 (89.3%)	
Upstaged	17 (22.4%)	14 (29.2%)	3 (10.7%)	

IQR, Interquartile range; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

upstaging, including patient age, use of NET, preoperative pathology, or preoperative tumor grade before matching. After matching patients by clinical grade, tumor biology, and cT-stage, use of NET decreased the odds of T-upstaging (OR 0.16, 95% CI 0.03–0.82), but had no effect on N-upstaging, meaning that patients who received NET were 84% less likely to demonstrate T-stage upstaging during the perioperative period compared with patients who did not receive NET. Similarly, maximum size on imaging also increased the odds of T-upstaging 3.28-fold (95% CI 1.00–10.7) after matching, while having no effect on N-upstaging (Table III).

Discussion

The COVID-19 pandemic put unprecedented stress on health-care institutions which were often already stretched thin before the onset of the pandemic. In order to free up healthcare personnel to work in ICUs and on COVID floors and to limit exposure of patients and personnel to carriers of the disease, many institutions across the globe were forced to improvise and attempt novel approaches in disease treatment.^{2,3} From telehealth to transfers of operative care to institutions with less COVID burden, surgery was no exception, and delaying care for patients with the most common but least aggressive BC subtype made intuitive sense. The hope was that treating these patients with NET for variable periods of time would allow for delay of their surgeries until the worst of the pandemic was over without clinical repercussions.^{5–9}

The data supporting this approach are limited and use of NET in ER+ BC remained infrequent before the pandemic.¹² Use of primary endocrine therapy as sole therapy has long been an option in elderly or comorbid patients who cannot undergo surgery, though long-term local control is suboptimal.¹⁹ In 2010, the American College of Surgeons Oncology Group (ACOSOG) Z1031 trial was the

first Phase III clinical trial comparing different modalities of NET which demonstrated that significant tumor downstaging could be achieved using 16–18 weeks of NET and allowed roughly 50% of mastectomy-only candidates to be eligible for breast-conserving surgery. The STAGE trial went on to support the safety of NET in premenopausal women as well,¹⁴ although uptake in this patient population remains limited. In aggregate, these studies evaluated 3–6 month duration of NET in T2–4c breast cancers and, despite these trials, its use continued to remain low before the pandemic.²⁰ Use of NET specifically in early-stage ER+ BC has only recently begun to be explored in the context of ongoing clinical trials.^{21,22} Even during the pandemic, a survey of breast cancer physicians found that over three-quarters used NET ‘rarely’ or ‘sometimes’ in ER+ BC patients before the pandemic and nearly half were comfortable delaying surgery by 2 months without NET in this patient group during the pandemic. It was therefore novel to recommend use of NET for patients with foreseeable delays to surgery during the pandemic.

Overall, patients who received NET at our institutions had favorable outcomes and there was no significant effect on pT- and pN-stages compared with clinical stages. When compared with the historical cohort of patients undergoing surgery within 35 days, there was no statistically significant difference in outcomes, despite the delays in surgery which were over 2.5 times longer. On multiple regression analysis after matching for tumor biologic features and cT-stage, use of NET was associated with a significantly reduced OR of 0.16 the odds of having T-upstaging compared with clinical stage. This supports the notion that NET offers a protective effect in patients receiving it before their surgery by halting tumor progression which may otherwise have occurred or resulted in initial tumor regression, although another reason for this stability could be the indolent nature of these tumors.

Table III
Conditional multiple logistic regression analysis for upstaging

Variables before matching	T-stage			N-stage		
	OR	95% CI	P value	OR	95% CI	P value
Age	1.02	0.99–1.05	0.2	0.98	0.95–1.01	.2
NET	0.62	0.19–1.68	0.4	0.56	0.12–1.88	.4
Preoperative pathology						
IDC	-	-	-	-	-	-
ILC	1.54	0.58–3.87	0.4	0.51	0.15–1.45	.2
Preoperative grade						
I	-	-	-	-	-	-
II	1.87	0.86–4.37	0.13	1.11	0.50–2.57	.8
III	1.12	0.06–7.77	>0.9	0.34	0.02–2.38	.3
Maximum size on imaging	0.68	0.45–1.00	0.063	2.40	1.67–3.58	<.001
Variables after matching	OR	95% CI	P value	OR	95% CI	P value
Age	1.01	0.96–1.07	0.7	1.01	0.97–1.06	.5
NET	0.16	0.03–0.82	0.028	0.45	0.09–2.24	.3
Maximum size on imaging	3.28	1.00–10.7	0.049	0.88	0.26–2.92	.8

OR, odds ratio; CI, confidence interval; NET, neoadjuvant endocrine therapy; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

Another finding to emerge from these data was the large proportion of patients in the historical cohort who had nodal upstaging at the time of surgery. This may be explained by the chosen timing of the historical cohort; these patients were selected from a group diagnosed between 2010–2013, a time where surgeons performed more axillary lymph node dissections (ALND).²³ This is reflected in our data, where 12 patients (25.0%) underwent ALND compared with 0 patients in our NET group. Previous studies have found that patients undergoing ALND often have more positive nodes when compared with patients undergoing SLNB, though ACOSOG Z0011 trial demonstrated that this is not associated with a difference in overall survival or disease-free survival.²⁴ However, in 2010–2013, many surgeons likely still opted for ALND over SLNB to stage their patients as the ACOSOG Z0011 trial was not published yet.^{23,24}

Strengths of this work include the prospective identification of patients receiving NET during the pandemic and the multi-institutional nature of the data collected. The major limitation of this paper is the small number of patients included in the NET group. At the onset of this study, we hypothesized that many patients may require NET at both of our high-volume institutions. The duration of the pandemic, the potential surgical delays, and the impact on patients were all unknown. However, our total number of patients affected by these guidelines was only 30 in both institutions. This may be explained by the fact that some patients were redirected to other academically affiliated but lower-volume centers to undergo surgery. Another possible explanation is that surgeons used their clinical judgment in assigning which patients could see their surgeries delayed versus those who could not. This is supported by the fact that our cohort of patients who received NET had significantly smaller tumors when compared with our historical cohort, implying that surgeons possibly selected patients with more favorable clinical staging to receive NET. Further supporting this hypothesis is the fact that provincial data have demonstrated that, province-wide, there was actually an increase in breast cancer surgeries between 1 March 2020 and 31 March 2020 when compared with the same period the previous year.²⁵ This may be due to institutional guidelines favoring same-day surgeries at this time and/or surgeons rushing to have their cases prioritized given the unknowns of the pandemic. In the following months, breast cancer surgeries went down by an average of 18% between 1 April 2020 and 20 June 2020 compared with the previous year, but this corresponds to the period of complete suspension of breast cancer screening, which may explain this decrease.²⁵ This is further supported by the fact that the number of

patients waiting for their breast cancer surgery during this period remained steady when compared with 2019.²⁵

There was also a significant discrepancy between the delay to surgery when compared with the duration of NET (median delay to surgery of 68 days versus median duration of NET of 33.5 days), which could possibly be explained by 2 factors. First, the date of diagnosis was pre-emptively defined as the date of the first positive biopsy to avoid bias in assigning the date of diagnosis between the NET and historical groups. This led to discordance between the date of diagnosis and the date that the patient first met with their treating surgeon. Second, it is possible, especially at the beginning of the pandemic, that physicians did not anticipate significant delays to surgery and therefore only began NET several days/weeks after initially meeting with the patient and consenting them for surgery. Administration of NET for this short of a duration is only beginning to be studied^{21,22}; it is therefore unclear whether this short course had any role in preventing disease progression or whether this lack of progression is inherent to the indolent nature of these types of tumors. However, some preliminary data do support that the tumor biology may already begin to be altered after as short a treatment course as 4 weeks.^{21,22} The true effect of short-course NET would be better elucidated in a study comparing patients who received NET during this period with patients who experienced similar delays to surgery but did not receive NET.

Beyond the pandemic, these data support the safety of offering NET to patients with early-stage ER+ tumors and foreseeable delays to surgery, though future prospective studies evaluating the outcomes of such patients should be undertaken. Another advantage of NET is that it may allow for evaluation of compliance and tolerability to endocrine therapy in older postmenopausal women with ER+ HER2- breast cancer, which may aid in decision-making of adjuvant therapies in these patient populations. Finally, use of NET may offer the opportunity to evaluate potential resistance patterns in tumors treated with endocrine therapy, which cannot be as readily studied in the adjuvant setting; this is currently being evaluated with ongoing clinical trials.^{21,22}

In conclusion, although use of NET in early-stage ER+ HER2- breast cancer remains limited, this study demonstrates that patients who received NET during the COVID-19 pandemic as a risk-mitigation strategy while their surgeries were delayed fared no worse than historical controls in terms of T- and N-upstaging despite over 2.5 times longer delays to surgery. As we emerge from the pandemic era, these findings may support use of NET for early-

stage ER+ tumors when the treating team anticipates significant delays to surgery. An alternative conclusion from this research may be that the traditionally quoted 28-day delay from diagnosis to surgery could be overly conservative when considering the tumor biology of these early breast cancers. This would also benefit from being studied in a prospective multi-institutional study.

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Conflict of interest/Disclosure

None of the authors have any conflict of interest to declare.

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Discussion

Dr. Zahraa Al-Hilli (Cleveland Clinic): The COVID-19 pandemic has posed a unique set of challenges for breast cancer screening and patients diagnosed with the disease. And certainly, reorganization of breast services meant that a number of patients diagnosed with hormone receptor-positive breast cancer were offered treatment with neoadjuvant endocrine therapy during delays in surgery. The data presented by the authors adds to a growing body of literature on neoadjuvant endocrine therapy and may give reassurance for patients most impacted by treatment delays during the pandemic.

I have 3 questions for the authors. First, the duration of treatment with neoadjuvant endocrine therapy in the studies is perhaps too short to demonstrate a change in tumor size. Data, including those from clinical trials on neoadjuvant endocrine therapy, included patients treated for an average of 4 months or longer. So, the impact of shorter treatment duration remains unclear. Can you comment on the duration of treatment with neoadjuvant endocrine therapy and how this could have impacted the results?

Second, your study compares patients treated with neoadjuvant endocrine therapy with patients who underwent primary surgery



in <35 days and without a delay. Did you consider having patients with a delay in time to surgery but not treated with neoadjuvant endocrine therapy as the control group?

And, finally, what lessons from your study can we take with us to the post-COVID era? Do you recommend that neoadjuvant endocrine therapy be considered for patients experiencing delays for other reasons, such as further workup or medical optimization prior to surgery?

Dr. Dilena: Thank you, Dr. Al-Hilli for your thoughtful questions. For the first question regarding the duration of NET, I agree with you the duration of NET was a little bit short in our NET group. So just to explain this a little bit. Our delays to surgery were, in fact, two and a half times longer in our NET group compared with our historical control. But our duration of NET treatment was only 34 days. This can be explained by a couple of factors. First is what we used to standardize our date of diagnosis; we used the date of the first positive biopsy as the date of diagnosis for all patients across both cohorts. Obviously, this would lead to a delay between the date of diagnosis and the date that the patient first met with the surgeon. This is one element that explains this discrepancy. The second element is that, and this is more hypothetical, that perhaps the surgeons, when they first met with patients and consented them for surgery, did not actually know that there would be significant delays to surgery at that time. And this, I am speaking a little bit anecdotally, but in collecting the data, we observed that this is the case for several patients, so basically the surgeon would meet with them, consent them for surgery, and then only realize afterwards that there would be significant delays to surgery because they met with them in early March, for example, and then called the patients at home and explained NET to these patients. So that is the second element that may explain the discrepancy between the 73 days and the 34 days in our NET group.

Now, whether or not this was long enough for NET to actually have an impact is kind of unknown in this case. As you mentioned, specifically NET for a downsizing of tumors is given for 4 months or more in most patients. In our case, it was much shorter than that, as you mentioned. Whether or not these patients did not have upstaging because they received NET remains a little bit unknown in this scenario.

The second question that you had was the duration—the delays to surgery in the historical control. The objective of our study was really to determine whether or not patients during COVID saw their tumors be upstaged or had poor outcomes pathologically due to the delays to surgery during the COVID pandemic. We did not actually want to compare patients with historical controls who had significant delays. We wanted to compare them with the standard of care. That is why we picked the 35 days. I agree, though, that it is an interesting idea to look back and try to find patients who had significant delays in the past and compare those patients, by matching them for delays to surgery and compare whether or not those patients saw significant upstaging or not during that time period and determine whether NET had a protective effect in these patients. But we would have to go back and collect additional data to determine this.

Finally, to address your third question on the takeaway points from these data, I think there are 2 ways to interpret this, and I am not sure which is right. One possible explanation is that NET was indeed protective even if it were given for a short period of time. As you mentioned in your first question, this was really a short period of time and no one has really evaluated the use of NET for just a month to know whether or not this actually had an impact on tumor downsizing or at least on preventing progression of tumors. I

think, like you mentioned, matching to patients who had significant delays to surgery and did not receive NET would be an interesting way to answer that question or to conduct a prospective RCT looking at those 2 kinds of patient populations. Another possible takeaway from this study, I think, is that perhaps we're overly conservative in our guidelines that recommend for operating on these patients within a month of diagnosis. If you think about the tumor biology of these small, luminal A type tumors, perhaps they never would have progressed in our 70 or so days. So maybe in 2 months and a half, they do not actually have that high likelihood of progressing and that explains our results, in which case perhaps we should change our guidelines and not be overly nervous about delaying care for these patients. And that is kind of the impression that was given in that survey, in the 2001 survey of physicians during the COVID—surgeons during the COVID-19 pandemic who were quite comfortable delaying their patients to OR by up to 2 months without treating them with NET. Maybe this is already a general impression among surgeons that is not really reflected in the data. But, again, these small, observational studies often raise more questions than they answer. I think that to adequately answer the questions, we would need proper prospective large RCTs.

Dr. Faaiza Vaince (Loyola Medical Center): I have 2 brief questions. Did you guys utilize Oncotype at all in determining whether this was somebody that needed to be ushered to surgery sooner than later prior to putting them on the endocrine treatment? That is actually what panned out for us during the early onset of the pandemic in determining whether we needed to usher somebody to surgery, and in our case, we did not stop doing those surgeries, or whether to delay it, particularly if the patient had reservations about being operated on during the pandemic. My other question is, can you comment on what the pitfalls might be, if there are any, in putting somebody on endocrine treatment if there are delays, for whatever reason, anticipated?

Dilena: Regarding Oncotype, yes, so we did collect the data. In our whole cohort of 30 patients, there were, I do not want to say an exact number, but I think there were fewer than 10 patients who actually had an Oncotype DX that was performed. We perform them quite selectively at our institution. Typically, a multi-institutional tumor board has determined whether or not a patient needs Oncotype DX, and usually it is actually after the surgery, so not under biopsy. Not initially prior to their surgery. This was not routinely performed for patients and the surgeons would not have known the Oncotype DX routinely before deciding whether or not the patients would go to surgery. I do think that is an interesting idea, trying to profile these tumors and know whether or not they're more proliferative as kind of a guideline of whether or not to operate on patients.

Your second question was the potential pitfalls of putting patients on NET. I think that it requires careful monitoring, so we know that a certain subset of patients will progress on NET, and I think that carefully monitoring those patients is usually the standard of care, especially when you are using NET to downsize tumors. The issue, of course, was that patients were really scared to come to the hospital, and I do not think that it would have been feasible to routinely perform ultrasound during this period. Of course, going forward in a non-pandemic world, then I think that it becomes more feasible to monitor patients with imaging if we are going to do longer term NET. The other potential pitfall, I would think, would just be the side effect profile of the endocrine therapy, but this is the same as for adjuvant therapies. (Applause)