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EPIDEMIOLOGY

Neoadjuvant endocrine therapy use in early stage breast cancer during the covid-19 pandemic

Ko Un Park[1,10] · Megan Gregory[2] · Joey Bazan[3] · Maryam Lustberg[4] · Shoshana Rosenberg[5] · Victoria Blinder[6] · Priyanka Sharma[7] · Lajos Pusztai[8] · Chengli Shen[1] · Ann Partridge[5] · Alastair Thompson[9]

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Abstract

Purpose Physician treatment preferences for early stage, estrogen positive breast cancer (ER + BC) patients were evaluated during the initial surge of the COVID-19 pandemic in the US when neoadjuvant endocrine therapy (NET) was recommended to allow safe deferral of surgery.

Methods A validated electronic survey was administered May–June, 2020 to US medical oncologists (MO), radiation oncologists (RO), and surgeons (SO) involved in clinical trials organizations. Questions on NET use included practice patterns for locoregional management following NET.

Results 114 Physicians from 29 states completed the survey—42 (37%) MO, 14 (12%) RO, and 58 (51%) SO. Before COVID-19, most used NET 'rarely' (49/107, 46%) or 'sometimes' (36, 33%) for ER + BC. 46% would delay surgery 2 months without NET. The preferred NET regimen was tamoxifen for premenopausal and aromatase inhibitor for postmenopausal women. 53% planned short term NET until surgery could proceed. Most recommended omitting axillary lymph node dissection (ALND) for one micrometastatic node after 1, 2, or 3 months of NET (1 month, $N = 56/93$, 60%; 2 months, $N = 54/92$, 59%; 3 months, $N = 48/90$, 53%). With longer duration of NET, omission of ALND decreased, regardless of years in practice, percent of practice in BC, practice type, participation in multidisciplinary tumor board, or number of regional COVID-19 cases.

Conclusion More physicians preferred NET for ER + BC during the pandemic, compared with pre-pandemic times. As the duration of NET extended, more providers favored ALND in low volume metastatic axillary disease. The Covid-19 pandemic affected practice of ER + BC; it remains to be seen how this may impact outcomes.

Keywords COVID-19 · Neoadjuvant endocrine therapy · Early stage breast cancer · Pandemic shutdown

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✉ Ko Un Park
Koun.park@ousmc.edu

[1] Division of Surgical Oncology, Department of Surgery, The Ohio State University Wexner Medical Center James Comprehensive Cancer Center, Columbus, OH, USA

[2] Department of Biomedical Informatics, The Ohio State University Wexner Medical Center, Columbus, OH, USA

[3] Department of Radiation Oncology, The Ohio State University Wexner Medical Center James Comprehensive Cancer Center, Columbus, OH, USA

[4] Division of Medical Oncology, Department of Medicine, The Ohio State University Wexner Medical Center James Comprehensive Cancer Center, Columbus, OH, USA

[5] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

[6] Memorial Sloan Kettering Cancer Center, New York, NY, USA

[7] Division of Medical Oncology, Department of Medicine, University of Kansas Medical Center, Westwood, KS, USA

[8] Section of Medical Oncology, Department of Medicine, Yale University, New Haven, CT, USA

[9] Department of Surgery, Baylor College of Medicine, Houston, TX, USA

[10] The Ohio State University Wexner Medical Center, 410 W 10th Ave, N908 Doan Hall, Columbus, OH 43210, USA

Introduction

The coronavirus disease 2019 (COVID-19) pandemic from the novel SARS-CoV-2 virus has disrupted oncology care in an unprecedented manner. Due to many factors including a shortage of personal protective equipment and need for social distancing, in many regions across the United States, oncology providers had to consider the patient's risk of contracting the virus versus tumor progression related to delays in cancer care. Weighing the relative low risk of disease progression in early stage breast cancer, the Society of Surgical Oncology (SSO) and American Society of Breast Surgeons (ASBrS) specifically recommended short-term delay of surgery in early stage estrogen-positive breast cancer [1, 2]. As a consequence, the use of endocrine therapy during deferment of surgery was recommended in many instances, resulting in complicated multidisciplinary considerations.

Historically, neoadjuvant endocrine therapy (NET) use in early stage estrogen positive breast cancer (ER + BC) in the United States has been only 3% [3, 4]. In general, NET has been used to downstage ER + BC more commonly in postmenopausal compared to premenopausal women. However, progression while on NET can occur and NET can affect downstream locoregional treatment considerations [5]. For instance, studies evaluating the safety of omitting completion axillary lymph node dissection in positive 1–3 sentinel lymph node for early stage breast cancer did not include patients who were treated with NET [6, 7].

The objective of this stakeholder survey study was to determine physician attitude and treatment preference in patients with early stage estrogen positive breast cancer (ER + BC) during the initial surge of the COVID-19 pandemic in the US. Specifically, we hypothesized there would be wide variations in physician preference with using NET, use of genomic assays in this setting, and surgical management of axilla after NET. This article summarizes the key findings from a national physician survey. Such information can provide valuable gauge for oncology physicians to assess their own approach to ER + BC and provide useful insight in current state of NET which can guide future study designs.

Methods

Survey development

In April 2020, we developed the COVID-19 Breast Provider Stakeholder Engagement Survey to evaluate COVID-19 pandemic-related breast cancer treatment delays in early stage ER + BC patients (Supplementary File). We followed a multi-step survey development process [8, 9], including literature review and interviews with subject-matter experts for conceptualization of construct and item generation, expert validation, and cognitive pretesting.

Using this survey development process, we identified three key domains to include in the survey: use of NET, management of sentinel lymph nodes (SLN) after NET, and management of radiation therapy after NET. To assess knowledge, we developed a clinical scenario based on previous publication testing for provider propensity for completion axillary lymph node dissection [10]. Participants were asked how likely they are to recommend omission of completion axillary lymph node dissection (ALND) in the following clinical scenario: "48-year-old woman with clinically node-negative cancer with a 1.5-cm, palpable, grade 3, infiltrating ductal carcinoma, estrogen receptor (ER) positive, progesterone receptor (PR) positive, and HER2 negative, undergoing lumpectomy and sentinel lymph node biopsy (SLNB). Pathology shows one SLN with micrometastasis and no extranodal extension. Prior to surgery, she was treated with tamoxifen due to COVID-19 pandemic."

We also sought to measure self-efficacy (i.e., perceived personal capability at performing a certain task [11, 12]) around management of the axilla via questions on a five-point, Likert-type response scale: 1 = not at all confident, 2 = slightly confident, 3 = moderately confident, 4 = quite confident, 5 = extremely confident.

After refining the items, cognitive pretesting was performed with seven breast cancer providers. They were asked to restate each item in their own words to ensure the respondent interpretation was as it was intended. They were specifically asked if any items were missing, redundant, or should be excluded from the survey. One item—a clinical scenario on accelerated partial breast irradiation—was added into the survey after cognitive pretesting. The survey was refined based on user pre-testing, with 24-items included in the final version. Demographic information collected included region of practice, years of practice, and percent of practice devoted to breast cancer.

Survey participants

The study was considered exempt from institutional IRB (2020E0405). Breast medical, surgical, and radiation oncologists practicing in the United States were invited to complete the survey. We administered the survey electronically (Qualtrics.com, Seattle, WA) from May 8–June 12, 2020. We sought to gain participation from physicians whose practice was primarily focused in breast oncology. The survey was distributed electronically to the members

of the Southwest Oncology Group (SWOG) Clinical Trial Network breast cancer working group ($N=238$) and Alliance for Clinical Trials in Oncology breast committee ($N=318$). Additional participation was solicited through social media posting, snowball, and chain referral sampling by asking participants to forward the survey link onto others who met the inclusion criteria [13].

Statistical analysis

We estimated the regional impact of the pandemic by comparing the state-wide total COVID-19 cases posted on the Center for Disease Control (CDC) COVID Data Tracker website (https://www.cdc.gov/covid-data-tracker/). We used the total COVID-19 per state recorded by CDC on May 9th, 2020 for purposes of analysis. Simple description and comparison of means were analyzed utilizing the data collected from the participants. In the clinical case scenarios, propensity for completion axillary lymph node dissection was analyzed comparing the provider characteristics including age, years in practice, percent of practice in breast cancer patients, hospital setting, and geographic location of practice. Categorical parameters were analyzed by Fisher's exact test. Propensity for ALND stratified by provider characteristics and demographics were analyzed using Fisher's exact test or Chi-square test. To compare practice pattern differences with regards to NET use, student's t test was used to compare the group differences, and ANOVA was employed for the comparisons of more than two groups. All analyses were conducted using STATA15 (StataCorp, College Station, TX). Statistical significance was defined as $p<0.05$.

Result

Participant characteristics

One hundred and fourteen providers (30/318 [9.4%] from Alliance, 35/238 [14.7%] from SWOG, and 49 from chain referral) from 29 US states completed the survey (Table 1, Supplemental Table 1). There were 42 (37%) medical oncologists (MO), 14 (12%) radiation oncologists (RO), and 58 (51%) surgical oncologists (SO). The majority (64%) dedicated ≥ 75% of their practice to breast oncology and 70% participated in multidisciplinary tumor board ≥ 75% of the time (Table 1). The respondents represented all types of Commission on Cancer programs and 42% of participants practiced at NCI designated comprehensive cancer centers. The majority of respondents practiced in a large urban or urban city setting (43% and 29%).

Table 1 Demographic of survey respondents

	Total (*N*, %)
Specialty	
Medical oncology	42 (37%)
Radiation oncology	14 (12%)
Surgery	58 (51%)
Participant source	
Alliance	30 (26%)
SWOG	35 (31%)
Chain referral	49 (43%)
Sex	
Female	68 (60%)
Male	27 (24%)
Not specified	19 (17%)
Percent of practice in breast	
< 15%	0
16–49%	7 (6%)
50–74%	16 (14%)
≥ 75%	73 (64%)
Not specified	18 (16%)
Age (year range)	
25–34	4 (2.8%)
35–44	43 (29.7%)
45–54	22 (15.2%)
55–64	16 (11.0%)
65–74	7 (4.8%)
75–84	2 (1.4%)
Missing	51 (35.2%)
Years in practice (average, SD)	14.3 ± 11.3
Practice setting	
Academic comprehensive cancer program	22 (19%)
Community cancer program	3 (3%)
Comprehensive community cancer program	14 (12%)
Free standing cancer center program (nonhospital-based)	2 (2%)
Hospital associate cancer program	3 (3%)
NCI designated comprehensive cancer center	48 (42%)
None of the above	2 (2%)
Not specified	20 (18%)
Geographic setting	
Rural (< 50,000)	2 (2%)
Small city (> 50,000 and < 1,50,000)	10 (9%)
Urban city (> 1,50,000 and < 10,00,000)	33 (29%)
Large urban city population (> 10,00,000)	49 (43%)
Not specified	20 (18%)
Multidisciplinary tumor board participation	
≤ 10%	1 (1%)
11–50%	4 (4%)
51–75%	9 (8%)
> 75%	80 (70%)
Not specified	20 (20%)

Use of NET

Prior to COVID-19, most respondents 'rarely' ($N=49/107$, 46%) or 'sometimes' ($N=36$, 33%) used NET for early stage ER + BC. Few respondents used NET prior to COVID-19 'often' ($N=13$, 12%), 'only in the context of a clinical trial' ($N=7$, 6.5%), or 'never' ($N=2$, 1.9%). Because of COVID-19, nearly half (46%) of the providers were willing to delay surgery up to 2 months and a smaller proportion (21%) for up to 3 months without use of NET (Table 2). Only 9% of respondents did not need to change their practice due to the pandemic. Most (66%) changed their practice based

Table 2 Use of NET during COVID-19 pandemic in early stage breast cancer

	Total (*N*, %)	Med onc	Rad onc	Surgeon
How long are you willing to delay surgery (without use of endocrine therapy)?				
Up to 1 month	25 (23%)	10 (24%)	0	15 (26%)
Up to 2 months	51 (46%)	17 (40%)	7 (64%)	27 (47%)
Up to 3 months	23 (21%)	9 (21%)	2 (18%)	12 (21%)
Up to 4 months	3 (3%)	2 (5%)	1 (9%)	0
Up to 6 months	8 (7%)	4 (10%)	1 (9%)	3 (5%)
Have you changed your practice during the current pandemic?				
Yes—institution mandated change to delay surgery	8 (25%)	4 (36%)	0	4 (29%)
Yes—based on multidisciplinary team discussion (no explicit institutional mandate to delay cancer surgery)	21 (66%)	6 (55%)	7 (100%)	8 (57%)
No—was not allowed by institution to change	0	0	0	0
No—was not necessary	3 (9%)	1 (9%)	0	2 (14%)
If using endocrine therapy before surgery, which regimen are you using?*				
Tamoxifen for all patients	0	0	0	0
Tamoxifen for premenopausal patients; aromatase inhibitor for postmenopausal patients	77 (81%)	26 (63%)	0	51 (94%)
Ovarian suppression with aromatase inhibitor for premenopausal patients; aromatase inhibitor for postmenopausal patients	18 (19%)	15 (37%)	0	3 (6%)
How are you staging the axilla prior to starting endocrine therapy?				
Exam only	28 (26%)	8 (19%)	2 (17%)	18 (33%)
Exam + US	77 (71%)	30 (71%)	10 (83%)	37 (67%)
Exam + US + cross sectional image (CT scan and/or breast MRI)	4 (4%)	4 (10%)	0 (0%)	0 (0%)
SLNB	0	0	0	0
If using endocrine therapy first (before surgery), are you*				
Sending genomic assay on biopsy specimen on all patients	28 (26%)	18 (44%)	1 (8%)	9 (16%)
Sending genomic assay on biopsy specimen on only select patients (ie. high grade, size on imaging/exam, high Ki-67)	51 (48%)	19 (46%)	8 (67%)	24 (44%)
Not sending genomic assay. Using PEPI score instead	4 (4%)	1 (2%)	1 (8%)	2 (4%)
Not sending genomic assay. Using Magee Equations for Estimating Oncotype DX Recurrence Score instead	2 (2%)	0	0	2 (4%)
None of above	21 (20%)	3 (7%)	2 (17%)	18 (33%)
If using endocrine therapy first, what duration do you plan to use it for the average patient?*				
Minimum 1 year for all patients	0	0	0	0
Minimum 6 months for all patients	7 (6%)	4 (10%)	0 (0%)	3 (5%)
Minimum 3 months for all patients	19 (18%)	7 (17%)	1 (8%)	11 (20%)
As short as possible (less than 3 months), until it is safe to proceed with surgery in light of COVID-19 situation	57 (53%)	14 (34%)	9 (75%)	34 (62%)
Duration of therapy depends on patient's risk of cancer progression (ie. tumor grade, percent hormone positivity)	25 (23%)	16 (39%)	2 (17%)	7 (13%)
If using endocrine therapy before surgery, do you plan to re-image the breast prior to surgery?*				
Yes, re-image all patients	27 (25%)	14 (34%)	1 (8%)	12 (22%)
No	8 (7%)	0 (0%)	2 (17%)	6 (11%)
Case by case basis	72 (67%)	27 (66%)	9 (75%)	36 (67%)

*$p<0.05$

on a multidisciplinary team based discussion and only 25% had institutional mandated changes to delay surgery in early stage ER + BC (Table 2). Most providers would perform a genomic assay on the biopsy specimen on all or selected patients prior to NET initiation, more frequently by MO compared to RO and SO (90% vs. 75% and 60%, $p < 0.05$). The most preferred regimen was tamoxifen (without ovarian suppression) for premenopausal patients and an aromatase inhibitor for postmenopausal patients. MO were more likely to recommend ovarian suppression with aromatase inhibitor for premenopausal women than SO (15/41 [37%] MO vs 3/54 [6%] SO, $P < 0.05$).

Most planned to use NET for as little time as possible until surgery could proceed (Table 3). Planned duration of therapy varied by provider specialty type—60% who planned to use NET as little time as possible were surgeons while 64% who planned to vary therapy depending on patient's risk were medical oncologists. Providers planning as short of duration of NET as possible tended to be from states with higher COVID-19 cases (average 74,451 cases) in May 2020 than those who planned minimum of 3 months (37,877 COVID-19 cases) or 6 months (28,636 COVID-19 cases) of NET, although this did not reach statistical significance ($p = 0.38$). The majority (85%) of those who planned to use NET for a minimum of 6 months had reported using NET prior to COVID-19 "sometimes" compared to only 25% who planned to use NET for as short as possible, although this did not reach statistical significance ($p = 0.085$). There was no significant difference in planned duration for NET by provider characteristics such as years in practice, percent effort of practice in breast, region of US, practice setting or geographic setting.

Management of axilla after NET

In a clinical scenario wherein the patient would typically be considered eligible for omission of completion ALND based on ACOSOG Z0011 [6], most providers recommended omitting ALND after 1, 2, or 3 months of NET (1 month, $N = 56/93$, 60%; 2 months, $N = 54/92$, 59%; 3 months, $N = 48/90$, 53%) (Fig. 1). With longer duration of therapy, the propensity for omitting ALND decreased (definitely omit after 6 months, $N = 25/91$, 27%; probably omit after 6 months, $N = 38/91$, 42%; definitely omit after 1 year, $N = 26/92$, 28%; probably omit after 1 year, $N = 29/92$, 32%). Omitting ALND was not associated with provider's years in practice, practice type or setting, participation in multidisciplinary tumor board, or number of COVID-19 cases in the provider's practicing state. Providers' percent of practice dedicated to BC, was significantly associated with extent of axillary surgery with 6 months of NET ($p = 0.02$) but this trend was not statistically significant with 1 year of NET ($p = 0.073$). After 6 months of NET, providers with a greater percentage of their practice dedicated to BC indicated an increased likelihood of completion ALND ($p = 0.039$) but this trend was not statistically significant with 1 year of NET ($p = 0.115$). With regards to management of patient's SLN after NET, physicians felt moderately confident (mean Likert score 3.58, range 1–5).

Discussion

This is the first study, to our knowledge, evaluating clinician perspective on NET use for early stage ER + BC during the COVID-19 pandemic. With the global spread of the novel SARS-CoV-2 virus and the resulting COVID-19 disease, oncologists worldwide had to weigh the risks of COVID-19 against safely providing timely breast cancer treatment [14–17]. Furthermore, in the United States, due to the need for preservation of personal protective equipment, hospital beds, and ventilators, many professional societies have recommended delaying non-urgent surgery including cancer surgery or altering it to best preserve scarce resources [1, 2, 18]. Consistent with the international trends and medical society recommendations, in this survey of US clinicians, we found that most clinicians changed their management views of early stage ER + BC during the COVID-19 pandemic by utilizing NET as initial treatment. Most planned to use NET for as short as possible until surgery could proceed. As duration of NET extended, more clinicians favored ALND when low volume axillary metastatic disease was found at surgery. This study highlights important gaps between clinician approach to NET and clinical trial data.

While the COVID-19 pandemic is unprecedented in modern times, some parallels can be drawn from the impact of natural disasters (e.g., hurricanes, earthquakes, tsunamis, flooding, and tornadoes) on cancer care delivery [19–21]. In a systematic review, common issues affecting cancer care after a natural disaster were infrastructure damage, workforce management, loss of medical records and tissue samples, need for evacuation of patients and staff, disruption to communication services, and lack of medications [20]. While the COVID-19 pandemic did not impact the physical integrity of healthcare facilities, many hospitals were stretched to maximum capacity, experiencing limitations in physical resources alongside a stressed healthcare workforce. Past studies on natural disasters have demonstrated delays in cancer treatments, in particular related to delays in patients seeking care after onset of noticeable symptoms [20]. However, change in management to a less 'popular' treatment regimen based on stress of the medical system has not been described previously. Furthermore, unlike natural disasters wherein a single major catastrophic event occurs in a short time frame, the current pandemic is lingering on with recurrent surges globally.

Table 3 Planned duration of NET for early stage, node negative, ER + BC

	Minimum 6 months	Minimum 3 months	As short as possible (less than 3 months), until safe to proceed with surgery	Duration depends on patient's risk of cancer progression	*p*-value
	N = 7	*N* = 19	*N* = 57	*N* = 25	
Have you changed your practice during the current COVID-19 pandemic?					0.369
Yes—institution mandated change to delay surgery	0 (0%)	0 (0%)	6 (29%)	2 (22%)	
Yes—based on multidisciplinary team discussion (no explicit institutional mandate to delay cancer surgery)	0 (0%)	1 (100%)	14 (67%)	6 (67%)	
No—was not necessary	1 (100%)	0 (0%)	1 (5%)	1 (11%)	
Multidisciplinary tumor board participation (% attendance)					0.059
≤ 10%	0 (0%)	1 (6%)	0 (0%)	0 (0%)	
11–50%	0 (0%)	1 (6%)	2 (4%)	1 (5%)	
51–75%	1 (14%)	2 (12%)	1 (2%)	5 (23%)	
> 75%	6 (86%)	13 (76%)	45 (94%)	16 (73%)	
Years in practice (average)	16.143 ± (13.409)	16.647 ± (9.650)	12.694 ± (11.439)	15.636 ± (11.721)	0.535
Percent of practice in breast					0.291
16–49%	0 (0%)	0 (0%)	4 (8%)	3 (14%)	
50–74%	2 (29%)	2 (12%)	6 (12%)	6 (27%)	
≥ 75%	5 (71%)	15 (88%)	40 (80%)	13 (59%)	
NET use prior to COVID-19 pandemic					0.085
Often	1 (14%)	5 (26%)	5 (10%)	2 (8%)	
Sometimes	6 (86%)	7 (37%)	13 (25%)	8 (33%)	
Rarely	0 (0%)	6 (32%)	27 (52%)	13 (54%)	
Only in clinical trials	0 (0%)	1 (5%)	5 (10%)	1 (4%)	
Never	0 (0%)	0 (0%)	2 (4%)	0 (0%)	
How long willing to delay surgery without use of endocrine therapy					0.727
Up to 1 month	1 (14%)	5 (26%)	12 (21%)	7 (28%)	
Up to 2 months	5 (71%)	7 (37%)	27 (48%)	10 (40%)	
Up to 3 months	1 (14%)	3 (16%)	13 (23%)	5 (20%)	
Up to 4 months	0 (0%)	2 (11%)	0 (0%)	1 (4%)	
Up to 6 months	0 (0%)	2 (11%)	4 (7%)	2 (8%)	
Region					0.802
Northeast	0 (0%)	3 (18%)	10 (21%)	4 (18%)	
Midwest	3 (43%)	5 (29%)	17 (35%)	8 (36%)	
South	0 (0%)	5 (29%)	8 (17%)	4 (18%)	
West	4 (57%)	4 (24%)	13 (27%)	6 (27%)	
COVID-19 cases (average)	28,636.571 ± 26154.048)	37,877.353 ± 23,555.512)	74,451.042 ± 1.08e + 05)	58,951.364 ± 89,852.554)	0.384
Practice Setting					0.383
NCI designated comprehensive cancer center	3 (43%)	8 (47%)	22 (46%)	15 (68%)	
Academic comprehensive cancer program	1 (14%)	6 (35%)	13 (27%)	2 (9%)	

Table 3 (continued)

	Minimum 6 months	Minimum 3 months	As short as possible (less than 3 months), until safe to proceed with surgery	Duration depends on patient's risk of cancer progression	*p*-value
	N = 7	*N* = 19	*N* = 57	*N* = 25	
Comprehensive community cancer program	1 (14%)	3 (18%)	8 (17%)	2 (9%)	
Free standing cancer center program (nonhospital-based)	1 (14%)	0 (0%)	1 (2%)	0 (0%)	
Hospital associate cancer program	0 (0%)	0 (0%)	2 (4%)	1 (5%)	
Community cancer program	0 (0%)	0 (0%)	1 (2%)	2 (9%)	
None of above	1 (14%)	0 (0%)	1 (2%)	0 (0%)	
Geographic practice setting					0.892
Large urban city	4 (57%)	9 (53%)	22 (46%)	14 (64%)	
Urban city	2 (29%)	6 (35%)	19 (40%)	6 (27%)	
Small city	1 (14%)	2 (12%)	6 (13%)	1 (5%)	
Rural	0 (0%)	0 (0%)	1 (2%)	1 (5%)	
Specialty					0.027
Medical oncology	4 (57%)	7 (37%)	14 (25%)	16 (64%)	
Radiation oncology	0 (0%)	1 (5%)	9 (16%)	2 (8%)	
Surgery	3 (43%)	11 (58%)	34 (60%)	7 (28%)	

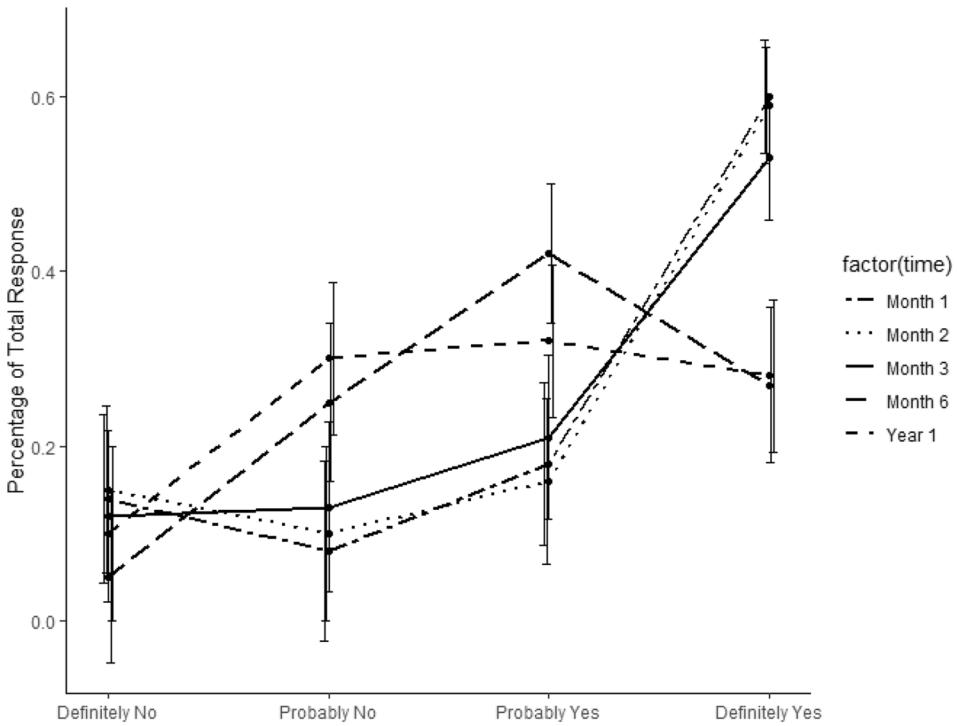

Fig. 1 Omission of ALND after varying NET duration in clinical scenario of patient with one micrometastasis in sentinel lymph node

Historically, endocrine therapy for early stage breast cancer has been recommended for patients who were deemed unfit for surgery at time of diagnosis [4]. In the United States, despite evidence from clinical trials such as P024 [22], IMPACT [23], and PROACT [24] supporting the use of NET for ER positive BC in postmenopausal

women, neoadjuvant chemotherapy was more commonly recommended for systematic therapy [4]. According to a National Cancer Database (NCDB) analysis study from 2012 to 2015, NET was used in only 2.3% of ER + BC compared to 12% who received neoadjuvant chemotherapy [25]. The American College of Surgeons Oncology Group (ACOSOG) Z1031 trial aimed to better select postmenopausal ER + BC patients for NET by randomizing patients to 16–18 weeks of exemestane, letrozole, or anastrazole [26]. Despite the ACOSOG Z1031 trial demonstrating favorable clinical response rates to NET and increased breast conservation surgery rates in those who were initially deemed mastectomy-only candidates, the use of NET overall has remained low in the United States, around 3% [3]. This trend is observed in our survey as 46% of clinicians reported they rarely used NET for ER + BC prior to the pandemic. While the interest in the use of NET may be driven by pandemic-related constraints, the shift presents an important opportunity to re-evaluate the current 'surgery first' treatment paradigm in ER + BC.

In our study we found that most physicians planned to use NET for as short as possible, despite evidence that therapeutic effect requires at least 3 months of administration. Although the use of ovarian suppression has not been tested in the neoadjuvant setting, 37% of medical oncologists stated that they would use ovarian suppression with aromatase inhibitor for premenopausal women. In order to address the uncertainties around use of NET in early stage ER + BC, Dowsett et al. subsequently published an international consortium expert opinion on NET [5]. In this article, Dowsett et al. suggest using estrogen and progesterone receptor positivity and Ki-67 (when available) in postmenopausal patients with ER +, HER2 negative BC to stratify them into three groups—NET, surgery, or neoadjuvant chemotherapy. The majority of patients with high ER and PR positivity could safely be controlled on NET [5]. Similarly, the ALTERNATE trial triaged postmenopausal patients with ER + BC by Ki-67 into chemotherapy or anastrazole ± fulvestrant and found only 2% of patients on NET had progression of disease on NET [27]. This study was presented at the most recent 2020 American Society of Clinical Oncology (ASCO) meeting, right at the cusp of when this present survey was administered [27]. We did not explicitly test the participants their knowledge on ALTERNATE trial data. However, medical oncologists were more likely than other physicians to vary the length of NET treatment based on patient and tumor characteristics, suggesting a shift in their practice for postmenopausal patients for good in some settings.

Our findings also indicate differences in acceptance of omission of ALND among clinicians based on duration of NET. The ACOSOG Z0011 10-year outcome data confirmed no significant difference in recurrence rates or survival after breast conservation based on omission of ALND in SLN positive disease [7, 28]. However, ACOSOG Z0011 did not explicitly include patients who were treated with NET. In a recent NCDB analysis of patients who underwent NET, 5 year overall survival did not differ between those who underwent SLNB versus ALND [29]. This held true when stratified by nodal status, suggesting that residual low volume of axillary disease after NET may not affect survival outcomes [29, 30]. In the present survey, we found that with longer duration of NET, more clinicians recommended completion ALND for low volume axillary disease. This finding presents an interesting predicament wherein for the same clinical scenario of low volume axillary disease with shorter duration of NET, clinicians recommended omission of ALND but as duration of NET increased to greater than 6 months ALND was strongly recommended. As the emphasis on omission of chemotherapy increases and more studies investigate the use of NET in ER + BC, the surgical management of the axilla in patients with low volume axillary disease treated with NET warrants further investigation and discussion.

At the time of the survey distribution, the SWOG 1007, the Treatment (Rx) for Positive Node, Endocrine Responsive Breast Cancer (RxPONDER) study data was yet to be presented or published [31]. Similar to TAILORx, the RxPONDER clinical trial prospectively stratified node positive ER + BC women using the 21 gene recurrence score (RS) to adjuvant chemotherapy versus endocrine therapy alone [31, 32]. These two large randomized clinical trials, TAILORx and RxPONDER, consistently demonstrated no survival benefit from adjuvant chemotherapy, and by extension, neoadjuvant use of an adjuvant regimen, in postmenopausal women with 0–3 positive lymph nodes and RS less than 26 [32, 33]. Considering the significant toxicities of chemotherapy it is hard to justify neoadjuvant chemotherapy in these patients in an attempt to clinically down stage the cancer or allow delay in surgery. There is also ample evidence from NET therapy trials that 4–6 months endocrine therapy is highly effective to clinically downstage ER + breast cancers. Based on these results we do anticipate greater use of NET and decreasing use of neoadjuvant chemotherapy in postmenopausal ER + breast cancer with RS > 26. However, it is also important to point out that there is no evidence that a brief use of NET leads to improved survival, or allow to formulate a more optimal postoperative therapy, compared to starting with surgery first.

This study is not without limitations. First, to swiftly collect survey response from a sample of breast oncology providers, we surveyed a limited national sample of providers. Despite chain referrals and utilization of major clinical trial network committees, our response rate was limited. The memberships to SWOG and Alliance breast committees are not limited to physicians and includes epidemiologists, patient advocates, biostatisticians and health services researchers. Thus the response rate is likely an

underestimation as it was calculated using the entire committee membership. Despite the response rate, there were 29 states and various geographic and practice settings represented, minimizing non-respondent bias and allowing for consideration of regional practice variations. The survey participants represented academically oriented physicians who actively participated in cooperative group clinical trials and activities and practiced in larger academic settings. Second, different oncology specialties were not equally represented in the survey—the majority of survey respondents were medical and surgical oncologists. We were not able to control for the impact of participation bias as non-participants may systematically differ in their responses. Third, the majority of participants had greater than 75% of practice in breast and the lower-volume surgeons were not equally represented. However, in a previous study, lower-volume surgeons were less likely to omit ALND in patients who met ACOSOG Z0011 criteria and thus the results of propensity for ALND will likely not change with inclusion of lower-volume surgeons [10]. Finally, we relied on clinician self-reported communication on NET use and there were no objective measures to correlate to actual clinical practice. The clinical outcome of patients treated with NET will be elucidated over time through longitudinal studies such as the Covid-19 and Cancer Consortium (CCC19) [34].

Conclusion

This study demonstrates key patterns in oncologists' preferences and attitudes regarding practice changes during the initial phase of the COVID-19 pandemic. In particular, NET use in early stage ER + BC increased during the initial phase of the pandemic but most physicians planned to use it as short of duration as possible. Interestingly, the management of the axilla after NET varied widely, indicating a need for future evaluation of locoregional management after NET. In the era of precision medicine, the management of early stage ER + BC hinges on minimizing unnecessary axillary surgery and utilizing genomic assays to guide chemotherapy decisions. With the utilization of NET during the COVID-19 pandemic, key questions are raised on use of NET in premenopausal women, use of genomic assays and axillary management. Understanding how clinicians interpret and extrapolate NET clinical trial data into real world practice can help guide the design of future clinical trials and guidelines on early stage ER + BC.

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Compliance with ethical standards

Conflict of interest The authors have no relevant financial disclosure or conflict of interest.

Ethical approval Ohio State University IRB was obtained.

Consent to participate Consent to participate in the survey was implied when participants completed the survey.

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