Endocrine Therapy Omission in Estrogen Receptor–Low (1%-10%) Early-Stage Breast Cancer

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ABSTRACT

PURPOSE Adjuvant endocrine therapy (ET) improves overall survival (OS) in estrogen receptor (ER)–positive early-stage breast cancer (BC). However, the benefit of ET for those with ER-low BC (ER 1%-10%) is unclear.

METHODS Using the National Cancer Database, we studied patients with high-risk stage I to III, ER-low BC (defined as immunohistochemistry 1%-10%) who received (neo)adjuvant chemotherapy and did or did not initiate ET. OS was analyzed with ET initiation as a time-dependent covariate using Cox proportional hazards regression.

RESULTS Of 10,362 patients with stage I to III ER-low BC, 7,018 received chemotherapy and met inclusion criteria. ET omission was 42% at 12 months and more common in patients with tumors that were progesterone receptor–negative, human epidermal growth factor receptor 2–negative, higher-grade (grade 2/3) and higher Ki-67 (≥20%; all $P < .001$) and those who received neoadjuvant chemotherapy (NAC; $P < .001$). With a median follow-up of 3 years, 586 deaths were observed. In a multivariable analysis, ET omission was associated with a higher risk of death (hazard ratio [HR], 1.23 [95% CI, 1.04 to 1.46]; $P = .02$), with a greater impact in those with higher ER levels: ER 1%-5% (HR, 1.15 [95% CI, 0.91 to 1.45]; $P = .24$) versus ER 6%-10% (HR, 1.42 [95% CI, 1.00 to 2.02]; $P = .048$). Among patients treated with NAC (n = 4,377, 62%), ET omission was associated with worse OS in those with residual disease (RD; HR, 1.26 [95% CI, 1.00 to 1.57]; $P = .046$) but not in those who achieved a pathologic complete response (HR, 1.06 [95% CI, 0.62 to 1.80]; $P = .84$).

CONCLUSION In ER-low, early-stage BC, ET omission is associated with significantly worse OS, especially in patients with RD after NAC and those with higher (6%-10%) ER levels. Until prospective data are available, patients with ER-low BC should be counseled regarding the potential benefit of ET.

ACCOMPANYING CONTENT

Appendix

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INTRODUCTION

The standard of care for patients diagnosed with estrogen receptor (ER)–positive breast cancer (BC) includes 5-10 years of adjuvant endocrine therapy (ET).[1,2] Adjuvant ET reduces BC recurrence, decreases BC mortality, and improves overall survival (OS), an effect independent of chemotherapy benefit.[1,3,4] However, adjuvant ET omission and decreased adherence to ET are associated with a higher risk of death.[5,6]

In 2010, ASCO and College of American Pathologists (CAP) reported guidelines that lowered the ER threshold for ER-positive BC from immunohistochemistry (IHC) ≥10% to ≥1% to standardize the assay and improve accuracy of ER as a predictive biomarker for endocrine sensitivity.[7] Given that ER-low tumors exhibit similar histologic characteristics and response to neoadjuvant chemotherapy (NAC) as ER-negative BC,[8,9] subsequent guidelines classified ER-low (1%-10%) BC as a separate entity from ER-positive BC.[10] However, the benefit of adjuvant ET in ER-low BC is not established.[8,9] Given this uncertainty, international guidelines have noted equipoise regarding recommending the use of ET in patients with ER-low BC,[10-12] with the Swedish Breast Cancer Group never lowering the ER cutoff[8] and several European studies suggesting returning the cutoff of ER-positive back to ER ≥10% (ie, not recommending ET in ER-low BC).[9,13] In addition, several clinical trials have chosen a pragmatic cutoff of ER ≤10% for eligibility of novel treatments for triple-negative BC (TNBC).[14-16]

Given this uncertainty, we sought to assess the frequency of ET omission and its association with OS in patients with

CONTEXT

Key Objective

To assess the effect of endocrine therapy (ET) omission in patients with estrogen receptor (ER)–low (immunohistochemistry 1%-10%) early-stage breast cancer.

Knowledge Generated

The National Cancer Database (2018-2020) identified 7,018 patients with early-stage ER-low breast cancer treated with chemotherapy. Endocrine therapy omission was common (42%) and associated with a higher risk of death compared with patients who received ET (hazard ratio [HR], 1.23 [95% CI, 1.04 to 1.46]; $P = .02$). Notably, patients with residual disease after neoadjuvant chemotherapy (HR, 1.26 [95% CI, 1.00 to 1.57]; $P = .046$) and those with higher ER levels (6%-10%; HR, 1.42 [95% CI, 1.00 to 2.02]; $P = .048$) had a higher risk of death when ET was omitted.

Relevance *(I. Cheng)*

The identification of higher mortality associated with ET omission in females with ER-low early-stage breast cancer, who received chemotherapy, highlights the importance in evaluating the potential benefit of ET for these patients.*

*Relevance section written by *JCO* Associate Editor Iona Cheng, PhD, MPH.

high-risk ER-low BC who receive chemotherapy using the National Cancer Database (NCDB).

METHODS

We performed a retrospective cohort study using the 2021 NCDB Participant User File (PUF). The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society containing deidentified clinical oncology information sourced from hospital registry data that represent >70% of newly diagnosed cancer cases in the United States, across 1,500 CoC-accredited facilities.[17] Our Institutional Review Board has deemed NCDB studies as exempt from review as all data in the NCDB are deidentified.

We queried the NCDB for BC cases from 2018 to 2020 as 2018 was the first year that ER was defined as a continuous variable with discrete percentages and ranges in deciles allowing classification of ER-positive tumors as 1%-10% or >10%. We defined ER-low as ER 1%-10%, in keeping with the definition of ER-low as recommended by the ASCO/CAP guidelines.[7] Per registry rules, the ER-percent value was abstracted from a pretreatment biopsy whenever possible and from surgical specimens only if a pretreatment measure was not available.[18] In cases where an ER range inconsistent with the CAP protocol was provided by the reporting institution, ranges spanning greater than 10 percentage points were coded as unknown and ranges spanning 10 or fewer percentage points were coded according to the lowest number in the range.[18]

Inclusion criteria were female patients with stage I to III, ER-positive BC. As patients who had been treated with chemotherapy have a higher risk of recurrence and BC-related death, we chose to focus our analysis only on patients who received NAC or adjuvant chemotherapy as these patients would have been treated like patients with TNBC. We classified NAC as chemotherapy initiated within the range of 30-365 days before definitive surgery. Similarly, patients were classified as receiving adjuvant chemotherapy if the chemotherapy initiation was after definitive surgery. The NCDB PUF included chemotherapy start time, but not chemotherapy end time. Therefore, it is unknown which patients who received NAC also received adjuvant chemotherapy. Patients who received NAC were classified as having pathologic complete response (pCR), defined as ypT0/ypTis, ypN0/ypN0i+,[19] or residual invasive disease in the breast (ypT1-4) and/or lymph nodes (ypN1-3).

Progesterone receptor (PR)–positive disease was defined as ≥1% receptor expression. Human epidermal growth factor receptor 2 (HER2) status was classified by using the summary result, which combines IHC, fluorescence in situ hybridization, and chromogenic in situ hybridization when performed.

Exclusion criteria included patients who did not receive treatment at the reporting facility or whose observation in the PUF was not the first primary cancer (tumor sequence >1), consistent with NCDB analysis recommendations,[20] stage IV breast cancer, male patients, or patients with noninvasive disease. Patients were also excluded if the receptor status, systemic treatments (chemotherapy and/or ET), or clinical outcomes were missing or unknown (Fig 1).

Endocrine therapy data provided in the NCDB PUF included two variables: (1) whether ET was administered as part of first-course therapy or not administered (eg, not planned, recommended but refused by patient, contraindicated, or

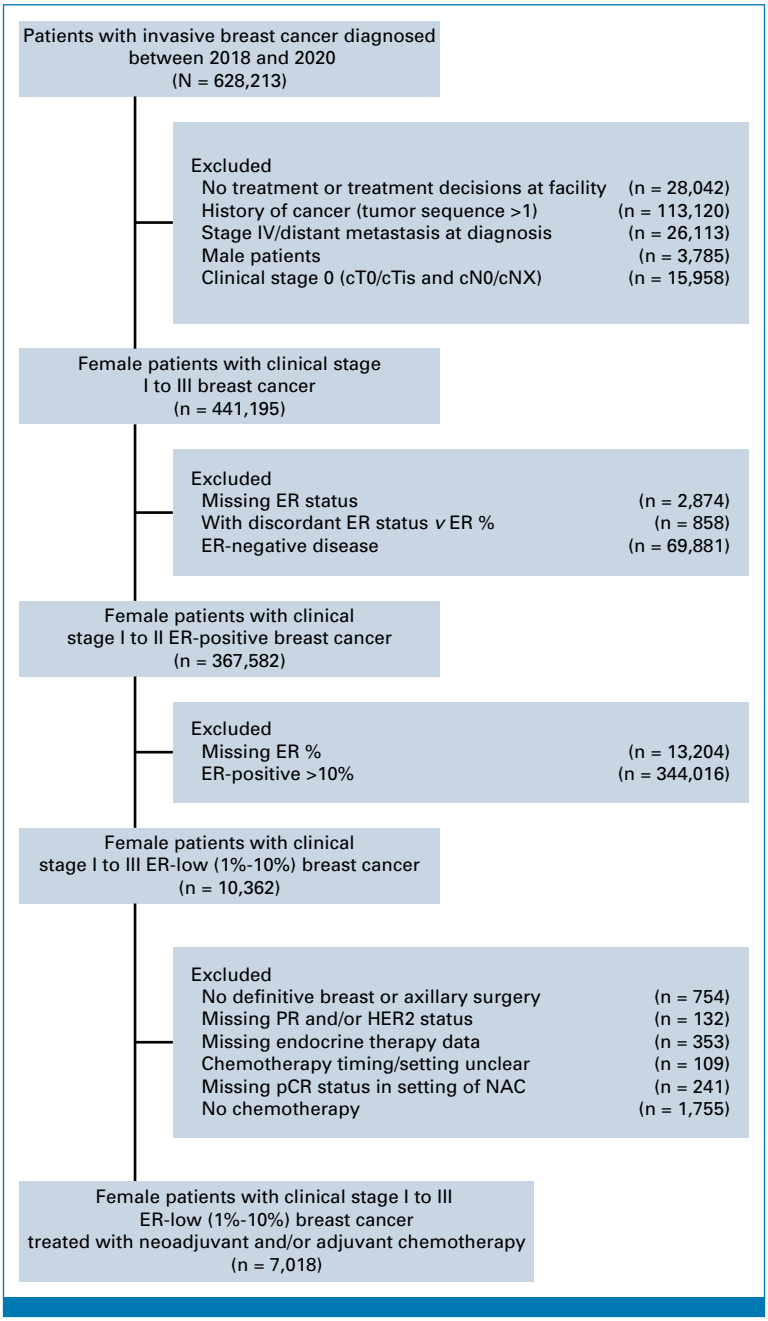

FIG 1. CONSORT diagram. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; NAC, neoadjuvant chemotherapy; pCR, pathologic complete response; PR, progesterone receptor.

recommended but not administered for other reasons) and (2) timing of ET start if appliable. Patients coded as receiving ET and with a timing of ET start (either before or after definitive surgery) were considered as having received adjuvant ET from that point onward. Systemic therapy duration, including the length of time patients were on ET, was not assessed because treatment stop times were not provided. Similarly, information regarding the specific ET agents and ET adherence was not available.

Descriptive statistics were reported using median and IQR or frequency and percentage as appropriate. The cumulative incidence of ET initiation after definitive surgery was estimated over time accounting for the competing risk of death. ET omission versus receipt at 1 year after definitive surgery was analyzed as a binary variable. Multivariable logistic regression was used to assess factors associated with receipt versus omission of ET with effects reported using odds ratios (ORs) and 95% CI.

OS was analyzed using Cox proportional hazards regression. Two approaches were used to avoid immortal time bias: (1) survival time was calculated from the date of definitive surgery rather than the date of diagnosis and (2) adjuvant ET initiation was modeled as a time-dependent covariate. Multivariable Cox proportional hazard regression was used to assess the adjusted effect of adjuvant ET omission. Adjustment variables were chosen to include all clinically relevant variables available in the NCDB without use of any variable selection procedures. To estimate the effect of adjuvant ET omission versus receipt for specific subgroups of interest in exploratory analyses, interaction terms were included in the model to derive subgroup-specific hazard ratio estimates. For descriptive purposes, unadjusted OS estimates were calculated using the method described by Simon and Makuch[21] to use adjuvant ET start time as a time-dependent covariate and plotted in a manner similar to Kaplan-Meier curves.

Analysis was performed using SAS (Version 9.4, SAS Institute Inc, Cary, NC) and R software (version 3.3.1)[22] including the cmprsk[23] and survival[24] packages. *P* values < .05 were considered statistically significant. Additional details are provided in Appendix 1 (online only).

RESULTS

A total 367,582 female patients with ER-positive stage I to III BC who had surgical resection were identified. Most of these tumors were ER >10% (344,016 [94%]), and an additional 13,204 (4%) were excluded because of unknown ER levels, leaving 10,362 (3%) with ER-low BC. In the ER-low cohort that met inclusion criteria, 7,018 received chemotherapy (62% NAC, 38% adjuvant chemotherapy) forming our primary analysis cohort (Fig 1). The percent of patients receiving NAC versus adjuvant chemotherapy increased significantly over the study period: 2018: 59%, 2019: 61%, and 2020: 68% (*P* < .001). Among patients treated with NAC, 49% achieved pCR, with the rate remaining stable during the study period (2018: 50%, 2019: 48%, 2020: 50%; *P* = .87).

The median age was 55 years, and most were White (73%). The tumors were PR-negative (73%), HER2-negative (65%), grade 3 (74%), and invasive ductal histology (92%). Grade, HER2, PR, and Ki67 were variables significantly associated with ET omission (Table 1). Menopausal status is not available in the NCDB; however, 34% were younger than 50 years and 66% were 50 years and older at diagnosis, and age category was not significantly associated with initiation of ET.

The cumulative incidence of ET initiation increased during the period 12 months after definitive surgery and then stabilized: 6 months: 39%, 12 months: 58%, and 18 months: 59% (Appendix Fig A1). Thus, 1 year was chosen as a clinically meaningful time point with an estimated rate of ET omission of 42% (95% CI, 41% to 44%). In a multivariable logistic regression analysis, ET omission was more common among patients with tumors that were PR− versus PR+ (OR, 1.81 [95% CI, 1.61 to 2.04]; *P* < .001), HER2− versus HER2+ (OR, 1.23 [95% CI, 1.10 to 1.37]; *P* < .001), Ki67 ≥20% (OR, 1.33 [95% CI, 1.06 to 1.68]; *P* < .001), grade 2 (OR, 1.53 [95% CI, 1.05 to 2.25]; *P* = .03), and grade 3 (OR, 1.82 [95% CI, 1.25 to 2.64]; *P* = .002), each versus grade 1 (Fig 2). Lower clinical T-category was not associated with ET omission, but patients with cN0 were more likely to omit ET (OR, 1.18 [95% CI, 1.05 to 1.34]; *P* = .007) as were patients who received NAC, regardless of response. Among patients treated with NAC, those with residual disease (RD) were more likely than patients with pCR to omit ET (adjusted OR, 1.24 [95% CI, 1.09 to 1.41]; *P* = .001). Patients diagnosed in 2020 were also significantly more likely to omit ET compared with patients diagnosed in 2018 (OR, 1.28 [95% CI, 1.13 to 1.45]; *P* < .001). Age, race, and ethnicity were not associated with ET omission.

The median follow-up was 3 years, and 586 deaths were observed. The 3-year OS for patients who omitted ET was 89.1% (95% CI, 87.8% to 90.5%) versus 92.3% (95% CI, 91.3% to 93.3%; Fig 3A). When controlling for age, comorbidity score, year of diagnosis, PR, HER2, clinical and pathologic stage, grade, and Ki67, the omission of ET was associated with worse OS (HR, 1.23 [95% CI, 1.04 to 1.46]; *P* = .02; Appendix Table A1). We assessed potential interactions between ET omission and age category and HER2 status with respect to the outcome of OS. Age (<50 *v* 50+ years, *P* = .60) and HER2 status (*P* = .86) had no significant interaction, and therefore, these interactions were not included in the final model.

Given that the assessment of OS was performed during COVID-19 pandemic, we performed two sensitivity analyses: (1) only patients who survived until the landmark of 12 months after definitive surgery and (2) only cases diagnosed between 2018 and 2019. The adjusted effect of ET omission on OS was maintained with HR 1.23 (95% CI, 1.01 to 1.51; *P* = .04) and HR 1.22 (95% CI, 1.00 to 1.47; *P* = .047), respectively.

We further performed exploratory analyses to identify subsets of patients who are most likely to be affected by ET omission (Table 2, Fig 3B). In patients treated with adjuvant chemotherapy, ET omission was not significantly associated with OS. Similarly, in those treated with NAC who experienced pCR, we observed no significant association between ET omission and OS (HR, 1.06 [95% CI, 0.62 to 1.80]; *P* = .84). By contrast, in those with RD after NAC, ET omission was significantly associated with worse OS (HR, 1.26 [95% CI, 1.00 to 1.57]; *P* = .046).

Evaluating ER levels, there was a nonuniform distribution of ER, clustering about 5% and 10%, with 1,512 (22%) only reporting a range (1%-10%; Appendix Table A2). Discrete ER percentage was available in 5,506 (78%) including ER 1%-5% (3,951; 72%) and ER 6%-10% (1,555; 28%). In this subgroup, ET omission was associated with worse OS in

TABLE 1. Characteristics of Patients With ER-Low Breast Cancer Based on Adjuvant ET Initiation Versus Omission 12 months After Definitive Surgery

Baseline Characteristic	Total (n = 7,018[a])	Adjuvant ET Not Initiated by 12 Months After Surgery (n = 2,723)	Adjuvant ET Initiated by 12 Months After Surgery (n = 3,774)	*P*
Age at diagnosis, years				.91
Median (IQR)	55 (46-64)	55 (45-64)	55 (46-64)	
Age category, years, No. (%)				.89
<50	2,389 (34.0)	930 (34.2)	1,295 (34.3)	
≥50	4,629 (66.0)	1,793 (65.8)	2,479 (65.7)	
Race, No. (%)				.36
White	5,066 (72.9)	1,950 (72.4)	2,748 (73.4)	
Black	1,312 (18.9)	530 (19.7)	675 (18.0)	
Asian	412 (5.9)	153 (5.7)	229 (6.1)	
Other	161 (2.3)	60 (2.2)	90 (2.4)	
Missing	67	30	32	
Ethnicity, No. (%)				.54
Not Spanish/Hispanic	6,214 (90.1)	2,424 (90.5)	3,334 (90.1)	
Spanish/Hispanic	679 (9.9)	253 (9.5)	367 (9.9)	
Missing	125	46	73	
Charlson-Deyo comorbidity score, No. (%)				.49
0	5,914 (84.3)	2,314 (85.0)	3,176 (84.2)	
1	836 (11.9)	308 (11.3)	463 (12.3)	
2+	268 (3.8)	101 (3.7)	135 (3.6)	
Primary payor, No. (%)				.61
Not insured	166 (2.4)	69 (2.6)	80 (2.1)	
Private insurance	4,223 (60.7)	1,639 (60.7)	2,308 (61.7)	
Medicaid	762 (11.0)	291 (10.8)	394 (10.5)	
Medicare	1,707 (24.5)	672 (24.9)	904 (24.2)	
Other government	96 (1.4)	31 (1.1)	53 (1.4)	
Missing	64	21	35	
Histology, No. (%)				.23
IDC	6,483 (92.4)	2,509 (92.1)	3,498 (92.7)	
ILC	187 (2.7)	67 (2.5)	109 (2.9)	
IMC	61 (0.9)	24 (0.9)	29 (0.8)	
Other	287 (4.1)	123 (4.5)	138 (3.7)	
Clinical T category, No. (%)				.41
cT0/Tis	24 (0.4)	11 (0.4)	12 (0.3)	
cT1	2,549 (37.4)	987 (37.2)	1,420 (39.0)	
cT2	3,165 (46.5)	1,251 (47.1)	1,661 (45.6)	
cT3	768 (11.3)	286 (10.8)	405 (11.1)	
cT4	303 (4.4)	120 (4.5)	142 (3.9)	
Missing	209	68	134	
Clinical N status, No. (%)				.88
cN0	4,401 (64.2)	1,744 (65.2)	2,382 (65.0)	
cN+	2,452 (35.8)	932 (34.8)	1,283 (35.0)	
Missing	165	47	109	
Grade, No. (%)				<.001
1	162 (2.3)	41 (1.5)	113 (3.0)	
2	1,605 (23.2)	560 (20.9)	957 (25.7)	
3	5,147 (74.4)	2,075 (77.5)	2,656 (71.3)	
Missing	104	47	48	

(continued on following page)

TABLE 1. Characteristics of Patients With ER-Low Breast Cancer Based on Adjuvant ET Initiation Versus Omission 12 months After Definitive Surgery (continued)

Baseline Characteristic	Total (n = 7,018[a])	Adjuvant ET Not Initiated by 12 Months After Surgery (n = 2,723)	Adjuvant ET Initiated by 12 Months After Surgery (n = 3,774)	*P*
PR status, No. (%)				<.001
Negative	5,123 (73.0)	2,178 (80.0)	2,565 (68.0)	
Positive	1,895 (27.0)	545 (20.0)	1,209 (32.0)	
HER2 status, No. (%)				<.001
Negative	4,581 (65.3)	1,852 (68.0)	2,356 (62.4)	
Positive	2,437 (34.7)	871 (32.0)	1,418 (37.6)	
Ki67, No. (%)				<.001
<20%	429 (12.4)	137 (9.9)	263 (14.7)	
≥20%	3,023 (87.6)	1,249 (90.1)	1,523 (85.3)	
Missing	3,566	1,337	1,988	
Breast operation, No. (%)				.91
BCS	3,535 (50.4)	1,397 (51.3)	1,931 (51.2)	
Mastectomy	3,483 (49.6)	1,326 (48.7)	1,843 (48.8)	
Chemotherapy group, No. (%)				<.001
NAC with pCR	2,165 (30.8)	854 (31.4)	1,154 (30.6)	
NAC with RD	2,212 (31.5)	938 (34.4)	1,011 (26.8)	
Adjuvant chemotherapy	2,641 (37.6)	931 (34.2)	1,609 (42.6)	

Abbreviations: BCS, breast conserving surgery; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; IMC, invasive mammary carcinoma; NAC, neoadjuvant chemotherapy; pCR, pathologic complete response; PR, progesterone receptor; RD, residual disease.

[a]n = 521 patients included in the study and summarized in the column of n = 7,018 are not included in the subsequent two columns because they either died or were lost to follow-up before reaching 12 months after definitive surgery and thus were excluded from the analysis comparing characteristics of patients initiating adjuvant ET within 12 months versus not initiating adjuvant ET.

those with tumors expressing ER 6%-10% (HR, 1.42 [95% CI, 1.00 to 2.02]; *P* = .048) but not ER 1%-5% (HR, 1.15 [95% CI, 0.91 to 1.45]; *P* = .24; Table 3).

DISCUSSION

Adjuvant ET has contributed substantially to the large declines in BC mortality observed in the United States and United Kingdom.[3,4] Despite this large benefit, there remains controversy regarding the benefit of ET in ER-low disease, with no modern randomized prospective trials examining the role of ET in ER-low BC. Given these limitations, we sought to evaluate the association of ET omission with OS in patients with documented ER-low BC treated with (neo)adjuvant chemotherapy. With a relatively short follow-up of 3 years, ET omission was associated with a 23% higher risk of death compared with patients who initiated ET, when controlling for several patient- and tumor-related factors. While ER-low BC represents only 3% of the NCDB ER-positive cohort, it is estimated that over 25,000 patients/year worldwide may be affected by these findings.

Various prospective studies have demonstrated that ER-low BC acts similar to TNBC. Biomarker analyses of ER-low tumors using the PAM50 subset of genes demonstrated that ER-low BC act most similar to the basal-like subtype of TNBC,[25] with similar pathologic features[8,26] and response rates to NAC.[9] Recently, neoadjuvant chemoimmunotherapy has demonstrated higher pCR rates in ER-low BC compared with ER >10% BC.[27,28] When examining survival, multiple studies suggest that patients with ER-low BC exhibit an intermediate prognosis, with worse OS compared with patients whose tumors express ER >10%, but better than those with TNBC.[8,29,30] These data might have contributed to the temporal shift of treatment away from adjuvant ET in ER-low BC. While the 2010 ASCO/CAP guidelines outlined recommendations for adjuvant ET according to ER status,[7] Swedish cancer guidelines did not recommend adjuvant ET for ER-low BC (defined by them as 1%-9%). A recent population-based analysis of Swedish patients with either ER 0% or ER-low (1%-9%) BC[8,31] demonstrated low rates (5.7%) of adjuvant ET use in patients with ER-low disease, with no significant differences in OS comparing ER 0% with ER-low BC. Notably, this study did not examine the impact of adjuvant ET omission in ER-low BC. By contrast, a population-based study involving 407 patients from China with ER-low BC (defined by them as 1%-10%) followed longitudinally for breast cancer–specific survival (BCSS) demonstrated a trend toward better BCSS in those who received ET versus no adjuvant ET (HR, 0.40 [95% CI, 0.14 to 1.14]).[32]

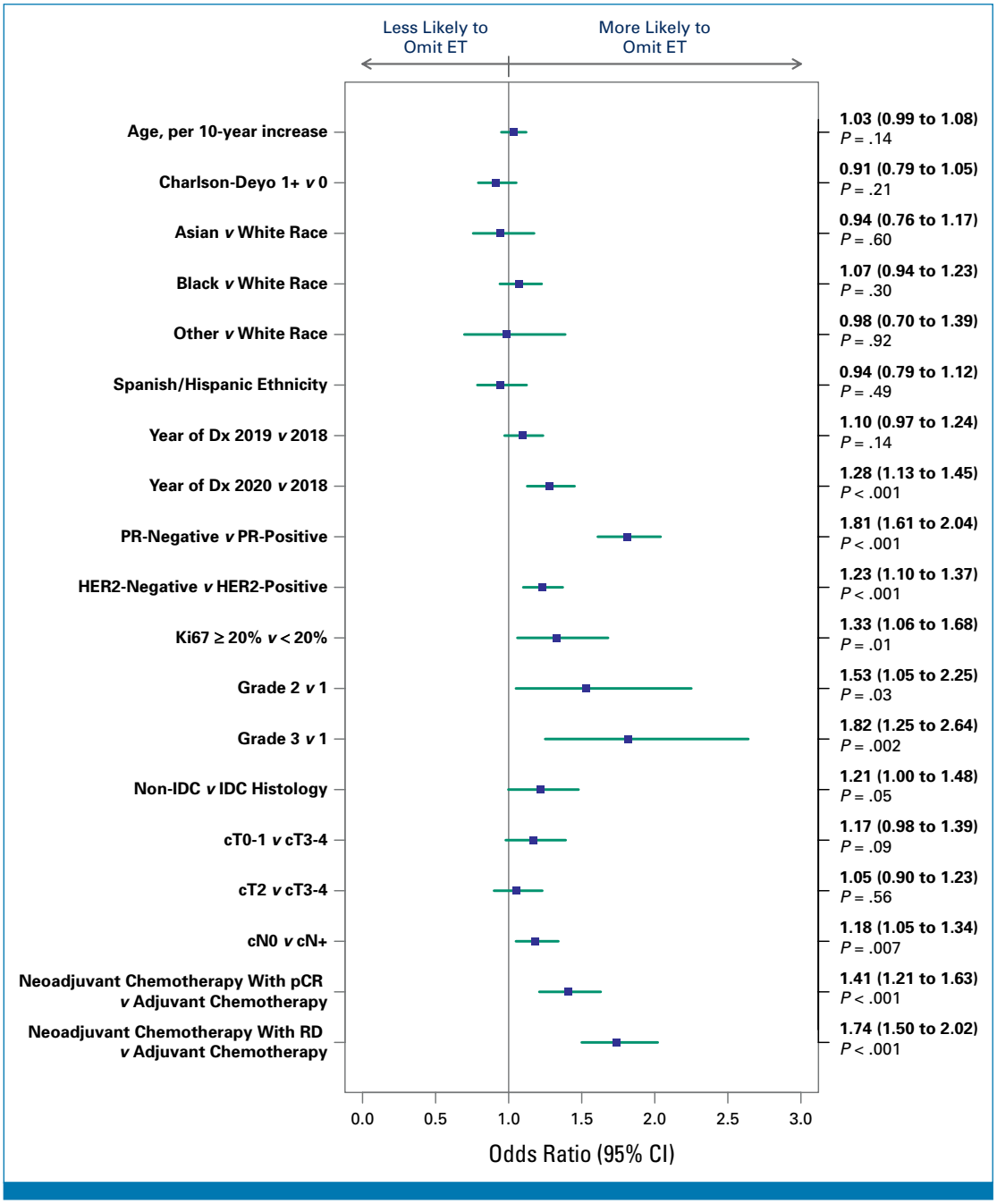

FIG 2. Forest plots evaluating factors associated with adjuvant ET omission in ER-low breast cancer. ET omission was significantly associated with PR-negative, HER2-negative tumors, Ki67 ≥20%, higher grade (2, 3), cN0 disease, and receipt of neoadjuvant chemotherapy using a multivariable regression analysis with all adjustment variables included. ET omission was also higher in 2020, during the COVID-19 pandemic. Age, race, ethnicity, and Charlson-Deyo comorbidity index were included in the multivariable regression model and were not significantly associated with ET omission. ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; pCR, pathologic complete response; PR, progesterone receptor; RD, residual disease.

In the EBCTCG analysis,[3] the impact of adjuvant tamoxifen was analyzed according to ER levels using a charcoal ligand binding assay: ER-0, ER 1-3, ER 4-9, and ER >10 fmol/mg cytosol protein. While no differences in recurrence or BC mortality were observed comparing patients randomly assigned to tamoxifen versus control in the ER-low group, a nonsignificant trend toward benefit was suggested in those with ER 4-9 fmol/mg cytosol protein.

To further examine the impact of ET omission according to discrete ER levels, we examined the subset of patients where discrete levels of ER were documented. In this subgroup, ET

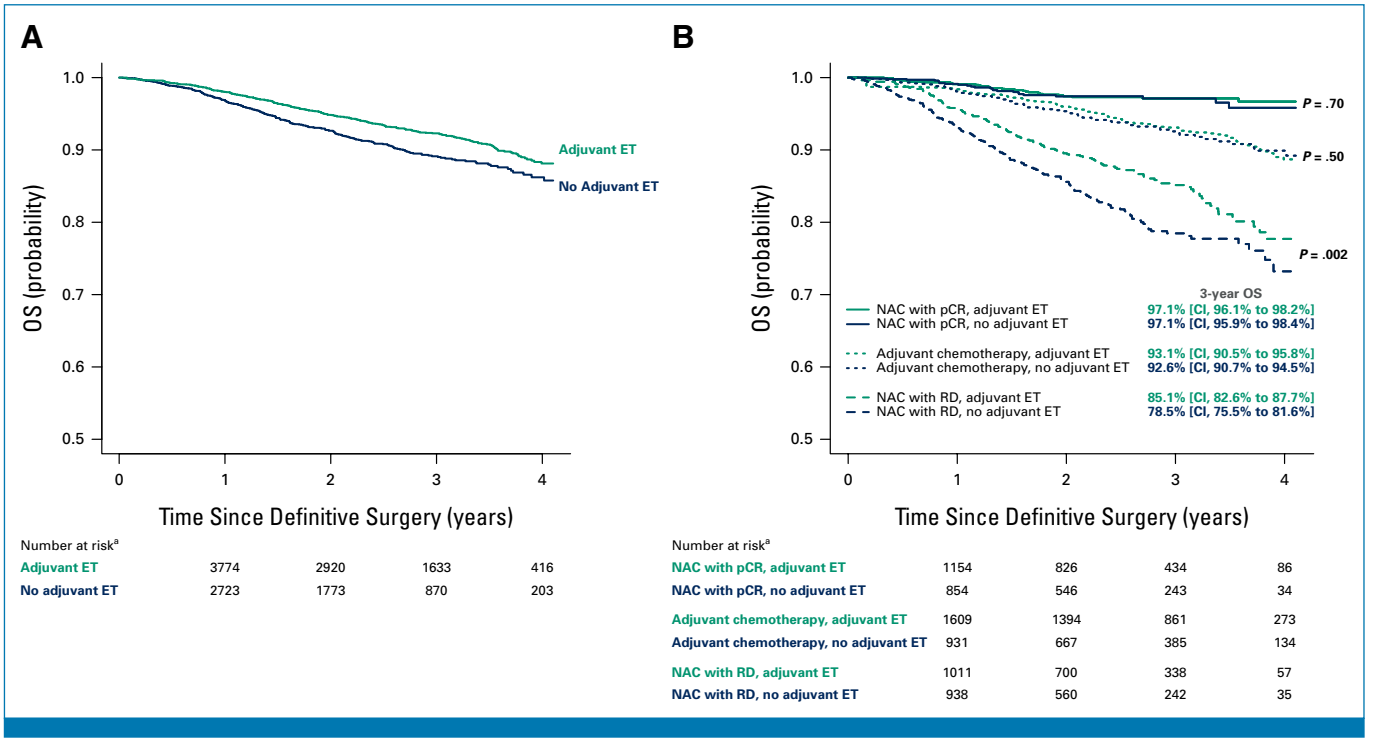

FIG 3. Kaplan-Meier curves demonstrate OS stratified by omission or receipt of ET. (A) In all patients stratified by omission or receipt of ET, OS was significantly worse in patients who omitted ET compared with those who received it. The 3-year OS for patients who omit ET was 89.1% (95% CI, 87.8% to 90.5%) compared with 92.3% (95% CI, 91.3% to 93.3%). (B) OS curves stratified by type of chemotherapy (adjuvant *v* neoadjuvant) and response to NAC. Patients who received adjuvant chemotherapy ($P = .70$) or with pCR after NAC ($P = .50$) had similar 3-year OS rates regardless of ET use. By contrast, OS was significantly worse for patients with RD after NAC ($P = .002$) who omitted ET versus those who received it. [a]Number at risk was presented starting at 1 year rather than 0 because adjuvant ET was generally initiated during follow-up rather than at baseline and was modeled as time-varying covariate, with 1 year being the approximate time point when changes in treatment status had stabilized and the number of patients at risk in the adjuvant ET group was at its maximum. ET, endocrine therapy; NAC, neoadjuvant chemotherapy; OS, overall survival; pCR, pathologic complete response; RD, residual disease.

omission was associated with worse OS in those with tumors expressing ER 6%-10% (HR, 1.42 [95% CI, 1.00 to 2.02]) but not ER 1%-5% (HR, 1.15 [95% CI, 0.91 to 1.45]). However, given the lack of quality control to assess the reproducibility of ER levels and limited follow-up, no conclusions can be made regarding the optimal ER cut point. In addition, the nonuniform distribution of ER, clustering at 5% and 10% (Appendix Table A2), suggests that in about one third of cases, the ER percentage was estimated at these levels. In the ER-low population, tumor heterogeneity including both basal-like and luminal cancer cell populations has been previously demonstrated, suggesting the need for further molecular and genetic characterization of these tumors.[33]

We identified several factors associated with higher rates of ET omission including tumoral factors such as PR, HER2, grade, and Ki67. It is possible that patients with these more aggressive tumor features may not be offered ET because of the perception that these tumors are less likely to respond to ET.[3] Interestingly, HER2-positive patients were more likely

TABLE 2. Exploratory Analysis Assessing the Association of ET Omission With OS According to Response to NAC

				OS HR (95% CI) ET Omitted *v* Received	
Response Based on Treatment	No.	No. of Deaths	3-Year OS (95% CI)	Unadjusted	Adjusted[a]
NAC with pathologic complete response	2,165	55	97.1% (96.3% to 97.9%)	1.11 (0.65 to 1.89) $P = .70$	1.06 (0.62 to 1.80) $P = .84$
NAC with residual disease	2,212	338	81.7% (79.8% to 83.7%)	1.40 (1.13 to 1.75) $P = .002$	1.26 (1.00 to 1.57) $P = .046$
Adjuvant chemotherapy	2,641	193	93.2% (92.2% to 94.3%)	1.10 (0.83 to 1.48) $P = .50$	1.10 (0.82 to 1.48) $P = .52$

Abbreviations: ET, endocrine therapy; HR, hazard ratio; NAC, neoadjuvant chemotherapy; OS, overall survival.
[a]Factors adjusted in the Cox regression model included age, race, ethnicity, Charlson-Deyo comorbidity score, year of diagnosis, progesterone receptor, human epidermal growth factor receptor 2, grade, Ki67, and clinical and pathologic stages.

TABLE 3. Exploratory Analysis Assessing the Impact of ET Omission on OS According to ER 1%-5% Versus 6%-10% Among the 5,506 (78%) Patients With a Discrete Immunohistochemistry ER Percent Staining Value Available

			OS HR (95% CI) ET Omitted *v* Received	
ER Range	No.	No. of Deaths	Unadjusted	Adjusted[a]
ER 1%-5%	3,951	317	1.28 (1.02 to 1.61) $P = .03$	1.15 (0.91 to 1.45) $P = .24$
ER 6%-10%	1,555	136	1.72 (1.22 to 2.43) $P = .002$	1.42 (1.00 to 2.02) $P = .048$

Abbreviations: ER, estrogen receptor; ET, endocrine therapy; HR, hazard ratio; NAC, neoadjuvant chemotherapy; OS, overall survival.
[a]Factors adjusted in the Cox regression model included age, race, ethnicity, Charlson-Deyo comorbidity score, year of diagnosis, progesterone receptor, human epidermal growth factor receptor 2, grade, Ki67, and clinical and pathologic stages.

to start ET than HER2-negative patients, which may reflect previous studies outlining the bidirectional cross talk between ER and HER2 and its role in treatment resistance.[34-36] To determine if HER2 status affected the association between ET omission and OS, an interaction between these variables was assessed and no significant interaction ($P = .86$) was found, suggesting a similar detrimental association between ET omission and OS regardless of HER2 status.

Another important factor that may contribute to ET omission is the receipt and response to NAC. We noted higher rates of ET omission in patients treated with NAC, with higher rates of omission with patients who have RD (48.1%) versus pCR (42.5%). However, the association of ET omission with poorer OS appeared to be confined to those with RD (HR, 1.26; $P = .046$), with no significant effect on OS in patients who achieved pCR after NAC (HR, 1.06, $P = .84$). The higher likelihood of ET omission in this group may be related to treatment fatigue, especially in those with RD where adjuvant capecitabine is a standard therapeutic approach in TNBC.[37] However, the RD that remains after NAC may be enriched with ER-positive clones that likely benefit from adjuvant ET. With recent US Food and Drug Administration approvals for the use of adjuvant ribociclib[38] and abemaciclib[39] in combination with ET and a secondary analysis of the monarchE study suggesting benefit of adjuvant abemaciclib even in ER-low BC,[40] patients with residual ER-low disease after NAC may benefit from escalation of ET that includes a CDK4/6 inhibitor.

There are several limitations to this study. This was a nonrandomized registry analysis of patients who received or did not receive ET, which limits the ability to control for factors that may contribute to the benefit of ET seen in select patients with ER-low BC. However, in the absence of prospective randomized clinical trials, this report provides the largest cohort of patients to examine the association between ET omission and OS in ER-low breast cancer. As our analysis was performed using data obtained during the COVID-19 pandemic, the number of deaths may be higher than in previous years. To address this concern, we performed two sensitivity analyses assessing OS in patients who survived >12 months from definitive surgery and excluding the year 2020 from our cohort, both of which demonstrated the robustness of our initial findings. Furthermore, detailed information about the adherence and duration of adjuvant ET and type of NAC regimens, disease recurrence, or whether death was BC-related was not collected. However, during this short period of follow-up, most deaths are likely to be related to BC, as substantiated by our observations of higher rates of BC death in those with RD after NAC. Finally, the limited follow-up period (3 years) is insufficient to capture later recurrences. Despite these limitations, sensitivity analyses analyzing subsets of patients who are most likely to derive ET benefit (those with RD after NAC and those with higher levels of ER) were in line with our hypothesis.

In summary, ET omission in patients treated with chemotherapy for ER-low, early-stage BC is associated with significantly worse OS. Subgroup analyses suggest that this association was clearest in patients with RD after NAC and those with higher (6%-10%) ER levels. Further research is needed to identify the biological subtypes of ER-low BCs that are most likely to benefit from ET. Until then, patients with ER-low BC should be counseled regarding the potential benefit of ET.

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Endocrine Therapy Omission in Estrogen Receptor–Low (1%-10%) Early-Stage Breast Cancer

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APPENDIX 1. METHODS

Number at Risk Table for Kaplan-Meier Curve of Overall Survival

The number at risk table was provided starting from the 1-year follow-up, the point at which treatment group changes had stabilized and the number of patients at risk in the endocrine therapy group was at its maximum (Appendix Fig A1).

All statistical analyses were performed by Tanya L. Hoskin.

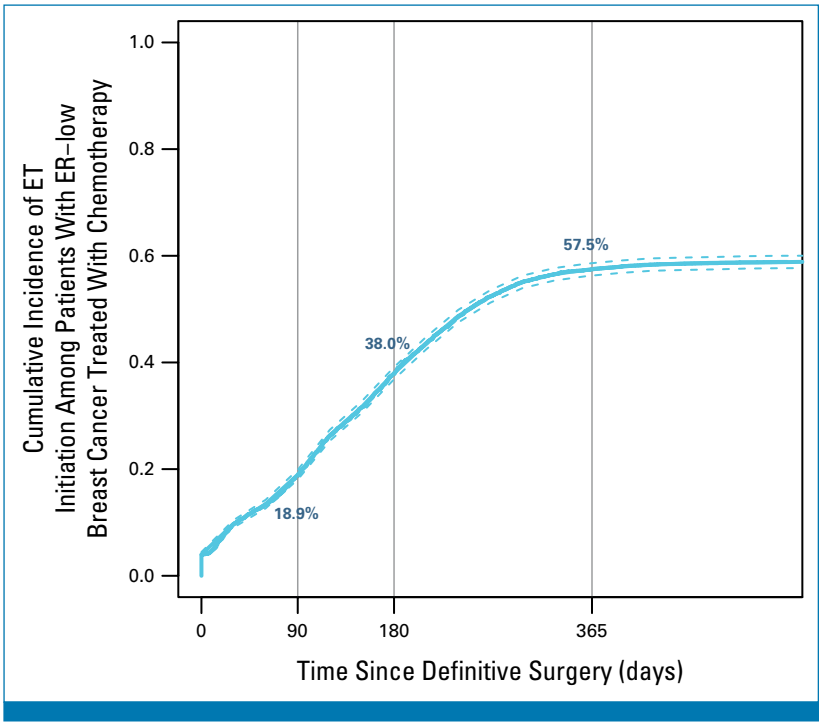

FIG A1. Cumulative incidence of ET initiation after definitive surgery in patients with ER-low breast cancer. ER, estrogen receptor; ET, endocrine therapy.

TABLE A1. Multivariable Cox Proportional Hazards Regression Model for Overall Survival Among Patients With Estrogen Receptor–Low Breast Cancer With the ET Start Modeled as a Time-Dependent Covariate

Parameter[a]	HR	95% HR Confidence Interval	*P*
ET, omission *v* receipt	1.23	1.04 to 1.46	.0184
Age, per 10-year increase	1.09	1.02 to 1.16	.0087
Charlson-Deyo comorbidity score, 1+ *v* 0	1.40	1.15 to 1.71	.0009
Race			
Asian *v* White	0.47	0.29 to 0.77	.0027
Black *v* White	1.01	0.82 to 1.24	.9298
Other *v* White	0.94	0.50 to 1.78	.8429
Unknown *v* White	0.29	0.04 to 2.14	.2237
Ethnicity			
Spanish/Hispanic *v* Non--Spanish/Hispanic	0.90	0.67 to 1.21	.4677
Unknown *v* Non-Spanish/Hispanic	0.51	0.21 to 1.25	.1401
Progesterone receptor, negative *v* positive	1.29	1.06 to 1.58	.0121
Human epidermal growth factor receptor 2, negative *v* positive	2.26	1.80 to 2.83	<.0001
Ki67			
≥20% *v* <20%	1.18	0.80 to 1.73	.4147
Unknown *v* <20%	1.30	0.89 to 1.91	.1725
Grade			
1 *v* 3	0.62	0.34 to 1.11	.1058
2 *v* 3	0.74	0.60 to 0.92	.0075
Unknown *v* 3	0.98	0.46 to 2.09	.9573
Clinical T category			
cT2 *v* cT1	1.30	1.04 to 1.62	.0203
cT3-4 *v* cT1	1.53	1.16 to 2.01	.0026
Unknown *v* cT1	0.52	0.24 to 1.14	.1011
Clinical N category			
cN1 *v* cN0	1.81	1.46 to 2.24	<.0001
cN2-3 *v* cN0	2.09	1.55 to 2.83	<.0001
Unknown *v* cN0	1.31	0.65 to 2.64	.4519
Pathologic T category[b]			
pT0/Tis *v* pT3-4	0.15	0.10 to 0.21	<.0001
pT1 *v* pT3-4	0.29	0.22 to 0.38	<.0001
pT2 *v* pT3-4	0.58	0.45 to 0.75	<.0001
Unknown *v* pT3-4	0.45	0.18 to 1.13	.0872
Pathologic N category[b]			
pN0 *v* pN2-3	0.34	0.26 to 0.44	<.0001
pN1 *v* pN2-3	0.54	0.43 to 0.69	<.0001
Unknown *v* pN2-3	0.40	0.12 to 1.31	.1316

Abbreviations: ET, endocrine therapy; HR, hazard ratio.
[a]Model also adjusted for the year of diagnosis as a stratification variable.
[b]Pathologic T and N categories represent ypT and ypN staging in patients treated with neoadjuvant chemotherapy.

TABLE A2. Distribution of ER Immunohistochemistry Percent as Reported in the National Cancer Database for Patients in Our ER-Low Breast Cancer Analysis Cohort (n = 7,018)

Reported Value for ER %	No. (%)
1	975 (13.9)
2	927 (13.2)
3	511 (7.3)
4	257 (3.7)
5	1,281 (18.3)
6	146 (2.1)
7	125 (1.8)
8	142 (2.0)
9	126 (1.8)
10	1,016 (14.5)
Reported as range 1%-10%	1,512 (21.5)

NOTE. Registrars are allowed to enter the percent of cells staining ER-positive as either a discrete numeric value or a range consistent with ASCO/College of American Pathologists guidelines.
Abbreviation: ER, estrogen receptor.