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Adjuvant endocrine therapy in patients with estrogen receptor-low positive breast cancer: A prospective cohort study

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ABSTRACT

Background: Little is known about the benefits of adjuvant endocrine therapy (ET) in low ER-positive breast cancer (1%–10%) patients. We analyzed the association between ET and breast cancer-specific survival (BCSS) in these patients with respect to the regimen and the duration of ET.

Methods: Patients were classified into three groups based on the regimen and duration of ET. The regimens included aromatase inhibitor (AI) monotherapy or sequential tamoxifen followed by an AI (AI/T + AI), or only tamoxifen and no ET. The duration of ET included 2–3 years and >3 years. Multivariate Cox regression analysis was employed to calculate the hazard ratios (HRs) with 95% confidence intervals (CIs).

Results: Of the 10,696 patients diagnosed with breast cancer between 2010 and 2020, 407 women were identified with ER-low positive disease and met the inclusion criteria. During a median follow-up of 5.2 years, patients who received ET improved BCSS. Of them, those with AI/T + AI had increased BCSS compared to patients without ET, after adjusting for demographics and tumor characteristics, especially in ER-low/HER-2-positive breast cancer. After additional adjustment for treatment mode, the association maintained a similar trend. Patients who received >3 years of ET was associated with a better DFS. There was no significant difference in BCSS between patients with 2–3 years and >3 years of ET.

Conclusion: For ER-low patients, findings suggest that ET with AI/T + AI may be a reasonable treatment alternative. This effect should be assessed in randomized studies.

1. Introduction

Estrogen receptor (ER) status plays an essential role in clinical decision-making and predicting outcomes for patients with breast cancer [1]. Patients with ER-positive tumors are generally considered eligible for endocrine therapy (ET). Thus, a precise assessment of ER status is pivotal to predict whether a patient may benefit from ET.

The 2020 American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) have recently shown that a >1% nuclear ER-positive expression is recommended as a reasonable threshold for "positive" ER expression, as determined by immunohistochemistry (IHC) [2]. Additionally, tumors that have ER positive rates of 1%–10% are now recognized as a new category referred to as ER-low positive breast cancer [3]. Furthermore, there is extensive evidence indicating that this new "ER-low" subtype accounts for 3%–9% of all patients and is significantly different from "ER-high (positive >10%)" and "ER-negative (positive <1%)" tumors in terms of both clinicopathologic and prognostic features [4–6]. Many studies have demonstrated that patients with ER-low positive tumors have more advanced disease and worse survival than those with ER-high positive tumors. When compared to ER-negative tumors, equally poor clinicopathologic features and prognosis have been observed in ER-low

Abbreviations: AI, aromatase inhibitors; ASCO, American Society of Clinical Oncology; BCIMS, Breast Cancer Information Management System; BMI, Body mass index; BCSS, breast cancer-specific survival; CAP, College of American Pathologists; CIs, Confidence intervals; DFS, disease-free survival; ER, estrogen receptor; ET, adjuvant endocrine therapy; HER2, Human epidermal growth factor receptor 2; HR, Hazard ratios; IHC, immunohistochemistry; IQR, interquartile range; PgR, progesterone receptor; T, tamoxifen; WCH, West China Hospital.

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positive breast cancer [4,5]. Similarly, the results of our previous study support these clinical findings in the ER-low group [7]. These results highlight the differences between patients with ER-low and ER-high positive breast cancer and remind us that the management of these two cancer types should be viewed separately.

To date, there has been no standardization of therapeutic strategies or guidelines for the treatment of ER-low positive breast cancer and studies focused on the benefits of ET for ER-low positive breast cancer have reported conflicting results. Previous studies have implied that although ER-low positive tumors are heterogeneous, they often respond to ET [4,8,9]. However, some retrospective studies have indicated that ET has little effect on patients with ER-low positive disease, similar to those with ER-negative tumors [7,10,11]. In consideration of the disease risks and possible benefits of the treatment, ET strategies for patients with ER-low positive breast cancer should be considered carefully. However, due to the small proportion of these patients, randomized controlled trials to explore the effect of ET on patients with ER-low positive breast cancer are challenging to conduct. Herein, we leveraged a prospective cohort of patients with ER-low positive breast cancer who were diagnosed in China between 2010 and 2020 to examine the associations between ET and cancer-specific survival in specific groups based on the regimen and duration of ET.

2. Materials and methods

2.1. Study population

Patients were enrolled from the Breast Cancer Information Management System (BCIMS), which has prospectively collected all information on patients with breast cancer at the West China Hospital (WCH) of Sichuan University since 2008. This study was approved by the Clinical Test and Biomedical Ethics Committee at the West China Hospital, Sichuan University (reference number 2012–130). All patients provided written informed consent forms. The 2010 ASCO/CAP guidelines [12] recommend that ER is considered positive if at least 1% positive tumor nuclei are detected in the sample. Using this criterion, we identified patients diagnosed with breast cancer between January 2010 and April 2020 via the BCIMS. Patients were treated with surgical resection and pathologically confirmed to have ER-low positive invasive early-stage breast cancer. We excluded male patients, patients with primary bilateral breast cancer or metastatic breast cancer, and patients without complete data on ET.

The primary independent variable of interest was ET regimen for ER-low positive breast cancer, classified as either aromatase inhibitor (AI) monotherapy or sequential tamoxifen followed by an AI (AI/T + AI), or only tamoxifen and no ET. Subset analyses were then performed according to the HER2 expression. Additionally, patients were separated into a further two groups according to the duration of ET: 2–3 years and >3 years of ET. All these patients did not interrupt ET due to disease recurrences or deaths at the enrolment and at baseline. To reduce the bias of the analysis, we did not include patients with <2 years of ET in the study.

The patient demographics included age, calendar year at diagnosis, residence, educational level (as proxies for socioeconomic status), menopausal status, and body mass index (BMI). According to the recommendation for Asian populations [13], BMI was classified as < 23 kg/m^2 (non-overweight) and ≥ 23 kg/m^2 (overweight). Clinical characteristics included progesterone receptor (PgR) status, human epidermal growth factor receptor 2 (HER2) status, Ki-67, CDK5/6, tumor size, nodal status, stage, histological type, and histological grade. Treatment modes were categorized as adjuvant chemotherapy, adjuvant radiotherapy and adjuvant trastuzumab therapy.

2.2. Immunohistology

Immunohistochemistry (IHC) was used to assess the expression of ER and PgR in tumor sections. HER2 status was assessed by IHC and fluorescence in *situ* hybridization (FISH), if needed. According to the 2020 ASCO/CAP guidelines for reporting ER (not PgR) status, if 1%–10% of the tumor cell nuclear staining was immunoreactive, the sample was termed ER-low positive with a recommended comment [2]. In our study, the pathologist was responsible for interpreting and scoring the IHC results.

2.3. Outcomes

BCSS was calculated as the time from the date of diagnosis to the date of death attributed to breast cancer. All patients who were still alive were censored at the date of the last follow-up. DFS was calculated as being from when the disease was cleared until any of the following events occurred, including local or regional recurrence, distant recurrence, metastasis, and death from any cause.

2.4. Statistical analysis

The demographic and clinical characteristics of patients with different ET regimens and ET durations are described in Table 1 and Table S1. Pearson's Chi-square test was used to assess the differences between groups.

Survival curves were calculated using the Kaplan–Meier method, and outcomes were compared by log–rank test. The median follow-up time was calculated using the reverse Kaplan–Meier method.

Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated from the Cox regression by contrasting different groups. In Model A, demographic factors, including age (as a continuous variable), calendar year at diagnosis, residence, educational level, BMI, and menopausal status, were adjusted. In Model B, we additionally adjusted for clinical characteristics, including tumor stage, CDK5/6 and histological grade. In Model C, the treatment modes, namely adjuvant chemotherapy, adjuvant radiotherapy and adjuvant trastuzumab therapy, were further controlled for.

All analyses were performed using STATA statistical software (version 16; STATA, College Station, TX, USA). A P-value < 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Between January 1, 2010, and April 30, 2020, there were 10,696 patients diagnosed with primary breast cancer at our institution, among whom, 491 (4.58%) had ER-low positive breast cancer. In light of the inclusion and exclusion criteria, 407 patients were finally included in the analysis (Fig. 1). Representative IHC staining images of ER expression are shown in Fig. 2; Among these patients, 133 (32.7% of 407 patients with a known ET regimen) were treated with AI/T + AI (Table 1), and 55 (13.5% of 407 patients with a known ET duration) received short-term (2–3 years) ET (Table S1).

Compared to patients treated with tamoxifen or without ET, those treated with AI/T + AI were older, mostly from urban areas, were likely to be well educated and postmenopausal, and their tumors were more likely to be CK5/6-negative. In patients treated with AI/T + AI or no ET, the tumors were more likely to be lymph node metastasis positive. Compared to patients without ET, patients treated either with AI/T + AI or tamoxifen were more likely to have stage I/II and grade III disease. These patients treated with AI/T + AI were also more likely to be treated with adjuvant radiotherapy and adjuvant trastuzumab ($P < 0.05$; Table 1). Additionally, compared to patients who received >3 years of ET, those who received 2–3 years of treatment were diagnosed, were well-educated and were more likely to be treated with adjuvant trastuzumab. Their tumors were more likely to be PgR-negative ($P < 0.05$; Table S1).

Table 1
Demographics and clinical characteristics of patients with estrogen receptor-low-positive breast cancer.

Characteristics	All (n = 407)	By ET regimen			
		AI/ tamoxifen + AI (n = 133)	Tamoxifen (n = 161)	No ET (n = 113)	
	No.(%)	No.(%)	No.(%)	No.(%)	P
Age					<0.01
Median (IQR), y	48 [43–55]	52 [47–56]	45 [40–49]	50 [43–59]	
Year at diagnosis					0.39
2010–2015	209 (51.35)	70 (52.63)	87 (54.04)	52 (46.02)	
2016–2020	198 (48.65)	63 (47.37)	74 (45.96)	61 (53.98)	
Residence					<0.01
Urban	278 (68.30)	103 (77.44)	96 (59.63)	79 (69.91)	
Rural	129 (31.70)	30 (22.56)	65 (40.37)	34 (30.09)	
Education, y					<0.01
≤ 6	79 (19.41)	23 (17.29)	34 (21.12)	22 (19.47)	
7-9	149 (36.61)	40 (30.08)	65 (40.37)	44 (38.94)	
10-12	86 (21.13)	44 (33.08)	21 (13.04)	21 (18.58)	
> 12	93 (22.85)	26 (19.55)	41 (25.47)	26 (23.01)	
BMI, kg/m^2					0.31
< 23	210 (51.60)	64 (48.12)	81 (50.31)	65 (57.52)	
≥ 23	197 (48.40)	69 (51.88)	80 (49.69)	48 (42.48)	
Menopausal status					<0.01
Premenopausal	211 (51.84)	42 (31.58)	118 (73.29)	51 (45.13)	
Postmenopausal	196 (48.16)	91 (68.42)	43 (26.71)	62 (54.87)	
PgR status					0.12
Negative	195 (47.91)	54 (40.60)	82 (50.93)	)59 (52.21)	
Positive	212 (52.09)	79 (59.40)	79 (49.07)	54 (47.79)	
HER2 status					0.06
Negative	164 (40.29)	45 (33.83)	73 (45.34)	46 (40.71)	
Positive	205 (50.37)	80 (60.15)	70 (43.48)	55 (48.67)	
Unknown	38 (9.34)	8 (6.02)	18 (11.18)	12 (10.62)	
Ki-67 level					0.30
< 14%	22 (5.41)	8 (6.02)	11 (6.83)	3 (2.65)	
≥ 14%	385 (94.59)	125 (93.98)	150 (93.17)	110 (97.35)	
CK5/6					0.01
Negative	238 (58.48)	94 (70.68)	82 (50.93)	62 (54.87)	
Positive	117 (28.75)	25 (18.80)	56 (34.78)	36 (31.86)	
Unknown	52 (12.78)	14 (10.53)	23 (14.29)	15 (13.27)	
Tumor size					0.35
T1	115 (28.26)	35 (26.32)	53 (32.92)	27 (23.89)	
T2	218 (53.56)	75 (56.39)	85 (52.80)	58 (51.33)	
T3	33 (8.11)	10 (7.52)	11 (6.83)	12 (10.62)	
T4	41 (10.07)	13 (9.77)	12 (7.45)	16 (14.16)	
Nodal status					<0.01
N0	172 (42.26)	55 (41.35)	81 (50.31)	36 (31.86)	
N1	133 (32.68)	48 (36.09)	51 (31.68)	34 (30.09)	
N2	34 (8.35)	12 (9.02)	7 (4.35)	15 (13.27)	
N3	68 (16.71)	18 (13.53)	22 (13.66)	28 (24.78)	
Stage					0.03
I	77 (18.92)	23 (17.29)	37 (22.98)	17 (15.04)	
II	201 (49.39)	70 (52.63)	83 (51.55)	48 (42.48)	
III	129 (31.70)	40 (30.08)	41 (25.47)	48 (42.48)	
Histological type					0.19
Ductal	390 (95.82)	129 (96.99)	156 (96.89)	105 (92.92)	
Others	17 (4.18)	4 (3.01)	5 (3.11)	8 (7.08)	
Histological grade					<0.01
I/II	71 (17.44)	27 (20.30)	29 (18.01)	15 (13.27)	
III	284 (69.78)	94 (70.68)	122 (75.78)	68 (60.18)	
Unknown	52 (12.78)	12 (9.02)	10 (6.21)	30 (26.55)	
Adjuvant chemotherapy					0.82
No	24 (5.90)	7 (5.26)	9 (5.59)	8 (7.08)	
Yes	383 (94.10)	126 (94.74)	152 (94.41)	105 (92.92)	
Adjuvant radiotherapy					<0.01
No	142 (34.89)	36 (27.07)	54 (33.54)	52 (46.02)	
Yes	265 (65.11)	97 (72.93)	107 (66.46)	61 (53.98)	
Adjuvant trastuzumab therapy					0.01
No	322 (79.12)	93 (69.92)	137 (85.09)	92 (81.42)	
Yes	85 (20.88)	40 (30.08)	24 (14.91)	21 (18.58)	

Note: BMI was classified into <23 kg/m^2 (non-overweight) and ≥23 kg/m^2 (overweight) according to the recommendation to Asian populations.
Abbreviations: BMI, Body mass index; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IQR, interquartile range; PgR, progesterone receptor; y, year.

3.2. Survival analysis

During the follow-up (median: 5.2 years, interquartile range: 3.7–8.1 years), 76 patients developed recurrence or metastasis, and 26 deaths were observed due to breast cancer. The 5-year BCSS rates were 94.7%, 93.2%, and 87.9% in the AI/T + AI, tamoxifen, and no ET groups, respectively. In the whole population, the results showed that tumors with larger size, more lymph node metastasis or higher stage were associated with worse BCSS. Similar patterns were noticed for DFS (Fig. S1). Compared to patients who did not received ET, those who received ET presented the advantage of BCSS (HR, 0.41; 95% CI, 0.19–0.91; P = 0.02), but not DFS (Fig. 3A and B). Furthermore, the results showed that patients treated with AI/T + AI had a better BCSS than those who received no ET (HR, 0.36; 95% CI, 0.13–0.97; P = 0.04).

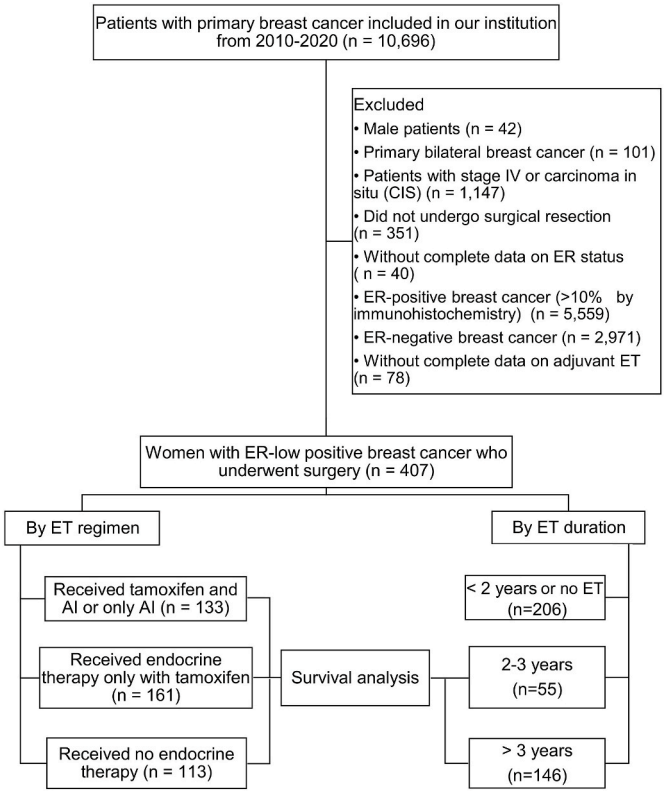

Fig. 1. Flow diagram of the patient selection in this study. Abbreviations: AI, aromatase inhibitors; ER, estrogen receptor; and ET, adjuvant endocrine therapy.

The relationship was attenuated between the tamoxifen and no ET groups, yet a trend remained (HR, 0.47; 95% CI, 0.19–1.13; P = 0.09) (Fig. 3C). However, there was no statistically significant difference in DFS among the three groups (Fig. 3D).

Additionally, the results showed no difference in BCSS between patients who received 2–3 years and >3 years of ET (HR, 0.25; 95% CI, 0.02–4.06; P = 0.33) (Fig. 4A). However, we found that patients who received >3 years of ET had increased DFS compared to those with 2–3 years of ET (HR, 0.16; 95% CI, 0.06–0.45; P < 0.01) (Fig. 4B).

Controlling for demographic characteristics, compared with patients who received no ET, those who received ET had a 63% decreased risk of cancer-specific mortality (95% CI, 0.17–0.83; P = 0.02). Patients treated with AI/T + AI exhibited a 71% decreased risk of cancer-specific mortality (95% CI, 0.10–0.81; P = 0.01) compared to patients with no ET (Table 2). After additional adjustment for clinical characteristics and treatment mode, the association was attenuated, yet a similar trend remained (HR 0.40, 95% CI 0.14 to 1.14, P = 0.06) between those who received AI/T + AI and those who received no ET. However, no statistically significant difference was found in terms of cancer-specific mortality between patients only treated with tamoxifen and no ET (HR 0.49, 95% CI 0.19 to 1.24, P = 0.13) (Table 2). There was no statistically significant difference in DFS between patients with no ET and patients treated with ET (HR 0.71, 95% CI 0.42 to 1.19, P = 0.19), treated with AI/T + AI (HR 0.77, 95% CI 0.42 to 1.43, P = 0.42) or treated with tamoxifen only (HR 0.64, 95% CI 0.35 to 1.18, P = 0.15) (Table 2).

In addition, patients who received >3 years of ET had a longer DFS than patients with 2–3 years of ET when adjusting for demographics, tumor characteristics, and treatment mode (HR 0.22, 95% CI 0.08 to 0.59, P = 0.003). However, there was no statistically significant difference in cancer-specific mortality between patients who received 2–3 years and those with >3 years of ET (HR 0.40, 95% CI 0.02 to 7.06, P = 0.53) (Table 2).

We further estimated the association of the ET regimen with BCSS and DFS according to HER2 expression in patients with ER-low positive breast cancer. Those who were treated with AI/T + AI showed an increased BCSS compared to patients without ET in ER-low positive and HER-positive breast cancer (Fig. S1). After adjusting for all confounders, we observed that those with AI/T + AI exhibited a 2% decreased risk of cancer-specific mortality, compared to those with no ET in both ER-low positive and HER-positive breast cancers (95% CI, 0.01–0.10; P = 0.05). However, there was no significant association between the mortality risks and ET regimen in patients with ER-low positive and HER-negative diseases. No statistically significant correlation was found between the ET regimen and the risk of disease metastasis in either subgroup (Table 3).

4. Discussion

In our study, we suggested that ET was closely associated with BCSS in ER-low positive breast cancer patients. To the best of our knowledge, this is the first study to demonstrate that patients with ER-low positive breast cancer who received AI/T + AI had increased BCSS. Furthermore, there was no significant difference in BCSS between patients who received 2–3 years and >3 years of ET.

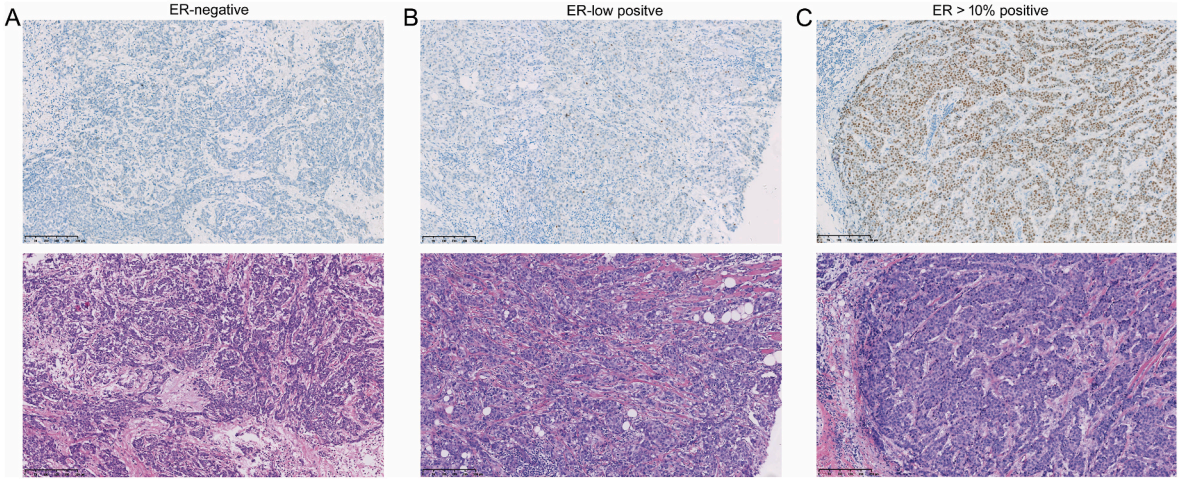

Fig. 2. Representative immunohistochemistry images (above) and corresponding H&E images (below) of breast tumors with (A) ER-negative expression, (B) ER-low expression, and (C) high ER expression. Abbreviations: ER, estrogen receptor.

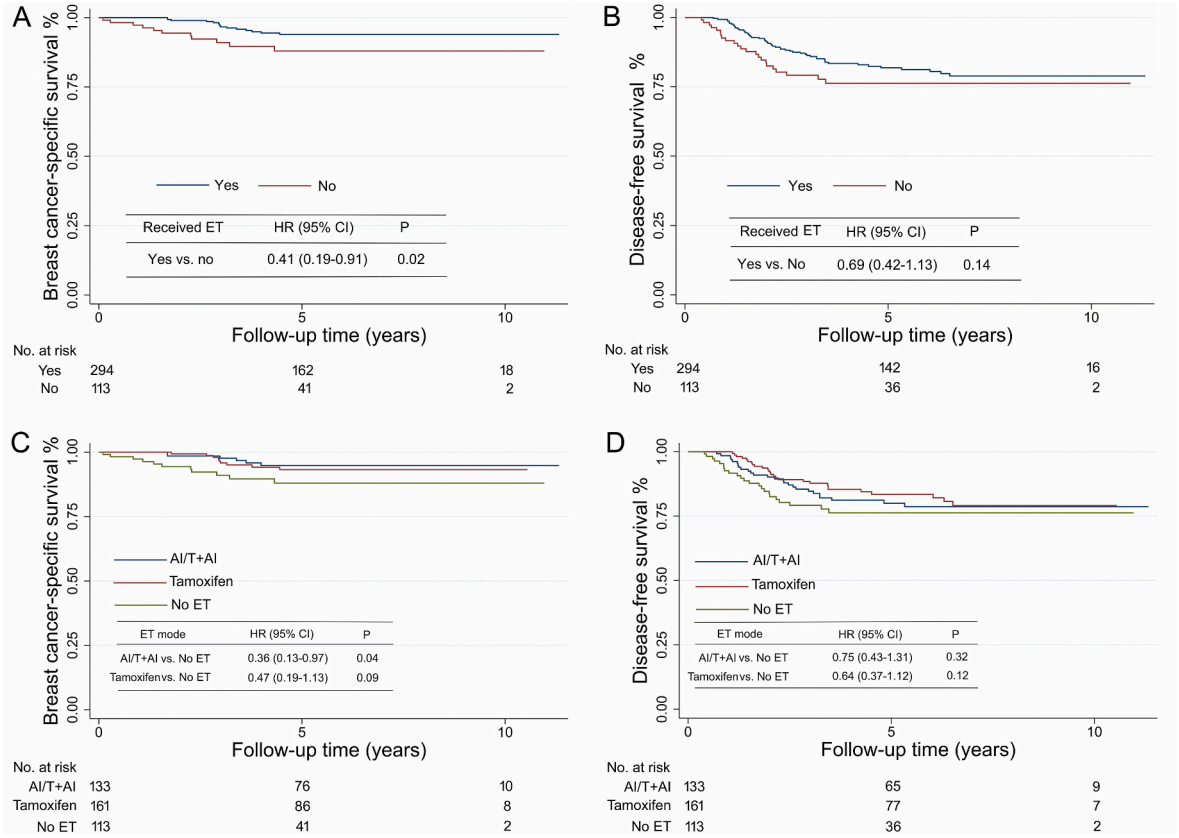

Fig. 3. Kaplan–Meier estimates of breast cancer-specific survival and disease-free survival according to endocrine therapy (A and B) and by endocrine therapy regimen (C and D).

We found that ER-low patients treated with mono- or sequential aromatase inhibitor therapy were more likely to be postmenopausal and positive for lymph node metastasis, while those treated with tamoxifen monotherapy were premenopausal and negative for lymph node metastasis. These were mainly based on the research and guidelines on endocrine therapy for hormone receptor-positive breast cancer patients: AIs rather than tamoxifen act as initial adjuvant therapy for postmenopausal women or patients with high risk factors (e.g. lymph node metastasis) [14]. Tamoxifen is approved for both pre- and postmenopausal women with hormone receptor-positive breast cancer. When compared to patients without ET, patients treated with ET either by AI/T + AI or by tamoxifen were more likely to have stage I/II and grade III disease. These patients treated with AI/T + AI were also more likely to be treated with adjuvant radiotherapy and adjuvant trastuzumab. In our study, we found that for patients who received no ET, a higher stage is one of the reasons for the poor prognosis. Nevertheless, after adjusting for demographics, tumor characteristics, and treatment mode, patients who received AI/T + AI still had a tendency to have increased BCSS compared with patients who received no ET.

ET is the fundamental treatment against ER-positive breast cancer, and tamoxifen and AIs are the most commonly used oral endocrine drugs. Tamoxifen is approved for both pre- and postmenopausal women with hormone receptor-positive breast cancer. It is recommended that postmenopausal women either receive upfront treatment with AI monotherapy, switch to AI therapy after 2–3 years of tamoxifen, or receive extended adjuvant ET after 5 years of tamoxifen [15–19]. For patients with fairly low ER-positive tumors, the results of some clinical trials have implied that AIs may be more effective than tamoxifen. However, as these studies only enrolled patients with ER $\geq$ 10% tumors, whether these findings can be extrapolated to ER-low tumors is unknown [20,21]. Both *in vitro* and *in vivo* studies have demonstrated that positive correlations exist between the presence of aromatase activity and response to aromatase inhibitors [22,23]. Additionally, tumor aromatase expression can help to identify ER-positive tumors with favorable long-term outcomes [21]. In our study, we found that patients with ER-low positive breast cancer who received AI monotherapy or sequential tamoxifen followed by AI had a more favorable BCSS than those who received no ET. However, there was no significant difference between tamoxifen monotherapy and no ET. Additionally, the subgroup analysis showed that our results were particularly meaningful for patients with ER-low positive and HER2-positive tumors.

Several mechanisms may contribute to the observed results. For postmenopausal women with endocrine-responsive early breast cancer, a lower recurrence and mortality rate is obtained with AI monotherapy compared to tamoxifen [24]. Sequential treatments involving tamoxifen and AIs may represent an effectual strategy considering treatment tolerability. Generally, AIs are recommended as part of standard adjuvant treatment for postmenopausal women [14]. AI plus ovarian suppression is preferred for premenopausal women, including those at high risk, to reduce the absolute risk of recurrence by 3% at 5 and 10 years [25]. These findings reflect the important impact of AIs throughout endocrine-responsive early breast cancer. Additionally, patients with PgR-negative breast cancer benefit more from AI than tamoxifen [26]. Our previous results have shown that ER-low patients were more likely to have advanced, PgR-negative, HER2-positive, or grade III disease than ER-high patients [7]. We found, however, that patients who were treated with AI/T + AI gained 2% benefits from BCSS only in ER-low and HER-2-positive breast cancer. Previous neoadjuvant studies have shown that in contrast to tamoxifen, AIs have similar efficacy in both HER2-positive and HER2-negative tumors [20,27,28]. The PERTAIN trial also demonstrated that pertuzumab plus trastuzumab and an AI are effective for the treatment of HER2-positive metastatic/locally advanced breast cancer [27]. However, the ER-positive breast cancer included in these studies did not distinguish between ER-low expression

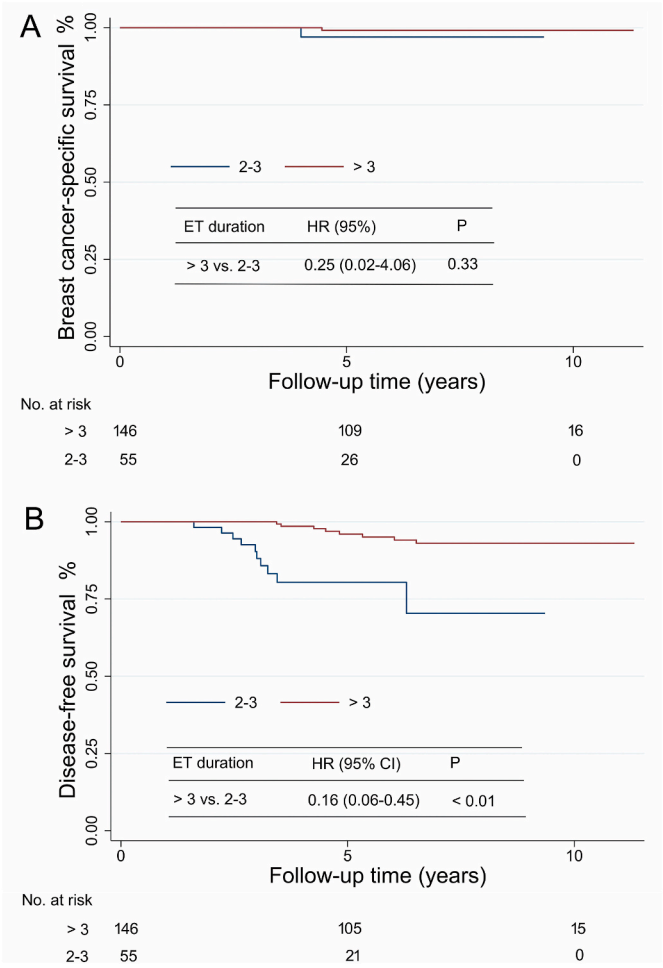

Fig. 4. Kaplan–Meier estimates of breast cancer-specific survival (A) and disease-free survival (B) according to endocrine therapy duration.

and ER-high expression. Most of them had ER-high expression. In our study, patients who received AI/T + AI in ER-low and HER-2-negative breast cancer showed no advantage of survival. This may be attributed to the intrinsic tumor characteristics of this subgroup, which are more inclined to triple-negative tumors and naturally insensitive to hormonal and anti-HER2 therapies [28]. Thus, ET, including AIs, might be an alternative for improving survival in patients with ER-low positive breast cancer, especially with ER-low and HER-2 positive breast cancer. However, this effect should be considered a hypothesis, and randomized studies are urgently needed to further investigate the endocrine responsiveness of ER-low patients.

Due to the long treatment period, ET should be assessed with consideration of the intensity, duration, and side effects, before properly escalating or de-escalating therapies based on possible benefits [29]. As in previous studies, multiple investigators have explored the role of extended ET, including tamoxifen or AI therapy, for 10 years in patients with a high risk for recurrence [30–32]. The benefits of ET are sufficient to recommend it to all patients, including those with low ER/PR expression. However, the side effects of tamoxifen and AIs must be considered. Tamoxifen exerts an estrogenic effect on the endometrium (promoting endometrial hyperplasia), the coagulation system (promoting thromboembolic events), bones (preventing osteoporosis), and lipids (preventing hyperlipidemia) [33]. AIs are better tolerated and elicit fewer of the aforementioned side effects but are still associated with an increased risk of musculoskeletal symptoms, osteopenia, osteoporosis, and fracture rate when compared to tamoxifen [24,34]. Considering this side effect profile, a realistic assessment of duration for ET in patients with ER expression between 1% and 10% is instrumental in making an informed decision. A recent study demonstrated that short-term ET of 2–3 years might be an alternative for patients who have ER-low positive breast cancer instead of the standard 5 years of treatment [8]. This discovery is of significant importance for optimizing ET treatment strategies for patients with ER-low positive breast cancer. Our data supported and showed that ER-low patients who received >3 years of ET had a significantly better DFS than those who received no ET, although there was no BCSS advantage of >3 years versus 2–3 years. Tumors with ER-low expression showed nearly 50% PR-negative, while tumors with ER-high expression may have only 10% PR-negative [7]. Adequate PR expression plays an essential role in activating the ER pathway, while the lack of PR expression may impair the ER pathway and reduce endocrine sensitivity [35]. In the ATAC trial [36], the results showed that compared to patients with ER-positive/PR-positive disease, those with ER-positive/PR-negative disease had more remarkable improvements in survival associated with anastrozole. Additionally, tumors with

Table 2
Associations of endocrine therapy regimen and duration with risks of breast cancer-specific and disease-free survival.

	Model A[a]		Model B[b]		Model C[c]	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Breast cancer-specific survival						
All patients						
Receiving ET vs. No ET	0.37 (0.17–0.83)	0.02	0.41 (0.19–0.92)	0.03	0.44 (0.20–1.00)	0.05
By ET regimen						
AI/T + AI vs. No ET	0.29 (0.10–0.81)	0.01	0.36 (0.13–0.91)	0.04	0.40 (0.14–1.14)	0.06
Tamoxifen vs. No ET	0.46 (0.18–1.19)	0.11	0.45 (0.18–1.15)	0.10	0.49 (0.19–1.24)	0.13
By ET duration, y						
> 3 vs. 2-3	0.26 (0.02–4.15)	0.34	0.40 (0.02–6.94)	0.53	0.40 (0.02–7.06)	0.53
Disease-free survival						
All patients						
Receiving ET vs. No ET	0.62 (0.37–1.02)	0.06	0.69 (0.41–1.15)	0.15	0.71 (0.42–1.19)	0.19
By ET regimen						
AI/T + AI vs. No ET	0.69 (0.39–1.24)	0.22	0.75 (0.41–1.37)	0.35	0.77 (0.42–1.43)	0.42
Tamoxifen vs. No ET	0.55 (0.30–0.99)	0.04	0.63 (0.35–1.15)	0.13	0.64 (0.35–1.18)	0.15
By ET duration, y						
> 3 vs. 2-3	0.21 (0.08–0.54)	<0.01	0.24 (0.09–0.65)	<0.01	0.22 (0.08–0.59)	<0.01

Abbreviations: AI, aromatase inhibitors; CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; T, tamoxifen.

[a] HRs were adjusted for age at diagnosis, calendar year at diagnosis, residence (urban or rural), education (≤6 years, 7–9 years, 10–12 years, or > 12 years), body mass index (<23 kg/m^2 or ≥ 23 kg/m^2), and menopausal status (premenopausal or postmenopausal).

[b] HRs were additionally adjusted for tumor stage (I, II, or III), CDK5/6 expression (negative, positive, or unknown) and histological grade (III or I/II/unknown).

[c] HRs were additionally adjusted for adjuvant chemotherapy (yes or no), adjuvant radiotherapy (yes or no) and adjuvant trastuzumab therapy (yes or no).

Table 3
Associations of endocrine therapy regimen with risks of breast cancer-specific mortality and disease metastasis according to the HER2 expression in patients with ER-low positive breast cancer.

	Model A[a]		Model B[b]		Model C[c]	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
ER-low positive and HER2-negative Breast cancer-specific mortality						
All patients						
Receiving ET vs. No ET	0.34 (0.11–1.08)	0.06	0.39 (0.12–1.21)	0.10	0.40 (0.09–1.78)	0.22
By ET regimen						
AI/T + AI vs. No ET	0.44 (0.13–1.53)	0.19	0.49 (0.13–1.85)	0.29	0.38 (0.08–1.71)	0.21
Tamoxifen vs. No ET	0.35 (0.09–1.40)	0.14	0.31 (0.07–1.27)	0.10	0.30 (0.07–1.29)	0.11
Disease metastasis						
All patients						
Receiving ET vs. No ET	0.49 (0.24–0.98)	0.04	0.55 (0.28–1.12)	0.09	0.59 (0.28–1.21)	0.15
By ET regimen						
AI/T + AI vs. No ET	0.65 (0.28–1.49)	0.31	0.72 (0.31–1.67)	0.44	0.77 (0.32–1.82)	0.55
Tamoxifen vs. No ET	0.45 (0.20–1.01)	0.05	0.49 (0.22–1.09)	0.08	0.53 (0.23–1.20)	0.13
ER-low positive and HER2-positive Breast cancer-specific mortality						
All patients						
Receiving ET vs. No ET	0.38 (0.10–1.48)	0.16	0.04 (0.01–0.83)	0.03	0.03 (0.01–1.52)	0.08
By ET regimen						
AI/T + AI vs. No ET	0.07 (0.01–0.77)	0.03	0.03 (0.01–0.43)	0.01	0.02 (0.01–0.10)	0.05
Tamoxifen vs. No ET	0.66 (0.15–3.06)	0.60	0.08 (0.01–1.74)	0.11	0.10 (0.01–4.28)	0.23
Disease metastasis						
All patients						
Receiving ET vs. No ET	0.77 (0.33–1.71)	0.51	0.68 (0.27–1.76)	0.43	0.65 (0.24–1.75)	0.39
By ET regimen						
AI/T + AI vs. No ET	0.83 (0.34–2.02)	0.26	0.58 (0.21–1.60)	0.29	0.56 (0.19–1.62)	0.28
Tamoxifen vs. No ET	0.68 (0.25–1.83)	0.44	0.74 (0.25–2.14)	0.58	0.86 (0.28–2.61)	0.78

Abbreviations: AI, aromatase inhibitors; CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; T, tamoxifen.

[a] HRs were adjusted for age at diagnosis, calendar year at diagnosis, residence (urban or rural), education ($\leq$6 years, 7–9 years, 10–12 years, or $>$ 12 years), body mass index (<23 kg/m^2 or $\geq$ 23 kg/m^2), and menopausal status (premenopausal or postmenopausal).

[b] HRs were additionally adjusted for tumor stage (I, II, or III), CDK5/6 expression (negative, positive, or unknown) and histological grade (III or I/II/unknown).

[c] HRs were additionally adjusted for adjuvant chemotherapy (yes or no), adjuvant radiotherapy (yes or no) and adjuvant trastuzumab therapy (yes or no, only in HER2-positive breast cancer analysis).

ER-low expression had a higher proportion of HER2-positive. Activation of HER2 could promote endocrine resistance and has been shown to dampen the therapeutic efficacy of tamoxifen in breast cancer with low ER [37,38]. Because of these biological characteristics in ER-low expression breast cancer, these tumors may usher in endocrine resistance earlier. Long-term ET may not bring further survival benefits to such patients. De-escalation of therapy duration might reduce the possible side effects of long-term treatment, improve patient compliance, and decrease financial toxicity. However, in light of the possible intrinsic bias of our study, whether it is appropriate to adopt de-escalating ET treatment over 3 years for patients with ER-low positive early breast cancer needs further validation.

One major merit of our study is the large-scale prospective cohort design with virtually complete follow-up, which largely limits the common sources of bias. We extracted data from a considerable number of patients in a maintained database. The rich information on demographic and clinical characteristics helped to separate the direct effect of ET on cancer-specific survival in ER-low positive breast cancer from the influences of tumor characteristics and treatment mode. Our study also had several limitations. Due to the scarcity of ER-low positive cases and relatively few deaths, the power to detect differences was limited in the subgroup analysis. Thus, we could not distinguish whether our conclusion applies to the general population or a specific group of people. We will continue to follow up with these patients for further analysis. Additionally, as this cohort is based on a regional medical center, the findings may not be generalizable to the population worldwide.

5. Conclusion

Our findings suggest that adjuvant AI treatment could improve the survival of patients with ER-low positive breast cancer, which provides novel insight into treatment strategies for this unique subgroup of patients.

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Data availability statement

The data and other items supporting the study results will be made available upon reasonable request.

Declaration of competing interest

The authors have declared no conflicts of interest.

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Ethics statement

This study was approved by the Clinical Test and Biomedical Ethics Committee at West China Hospital, Sichuan University (No. 2012–130). Written consent was obtained from all participants.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2022.09.008.

References

[1] Lumachi F, Brunello A, Maruzzo M, Basso U, Basso SM. Treatment of estrogen receptor-positive breast cancer. Curr Med Chem 2013;20(5):596–604.

[2] Allison KH, Hammond MEH, Dowsett M, McKernin SE, Carey LA, Fitzgibbons PL, Hayes DF, Lakhani SR, Chavez-MacGregor M, Perlmutter J, Perou CM, Regan MM, Rimm DL, Symmans WF, Torlakovic EE, Varella L, Viale G, Weisberg TF, McShane LM, Wolff AC. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. J Clin Oncol 2020;38(12):1346–66.

[3] Yu KD, Cai YW, Wu SY, Shui RH, Shao ZM. Estrogen receptor-low breast cancer: biology chaos and treatment paradox. Cancer Commun 2021;41(10):968–80.

[4] Fei F, Siegal GP, Wei S. Characterization of estrogen receptor-low-positive breast cancer. Breast Cancer Res Treat 2021;188(1):225–35.

[5] Poon IK, Tsang JY, Li J, Chan SK, Shea KH, Tse GM. The significance of highlighting the oestrogen receptor low category in breast cancer. Br J Cancer 2020;123(8):1223–7.

[6] Fusco N, Ragazzi M, Sajjadi E, Venetis K, Piciotti R, Morganti S, Santandrea G, Fanelli GN, Despini L, Invernizzi M, Cerbelli B, Scatena C, Criscitiello C. Assessment of estrogen receptor low positive status in breast cancer: implications for pathologists and oncologists. Histol Histopathol 2021;36(12):1235–45.

[7] Luo C, Zhong X, Fan Y, Wu Y, Zheng H, Luo T. Clinical characteristics and survival outcome of patients with estrogen receptor low positive breast cancer. Breast 2022;63:24–8.

[8] Cai YW, Shao ZM, Yu KD. De-escalation of five-year adjuvant endocrine therapy in patients with estrogen receptor-low positive (immunohistochemistry staining 1%-10%) breast cancer: propensity-matched analysis from a prospectively maintained cohort. Cancer 2022;128(9):1748–56.

[9] Viale G, Regan MM, Maiorano E, Mastropasqua MG, Golouh R, Perin T, Brown RW, Kovács A, Pillay K, Ohlschlegel C, Braye S, Grigolato P, Rusca T, Gelber RD, Castiglione-Gertsch M, Price KN, Goldhirsch A, Gusterson BA, Coates AS. Chemoendocrine compared with endocrine adjuvant therapies for node-negative breast cancer: predictive value of centrally reviewed expression of estrogen and progesterone receptors–International Breast Cancer Study Group. J Clin Oncol 2008;26(9):1404–10.

[10] Wang S, Li J, Jiang Z, Yin Y, Liu Y, Wang H, Teng Y-e, Ma L, Song Y, Fu P. Breast cancer patients with low estrogen receptor expression gain no significant survival benefit from endocrine therapy: a real-world study from China. Translational Breast Cancer Res. 2020;1:14. 14.

[11] Chen T, Zhang N, Moran MS, Su P, Haffty BG, Yang Q. Borderline ER-positive primary breast cancer gains No significant survival benefit from endocrine therapy: a systematic review and meta-analysis. Clin Breast Cancer 2018;18(1):1–8.

[12] Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, Fitzgibbons PL, Francis G, Goldstein NS, Hayes M, Hicks DG, Lester S, Love R, Mangu PB, McShane L, Miller K, Osborne CK, Paik S, Perlmutter J, Rhodes A, Sasano H, Schwartz JN, Sweep FC, Taube S, Torlakovic EE, Valenstein P, Viale G, Visscher D, Wheeler T, Williams RB, Wittliff JL, Wolff AC. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 2010;28(16):2784–95.

[13] Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363(9403):157–63.

[14] Regan MM, Neven P, Giobbie-Hurder A, Goldhirsch A, Ejlertsen B, Mauriac L, Forbes JF, Smith I, Láng I, Wardley A, Rabaglio M, Price KN, Gelber RD, Coates AS, Thürlimann B. Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1-98 randomised clinical trial at 8·1 years median follow-up. Lancet Oncol 2011;12(12):1101–8.

[15] Burstein HJ, Lacchetti C, Anderson H, Buchholz TA, Davidson NE, Gelmon KA, Giordano SH, Hudis CA, Solky AJ, Stearns V, Winer EP, Griggs JJ. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: ASCO clinical practice guideline focused update. J Clin Oncol 2019;37(5):423–38.

[16] Burstein HJ, Temin S, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, Giordano SH, Hudis CA, Rowden D, Solky AJ, Stearns V, Winer EP, Griggs JJ. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: american society of clinical oncology clinical practice guideline focused update. J Clin Oncol 2014;32(21):2255–69.

[17] Park YH, Senkus-Konefka E, Im SA, Pentheroudakis G, Saji S, Gupta S, Iwata H, Mastura MY, Dent R, Lu YS, Yin Y, Smruti BK, Toyama T, Malwinder S, Lee SC, Tseng LM, Kim JH, Kim TY, Suh KJ, Cardoso F, Yoshino T, Douillard JY. Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with early breast cancer: a KSMO-ESMO initiative endorsed by CSCO, ISMPO, JSMO, MOS, SSO and TOS. Ann Oncol 2020;31(4):451–69.

[18] Li JB, Jiang ZF. [Chinese society of clinical oncology breast cancer guideline version 2021: updates and interpretations]. Zhonghua Yixue Zazhi 2021;101(24):1835–8.

[19] Chumsri S, Howes T, Bao T, Sabnis G, Brodie A. Aromatase, aromatase inhibitors, and breast cancer. J Steroid Biochem Mol Biol 2011;125(1–2):13–22.

[20] Ellis MJ, Coop A, Singh B, Mauriac L, Llombert-Cussac A, Jänicke F, Miller WR, Evans DB, Dugan M, Brady C, Quebe-Fehling E, Borgs M. Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. J Clin Oncol 2001;19(18):3808–16.

[21] Ellis MJ, Miller WR, Tao Y, Evans DB, Chaudri Ross HA, Miki Y, Suzuki T, Sasano H. Aromatase expression and outcomes in the P024 neoadjuvant endocrine therapy trial. Breast Cancer Res Treat 2009;116(2):371–8.

[22] Chen S. Aromatase and breast cancer. Front Biosci 1998;3:d922–33.

[23] Chen S, Zhou D, Okubo T, Kao YC, Eng ET, Grube B, Kwon A, Yang C, Yu B. Prevention and treatment of breast cancer by suppressing aromatase activity and expression. Ann N Y Acad Sci 2002;963:229–38.

[24] Kharb R, Haider K, Neha K, Yar MS. Aromatase inhibitors: role in postmenopausal breast cancer. Arch Pharm (Weinheim) 2020;353(8):e2000081.

[25] Aromatase inhibitors versus tamoxifen in premenopausal women with oestrogen receptor-positive early-stage breast cancer treated with ovarian suppression: a patient-level meta-analysis of 7030 women from four randomised trials. Lancet Oncol 2022;23(3):382–92.

[26] Dixon JM, Jackson J, Hills M, Renshaw L, Cameron DA, Anderson TJ, Miller WR, Dowsett M. Anastrozole demonstrates clinical and biological effectiveness in oestrogen receptor-positive breast cancers, irrespective of the erbB2 status. Eur J Cancer 2004;40(18):2742–7.

[27] Smith IE, Dowsett M, Ebbs SR, Dixon JM, Skene A, Ju Blohmer, Ashley SE, Francis S, Boeddinghaus I, Walsh G. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. J Clin Oncol 2005;23(22):5108–16.

[28] Dowsett M, Cuzick J, Wale C, Howell T, Houghton J, Baum M. Retrospective analysis of time to recurrence in the ATAC trial according to hormone receptor status: an hypothesis-generating study. J Clin Oncol 2005;23(30):7512–7.

[29] Rimawi M, Ferrero JM, de la Haba-Rodriguez J, Poole C, De Placido S, Osborne CK, Hegg R, Easton V, Wohlfarth C, Arpino G. First-line trastuzumab plus an aromatase inhibitor, with or without pertuzumab, in human epidermal growth factor receptor 2-positive and hormone receptor-positive metastatic or locally advanced breast cancer (PERTAIN): a randomized, open-label phase II trial. J Clin Oncol 2018;36(28):2826–35.

[30] Deyarmin B, Kane JL, Valente AL, van Laar R, Gallagher C, Shriver CD, Ellsworth RE. Effect of ASCO/CAP guidelines for determining ER status on molecular subtype. Ann Surg Oncol 2013;20(1):87–93.

[31] Curigliano G, Burstein HJ, Winer EP, Gnant M, Dubsky P, Loibl S, Colleoni M, Regan MM, Piccart-Gebhart M, Senn HJ, Thürlimann B, André F, Baselga J, Bergh J, Bonnefoi H, Brucker SY, Cardoso F, Carey L, Ciruelos E, Cuzick J, Denkert C, Di Leo A, Ejlertsen B, Francis P, Galimberti V, Garber J, Gulluoglu B, Goodwin P, Harbeck N, Hayes DF, Huang CS, Huober J, Hussein K, Jassem J, Jiang Z, Karlsson P, Morrow M, Orecchia R, Osborne KC, Pagani O, Partridge AH, Pritchard K, Ro J, Rutgers EJT, Sedlmayer F, Semiglazov V, Shao Z, Smith I, Toi M, Tutt A, Viale G, Watanabe T, Whelan TJ, Xu B. De-escalating and escalating treatments for early-stage breast cancer: the st. Gallen international expert consensus conference on the primary therapy of early breast cancer 2017. Ann Oncol 2017;28(8):1700–12.

[32] Goss PE, Ingle JN, Pritchard KI, Robert NJ, Muss H, Gralow J, Gelmon K, Whelan T, Strasser-Weippl K, Rubin S, Sturtz K, Wolff AC, Winer E, Hudis C, Stopeck A, Beck JT, Kaur JS, Whelan K, Tu D, Parulekar WR. Extending aromatase-inhibitor adjuvant therapy to 10 years. N Engl J Med 2016;375(3):209–19.

[33] Tjan-Heijnen VCG, van Hellemond IEG, Peer PGM, Swinkels ACP, Smorenburg CH, van der Sangen MJC, Kroep JR, De Graaf H, Honkoop AH, Erdkamp FLG, van den Berkmortel F, de Boer M, de Roos WK, Linn SC, Imholz ALT, Seynaeve CM. Extended adjuvant aromatase inhibition after sequential endocrine therapy (DATA): a randomised, phase 3 trial. Lancet Oncol 2017;18(11):1502–11.

[34] Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E, Duijm-de Carpentier M, Putter H, van den Bosch J, Maartense E, van Leeuwen-Stok AE, Liefers GJ, Nortier JWR, Rutgers EJT, van de Velde CJH. Optimal duration of extended adjuvant endocrine therapy for early breast cancer; results of the IDEAL trial (BOOG 2006-05). J Natl Cancer Inst 2018;110(1).

[35] de Cremoux P, Diéras V, Poupon MF, Magdelénat H, Sigal-Zafrani B, Fourquet A, Pierga JY. [Tamoxifen and aromatase inhibitors in the treatment of breast cancer in menopausal women: pharmacological and clinical aspects]. Bull Cancer 2004;91(12):917–27.

[36] Dutta U, Pant K. Aromatase inhibitors: past, present and future in breast cancer therapy. Med Oncol 2008;25(2):113–24.

[37] Cui X, Schiff R, Arpino G, Osborne CK, Lee AV. Biology of progesterone receptor loss in breast cancer and its implications for endocrine therapy. J Clin Oncol 2005;23(30):7721–35.

[38] Arpino G, Weiss H, Lee AV, Schiff R, De Placido S, Osborne CK, Elledge RM. Estrogen receptor-positive, progesterone receptor-negative breast cancer: association with growth factor receptor expression and tamoxifen resistance. J Natl Cancer Inst 2005;97(17):1254–61.