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ORIGINAL RESEARCH

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Characteristics and prognosis of young breast cancer patients with low expression of estrogen receptor

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Abstract

To evaluate the clinical characteristics and prognosis of young breast cancer patients with an ER of 1%–10%. Breast cancer patients aged ≤35 years old were selected and classified into three groups, ER-negative group, ER-low positive group (ER positivity: 1%–10%) and ER-high positive group (ER positivity: ≥10%), to compare their clinicopathological characteristics and prognosis. Of the 1387 patients assessed, 30.4% were ER-negative, 4.3% were ER-low positive, and 65.3% were ER-high positive. There was no difference in age, Tumor Node Metastasis (TNM) stage, histological type, adjuvant chemotherapy and adjuvant radiation therapy among the three groups ($p > 0.05$). A higher histological grade and greater Human Epidermal Growth Factor Receptor-2 (HER-2) positivity were observed in the ER-low positive group than in the ER-high positive group ($p < 0.001$). The number of patients with Progesterone Receptor (PR) negative in the ER-low positive group was between the other two groups. The recurrence rate of breast cancer in the ER-low positive group was 27.1%, which was similar to that of the ER-negative group (28%; $p > 0.05$) but higher than the ER-high positive group (21.4%; $p = 0.03$). After a median follow-up of 74 months, the ER-high positive group had the longest Disease Free Survival (DFS) compared with the ER-negative group ($p < 0.0001$) and ER-low positive group ($p < 0.05$), while there was no significant difference in DFS between the latter two groups ($p = 0.73$). Similarly, the ER-high positive group had the longest Overall Survival (OS) than the ER-negative group ($p < 0.0001$) and the ER-low positive group ($p < 0.05$), while there was no statistical difference in OS between the latter two groups ($p = 0.77$). After endocrine therapy, no improvement in DFS ($p = 0.71$) and OS ($p = 0.54$) was observed in the ER-low positive group. In young breast cancer patients, the clinicopathological characteristics of the ER-low positive group were different from the ER-high positive group but were more similar to the ER-negative group. The DFS and OS were shorter than the ER-high group, and despite receiving endocrine therapy, DFS and OS of the ER-low positive group were not significantly prolonged.

Keywords

Breast cancer; Young age; Estrogen receptor; Low positive; Survival

1. Introduction

The incidence of breast cancer is very low in young women under 35 years old, accounting for only 2% to 4.8% of new breast cancer cases [1], and clinical research on these patients is limited. Some studies reported that young breast cancer patients were more likely to have features of late-stage disease, high invasiveness and a negative hormone receptor status [2]. For patients with low ER positivity, there is evidence suggesting that patients with ER-positive 1%–10% are younger and have a more advanced disease compared to patients with ER positivity ≥10% [3]. However, the clinicopathological features and prognosis of young breast cancer patients with low ER positivity are limited, and there is little evidence on the benefit of endocrine therapy in this group.

In this study, we explored the clinicopathological and prognostic characteristics of young breast cancer patients with low ER positivity compared with those having high or negative ER positivity.

2. Patients and methods

This study investigated the data of patients with primary breast cancer who were surgically treated from January 2006 to December 2016 at the Tianjin Medical University Cancer Institute and Hospital, Tianjin, China. Patients were eligible if: (1) they were less than or equal to 35 years old, (2) female, (3) had a confirmed pathological diagnosis using core biopsy or

surgical specimens, (4) had to have ER assessment, (5) disease stage were 0-IIIc according to the 8th edition of American Joint Committee on Cancer (AJCC) breast cancer staging system, (6) had complete clinicopathological data. If the tumor was removed at other hospitals before admission, their pathological wax slides were re-assessed at our hospital to confirm the diagnosis of breast cancer. Patients were excluded if: (1) they had other malignant tumors when diagnosed with breast cancer. (2)The patient did not receive radical surgery.

All patients were treated according to the latest National Cancer Integrated Network (NCCN) breast cancer diagnosis and treatment guidelines. According to ER status, the patients were distributed into three groups: ER-negative group, ER-low group (ER positivity: 1%–10%) and ER-high group (ER positivity: ≥10%). Immunohistochemical criteria for ER positivity was positive staining localized to the nucleus, with over 1% of the cells being positive.

The clinical and pathological data of the patients were retrieved and sorted, and their follow-up data were assessed. The last date of follow-up was 31 December 2019. The study endpoints were the recurrence rate, overall survival (OS) (time from surgery to death from any reasons) and disease-free survival (DFS) (time from surgery to the first event, including any local, regional, or distant metastasis, second primary, contralateral *in situ* or invasive breast cancer or death due to any reason).

3. Statistical analysis

The SPSS (v20.0, IBM Corp., Armonk, NY, U.S.A) software was used for statistical analyses. The age of each group was compared with the *t*-test. We evaluated and compared clinical and pathological characteristics as well as treatment characteristics using the chi-square test between groups. The Kaplan Meier method was used to draw survival curves and to compare the OS and DFS between groups using the log-rank test. All p values were two-tailed, and $p \leq 0.05$ was considered significant.

4. Results

4.1 Patient and tumor characteristics

The data of a total of 1387 patients were eligible for this study. Of them, 422 (30.4%) were ER-negative (Fig. 1), 59 (4.3%) were ER-low positive (Fig. 2), and 906 (65.3%) were ER-high positive (Fig. 3). In the ER-low positive group, the median percentage of ER positivity was 2 (mean: 2.8, range: 1–5). Of note, no patients had an ER positivity ≥6%. The median age at diagnosis of the entire cohort was 32 years (mean 31.03, range: 5–35).

Patient and tumor characteristics in the three groups based on ER staining are shown in Table 1. There was no difference in age, pathological TNM stage and histological type among the three groups. Compared with the ER-negative and ER-low positive groups, the ER-high positive group had more patients with histological grade 2 and fewer patients with grade 3 ($p < 0.001$), while no difference was observed in histological grade between the ER-negative and ER-low positive groups. The

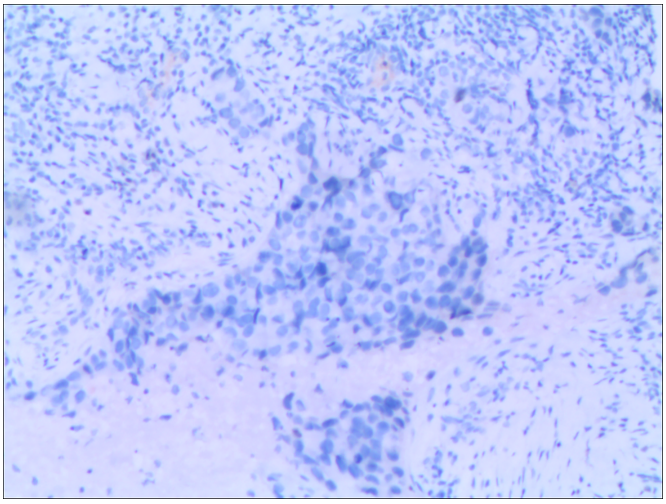

FIGURE 1. Immunohistochemical image of ER negative (×100).

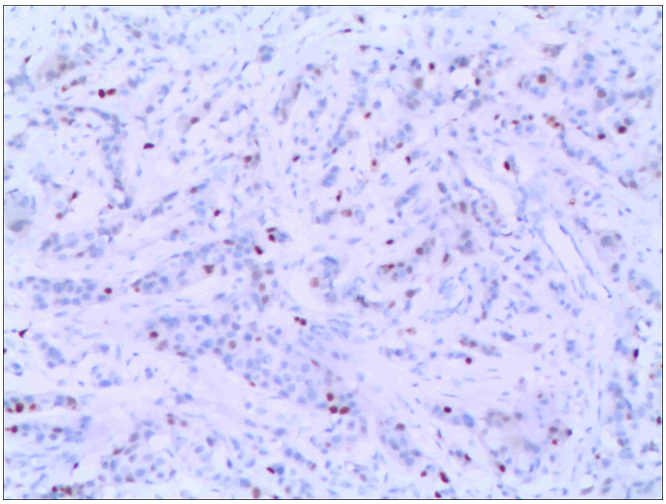

FIGURE 2. Immunohistochemical image of ER-low positive (×100).

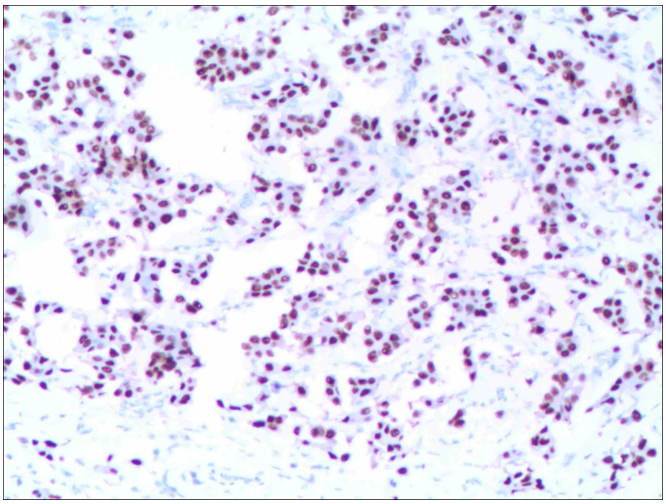

FIGURE 3. Immunohistochemical image of ER-high positive (×100).

T-stage was recorded as T0/TIS, T1, T2, T3 and T4. If the breast lesion was removed for pathological biopsy in another hospital before admission, the tumor T stage was marked as NA (Not Available). The Chi-square test showed a significant difference in T-stage among the three groups. Further analysis indicated that T3 patients in the ER-low positive groups were significantly higher than those in the ER-negative group, and there was no statistical difference in other T-stage between the three groups. In terms of lymph node metastasis, compared with the other two groups, the ER-negative group had the most N0 patients, while the ER-low positive group had the most N3 patients ($p = 0.001$). The number of HER-2 positive patients in the ER-high positive group was less than that in the other two groups ($p < 0.001$). In the ER-negative group, 87.2% of cases were progesterone receptor (PR) negative, 4.3% were PR-low positive, and 7.1% were PR-high positive. Comparatively, in the ER-low positive group, 25.4% of the cases were PR negative, 55.9% were PR-low positive and 16.9% were PR-high positive, while in the ER-high positive group, they were 7.4%, 7.5% and 72.7%, respectively. The least number of patients with PR-negative and the greater number of patients with PR-high positive was observed in the ER-high positive group ($p < 0.001$). A larger number of patients in the ER-high positive group underwent neoadjuvant chemotherapy compared with the other two groups ($p = 0.002$).

Adjuvant treatments, follow-up and recurrence in the three groups are shown in Table 2. The median follow-up time of the three groups was 74.5 (range: 3–165) months, 64 (range: 10–166) months and 74.5 (range: 10–167) months, respectively. There was no significant difference in the follow-up time, adjuvant chemotherapy and adjuvant radiation therapy between the three groups. In terms of endocrine therapy, differences were observed between the three groups, in which the ER-negative group underwent the least cycle of endocrine therapy while the ER-high positive group received the most number of endocrine therapy (10.2% *vs.* 47.5% *vs.* 97.5%; $p < 0.001$).

Since some patients with ER positivity did not receive endocrine therapy, we divided them into two categories: those with endocrine therapy and those without endocrine therapy, and compared their recurrence rates at different ER positive levels. The results showed that the recurrence rate of patients who received endocrine therapy was significantly different from those without endocrine therapy in all three groups ($p = 0.002$). Further analysis showed a significant statistical difference in recurrence rates between the ER-high positive and ER-negative groups. The recurrence rates of the three groups were also significantly different and were 44.2%, 25.8% and 21.2% in the ER-negative, ER-low positive and ER-high positive groups, respectively ($p = 0.031$). Pairwise comparison showed significant statistical difference between the ER-negative group and the ER-high positive group, whereby the recurrence rate of the latter was the lowest. In comparison, there was no statistical difference in recurrence rate among the three groups of patients who did not receive endocrine therapy.

4.2 Survival outcomes

At a median follow-up of 74 (range: 3–167) months, using the log-rank test, we found significant differences in DFS and OS among the three groups ($p < 0.0001$). The ER-high positive group had the longest DFS, 133.4 months, compared with the ER-negative group, 123.4 months ($p < 0.0001$) and the ER-low positive group, 124.5 months ($p < 0.05$), while there was no significant difference between the ER-negative group and the ER-low positive group ($p = 0.73$) (Fig. 4).

Similarly, there were significant differences in OS among the three groups ($p < 0.0001$). The median OS of the ER-high positive group (150.9 months) was superior to the ER-negative group (137.9 months; $p < 0.0001$) and ER-low positive group (139.1 months; $p < 0.05$), while there was no statistical difference between the OS of the latter two groups ($p = 0.77$) (Fig. 5).

Upon comparing the survival of patients with ER-low positive with or without endocrine therapy, we found no significant difference in DFS between patients with and without endocrine therapy in the ER-low positive group ($p = 0.71$) (Fig. 6). In addition, there was no significant difference in OS between patients with and without endocrine therapy in the ER-low positive groups ($p = 0.54$) (Fig. 7).

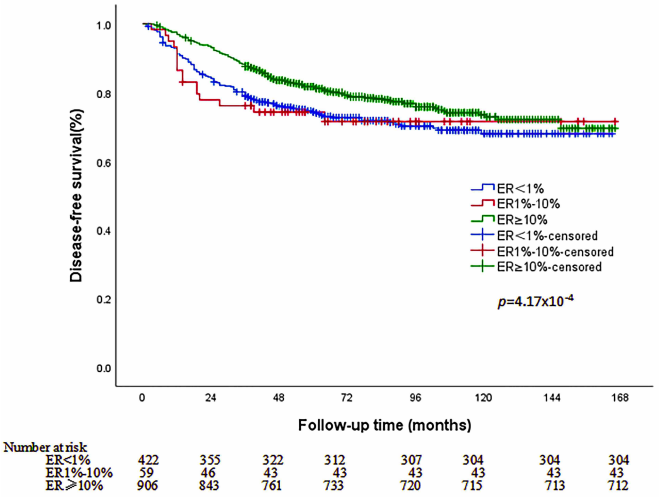

FIGURE 4. The disease-free survival of the three groups based on ER positivity. ER, estrogen receptors.

5. Discussion

Breast cancer is the most common female tumor and the first cause of cancer death among women, even in young women, and is also a leading cause of cancer-related death worldwide [4]. Young breast cancer patients are more likely to be diagnosed with more advanced stage disease due to more aggressive tumor characteristics, such as high-grade tumors, a higher proportion of human epidermal growth factor receptor 2 (HER-2)-positive and triple-negative histology, compared with older women [5]. In addition, the prognosis of young patients is worse than the elderly [6, 7]. Therefore, young patients, as a special group, were examined in this study. Similar to patients of other age, endocrine therapy is also an important treatment in young breast cancer patients. Recent

TABLE 1. Patient and tumor characteristics in the three groups based on ER staining.

Factors	ER staining			*p*-value
	<1% (n = 422)	1%–10% (n = 59)	≥10% (n = 906)	
Age at diagnosis, years				
Mean	30.11	30.64	31.27	0.952
Median (range)	31 (5–35)	31 (18–35)	32 (18–35)	
Clinical TNM stage				
0	9 (2.1)	1 (1.7)	16 (1.8)	
I	99 (23.5)	8 (13.6)	223 (25.7)	
II	200 (47.4)	27 (45.8)	414 (45.7)	0.494
III	83 (19.7)	19 (32.2)	184 (20.3)	
NA	31 (7.3)	4 (6.8)	69 (7.6)	
Postoperative pathological tumor stage				
0/Tis	11 (2.6)	1 (1.7)	15 (1.7)	
1	137 (32.5)	14 (23.7)	337 (37.2)	
2	198 (46.9)	28 (47.5)	394 (43.5)	0.011
3	25 (5.9)[a]	9 (15.3)[a]	70 (7.7)	
4	13 (3.1)	1 (1.7)	6 (0.7)	
NA	38 (9.0)	6 (10.2)	84 (9.3)	
Histology				
IDC/DCIS	395 (93.6)	52 (88.1)	839 (92.6)	
ILC	1 (0.2)	0 (0.0)	8 (0.9)	0.272
Mixed	2 (0.5)	1 (1.7)	2 (0.2)	
Others	24 (5.7)	6 (10.2)	57 (6.3)	
Tumor stage				
I	8 (1.9)	1 (1.7)	30 (3.3)	
II	261 (61.8)	37 (62.7)	716 (79.0)[b]	<0.001
III	123 (29.1)	16 (27.1)	90 (9.9)[b]	
NA	30 (7.1)	5 (8.5)	70 (7.7)	
Pathologic nodal stage				
N0	255 (60.4)[b]	24 (40.7)	475 (52.4)	
N1	83 (19.7)	17 (28.8)	240 (26.5)	
N2	45 (10.7)	4 (6.8)	87 (9.6)	0.001
N3	30 (7.1)	14 (23.7)[b]	87 (9.6)	
NA	9 (2.1)	0 (0.0)	17 (1.9)	
HER-2 status				
Positive	117 (27.7)	20 (33.9)	122 (13.5)[b]	
Negative	278 (65.9)	34 (57.6)	716 (79.0)	<0.001
NA	27 (6.4)	5 (8.5)	68 (7.5)	
PR status				
Positive <1%	368 (87.2)[c]	15 (25.4)[c]	67 (7.4)[c]	
Positive 1%–9%	18 (4.3)	33 (55.9)	68 (7.5)	<0.001
Positive ≥10%	30 (7.1)[c]	10 (16.9)[c]	659 (72.7)[c]	
NA	6 (1.4)	1 (1.7)	112 (12.4)	
Preoperative chemotherapy				
Yes	326 (77.3)	40 (67.8)	753 (83.1)[b]	0.002
No	96 (22.7)	19 (32.2)	153 (16.9)	

NA, not available; IDC, invasive ductal carcinoma; DCIS, ductal carcinoma in situ; ILC, invasive lobular carcinoma; PR, progesterone receptor. ER, estrogen receptors; HER, human epidermal growth factor receptor. TNM, Tumor Node Metastasis.

a: There was a difference between the two groups marked with a.

b: There was a difference between the group marked with b and the other two groups.

c: There were differences among the three groups.

TABLE 2. Adjuvant treatments, follow-up and recurrence in the three groups based on ER staining.

Factors	ER staining			*p*-value
	<1% (n = 422)	1%–10% (n = 59)	≥10% (n = 906)	
Adjuvant chemotherapy				
Yes	404 (95.7)	56 (94.9)	861 (95)	
No	11 (2.6)	2 (3.4)	31 (3.4)	0.961
NA	7 (1.7)	1 (1.7)	14 (1.5)	
Adjuvant endocrine therapy				
Yes	43 (10.2)[b]	31 (47.5)[b]	883 (97.5)[b]	
No	387 (89.6)[b]	28 (52.5)[b]	20 (2.2)[b]	<0.001
NA	1 (0.2)	0 (0.0)	3 (0.3)	
Adjuvant radiation therapy				
Yes	219 (51.9)	33 (55.9)	453 (50.0)	
No	199 (47.2)	23 (39)	438 (48.3)	0.118
NA	4 (0.9)	3 (5.1)	15 (1.7)	
Follow-up time, months				
Mean	80.23	70.32	79.89	0.122
Median (range)	74.5 (3–165)	64.0 (10–166)	74.5 (10–167)	
Recurrence				
Yes	118 (28.0)[a]	16 (27.1)	194 (21.4)[a]	0.031
No	304 (72.0)	43 (72.9)	712 (78.6)	
Recurrence in patients who received endocrine therapy				
Yes	19 (44.2)[a]	8 (25.8)	188 (21.2)[a]	0.002
No	24 (55.8)	23 (74.2)	698 (78.8)	
Recurrence in patients who did not receive endocrine therapy				
Yes	99 (26.1)	8 (28.6)	6 (30.0)	0.896
No	280 (73.9)	20 (71.4)	14 (70.0)	

a: There was a difference between the two groups marked with a.
b: There were differences among the three groups.

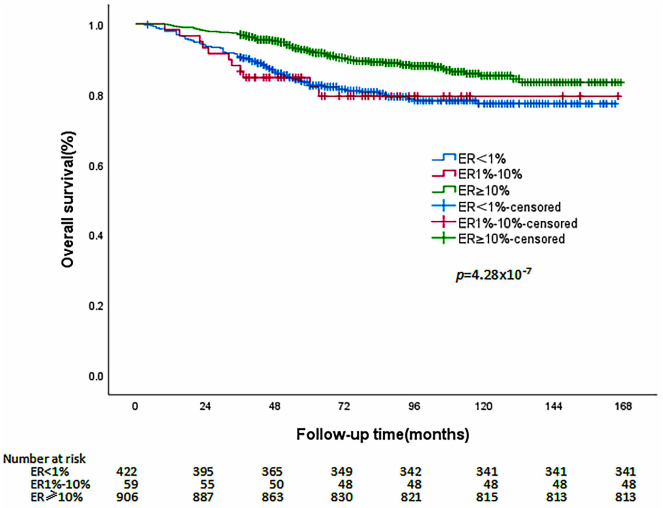

FIGURE 5. The overall survival of the three groups based on ER positivity. ER, estrogen receptors.

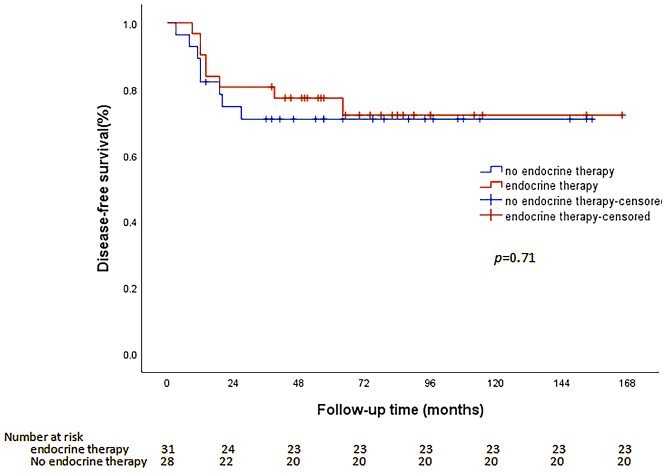

FIGURE 6. The disease-free survival of patients with or without endocrine therapy in the ER-low positive group.

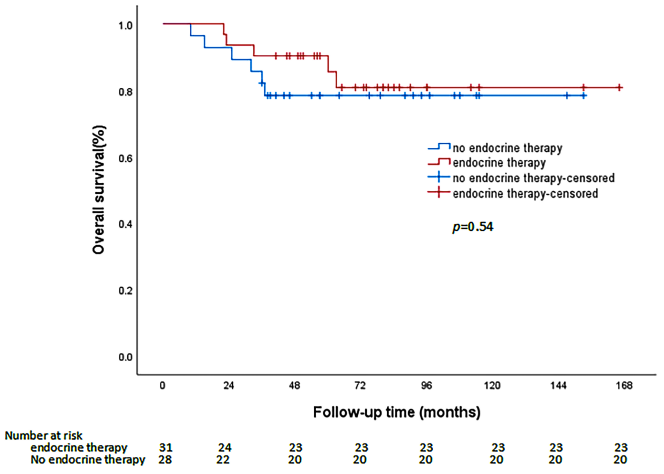

FIGURE 7. The overall survival of patients with or without endocrine therapy in the ER-low positive group.

updates of the TEXT and SOFT trials confirmed previous data and supported endocrine therapy for breast cancer patients [8, 9]. Even in new adjuvant treatment of young patients, endocrine therapy is still under investigation [10]. This study mainly focused on the pathological and clinical characteristics of different expression states of ER in young patients and the difference in prognosis.

The premise of endocrine therapy is ER-positivity. The criterion for ER positivity in breast cancer is an ER positivity ≥10% on immunohistochemistry. In 2010, the ASCO/CAP (American Society of Clinical Oncology/College of American Pathologists) guidelines decreased the threshold for ER positivity to 1% [11], which is now widely accepted. Some studies showed a beneficial response to anti-estrogen therapy in such cancers with ER positivity 1%–10% [12]. However, few studies have shown that increased ER expressions might have increased benefits from hormonal therapy [13]. Some follow-up studies showed that in patients with low ER expression (ER positivity, 1%–10%), their clinicopathological characteristics and prognosis were similar to ER-negative patients [14], but the effects of endocrine therapy were not satisfactory for them. Further, there are no studies concerning any potential benefits from endocrine therapy in young breast cancer patients with low expression levels of ER. The incidence rate of breast cancer in young people is increasing annually [15], yet studies on young breast cancer patients with low ER expression, despite urgently needed, remain limited. Considering the long-term economic burden, potential adverse events of endocrine therapy (*i.e.*, cardiovascular, bone morbidity, cognitive impairment, *etc.*), and the choice of suspending treatment for young women's childbearing [16], it is very important to determine whether young breast cancer patients with ER-low positive require endocrine therapy. Therefore, one aspect of this study was to focus on the potential benefits of young female patients with low ER expression from endocrine therapy.

At present, there is no unified standard for the age definition of young breast cancer patients, and they have been grouped as ≤40, ≤35 and ≤30 years old [17]. The ESO-ESMO (European School of Oncology/European Society for Medical Oncology) considers 40 years as the boundary [18]; however, Han *et al.* [19] reported that for breast cancer patients under 35 years old, the risk of death decreased by 5% for every increase in one year of age, while in premenopausal patients over 35 years old, no change in death risk with age was observed, which seems to support the view of 35 years old as the optimal threshold for age. The TEXT and SOFT trials reported that patients under 35 years old benefited the most from OFS (Ovarian Function Suppression) [20]. Thus, based on current evidence and literature, we defined young breast cancer patients as those ≤35 years old in this study.

Breast cancer in women ≤35 years is rare, comprising of 2%–4.8% of the newly diagnosed cases [1]. We identified 1387 patients with primary breast cancer treated at our hospital from January 2006 to December 2016, of whom 30.4%, 4.3% and 65.3% were ER-negative, ER-low positive and ER-high positive. However, according to M Yi's research, among the breast cancer population regardless of age, this proportion were 16.9%, 2.6% and 80.5%, respectively [3]. In the ER-low positive group of this study, ER positivity ranged from 1% to 5%, and there were no patients with ER positivity ≥6%. Two previous studies indicated that patients with ER positivity

ranged between 1% to 5% and accounted for the majority of the cases, while the proportion of patients with ER positivity >6% was lesser, at 66.9% *vs.* 33.1% and 92% *vs.* 8%, respectively [3, 21].

There was no difference in age, TNM stage, histological type and adjuvant chemotherapy between the three groups in this study. Although they were both classified as ER-positive, patients with ER-low positive were found to have different clinical and pathologic characteristics from ER-high positive patients but similar to those in the ER-negative group, which was concordant with a previous study [22]. Compared with the ER-high positive group, patients with ER-low positive had higher histological grade, more lymph node metastasis, HER-2 positive and PR negative or low PR expression cases. Deyarmin *et al*. [23] investigated the molecular subtypes of ER-low positive tumors and observed that low-ER-staining tumors were clinicopathologically more similar to ER-negative than ER-positive tumors, with 88% being basal-like or HER-2-enriched.

Since previous studies have shown that breast-conserving therapy is safe in young patients [24], patients in this study received breast-conserving surgery or mastectomy according to their tumor condition, and their median follow-up was 74 months. The results of postoperative follow-up showed that the DFS of the young women was 79% at 5 years and 72% at 10 years, and their OS was 88% at 5 years and 82% at 10 years. According to data from the American Cancer Society, among all women with invasive breast cancer, their OS was 89% at 5 years and 83 % at 10 years [25]. In a study comprising of breast cancer patients aged ≤40 years and a median follow-up of 124 months, the authors reported a DFS of 93% at 5 years and 84.5% at 10 years, while the OS was 93% and 86.5% [24]. In this present study, we found that the DFS and OS of the ER-low positivity group were significantly lower than those in the ER-high positive group and similar to those in the ER-negative group. Moreover, for patients in this group, even if they received endocrine therapy, no significant improvements in their DFS and OS were observed. One of the reasons for such poor effects of endocrine therapy in patients with low ER expression might be the lack of PR expression [26]. In addition, in this study, we found that the proportion of negative or low expression levels of PR in ER low expression group was significantly higher than in the ER-high positive group. A previous study showed that the survival of patients in the ER-low positive group was between those of the ER-negative group and ER-high positive group, and after examining the molecular phenotypes of the low ER staining tumors, the authors found that 48% of the low-ER tumors were ER negative and the survival of this group was intermediate of ER-positive (≥10%) and ER-negative (<1%) [27]. Since all patients in this study were ER-positive <6%, we did not further classify the patients with ER-low positive breast cancer. In a retrospective study comprising of 1257 patients, the authors reported that the proportion of ER/PR was <1%, ER/PR was 1%–5% and ER/PR was 6%–10%, and after a median follow-up of 40 months, they found no significant difference in 3-year recurrence-free survival (RFS) or OS between the three groups of patients. Among the 1257 enrolled patients, 118 patients received endocrine therapy, of which 81 patients with ER-positive 1%–10%. Receipt of hormonal therapy did not significantly impact RFS within people with ER-positive 1%–5% (p = 0.57) but it had a marginal impact among people with ER-positive 6%–10% (p = 0.05). And hormonal therapy did not significantly impact OS within the patients with ER-positive 1%–10% (Group ER-positive 1%–5%: p = 0.53; Group ER-positive 6%–10%: p = 0.23) [21]. Thus, these suggested that in the ER low expression group, the expression level of ER might have no significant effect on the prognosis of the patients.

This study had some limitations. First, this was a retrospective study, and treatment was not assigned in a randomized fashion. Due to the loss of follow-up and incomplete data, some patients could not be included for analysis. Second, As this study is part of a series of studies, the follow-up deadline is somewhat out-dated. We will update the data in future reports. Third, the number of patients in the ER-positive (1%–9%) group was too small, with only 59 cases, and we could not further distinguish the clinicopathological characteristics and prognosis of patients with different ER expression levels. Therefore, for young patients with ER-low positive, further research is still needed to guide more accurate and comprehensive treatments.

6. Conclusions

In conclusion, young breast cancer patients with ER-low positive disease have clinical and pathological characteristics more similar to ER-negative than ER-high positive patients, and they do not appear to benefit from endocrine therapy. Although breast cancer patients ≤35 years old still account for a small proportion of the overall breast cancer patients, the absolute number of these cases is huge due to the high incidence rate of breast cancer. Thus, it is necessary to make further efforts to identify this population's molecular subtypes to confirm the positive boundary of ER expression in young breast cancer patients.

AUTHOR CONTRIBUTIONS

HL—designed the research study. SW and YL—performed the research. SW and XQ—analyzed the data. SW—wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All patients provided signed informed consent prior to treatment initiation, and this study was approved by the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital (NO.bc2020071).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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