RESEARCH ARTICLE

Full Compliance of Adjuvant Endocrine Therapy Is Associated with Higher Disease-Free Survival in Hormone Receptor-Positive and HER2-Negative Chinese Breast Cancer Patients with First Tumor Recurrence

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Abstract

   Purpose: To characterize the compliance status of adjuvant endocrine therapy (aET) and its relationship with disease-free survival (DFS) in hormone receptor-positive (HR+) and HER2-negative (HER2−) in Chinese breast cancer (BC) patients with first tumor recurrence. **Methods:** All women with primary unilateral stage I – III HR+HER2− BC and first tumor recurrence in 2008 - 2018 at our institution were identified. Full (vs. none/partial) compliance of aET was classified from records. Multivariate Cox regression estimated the hazard ratio (HR), its 95% confidence interval (CI), and p value. DFS. Covariates included age, T stage, N stage, pathology, tumor grade, LVI, chemotherapy, radiotherapy. **Results:** A total 258 patients had average age 47.4 years at BC diagnosis and median DFS 31.7 months. Patients with ipsilateral (contralateral) region and organ recurrence were 47.7% (19.8%) and 71.9%. Compared to the patients with none/partial compliance of aET, the full compliance patients (54.3%) had a higher DFS (median 35.0 vs. 25.2 months, p=0.009). Multivariate analysis showed that the full compliance of aET was associated with a lower HR 0.614 (95%CI 0.467 – 0.807, p<0.001) on recurrence. Early discontinuation (67.5%, 56/83) due to the drug side effects was the top reason for partial compliance of aET. **Conclusions:** Full compliance of aET was quite low in Chinese HR+HER2− BC patients. However, it was associated with a 38.6% lower risk of first tumor recurrence. To search for effective tools to improve the compliance of aET in this population should be stressed.

   Keywords: Breast cancer- hormone receptor-positive- endocrine therapy- drug compliance- disease-free survival

Introduction

   The receptor-based systemic therapies are increasingly important for both tumor and mortality control in breast cancer (BC) patients (Caparica, 2019; Waks and Winer, 2019). Among them, the effectiveness of adjuvant endocrine therapy (aET) for 5 - 10 years in hormone receptor-positive (HR+, estrogen or progesterone receptor-positive [ER+/PR+]) and HER2-negative (HER2−) BC patients has been evidenced for years (Burstein et al., 2019). The recent studies even showed that aET alone is an adequate adjuvant systemic therapy for the early HR+ HER2− BC patients which have carcinoma in situ, cT1N0, 1 - 2 axillary metastatic lymph nodes (LN), and low 21-gene recurrence index score (Sparano et al., 2019; Ahmed et al., 2020). Some studies further indicated that the neoadjuvant endocrine therapy (nET) with suitable drugs

for certain duration could provide a equivalent clinical benefit to neoadjuvant chemotherapy (NAC) in locally advanced HR+ HER2− BC patients (Madigan et al., 2020). However, in contrary to these findings, a low compliance of oral aET continues to be a prevalent issue in many countries for different reasons. The reasons behind are often involved with a wide range of numerous elements on patient, physician, side effects, drug cost, and others (Farias and Du 2017; Paranjpe et al., 2019; Clancy et al., 2020; Hwang et al., 2020; Peddie et al., 2021). So far, the majority of studies on the compliance of aET were conducted in the developed countries and mostly among the non-Asian BC patients (Clancy et al., 2020; Peddie et al., 2021). Given the affirmative roles of race and healthcare system in influencing compliance of oral aET, we decided to have a retrospective analysis on a cohort of HR+HER2− Chinese BC patients with first tumor

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recurrence over a period of time. In the study, we aimed to explore how they had faithfully taken the prescribed aET drugs, and characterize the risk profile of compliance status of patients on disease-free survival (DFS).

Materials and Methods

Patients and study design

All women with unilateral stage I – III HR+HER2− BC patients with first tumor recurrence in 2008 – 2018 at our institution were identified for the study. All recurrence diagnosis were supported by imaging of ultrasound, CT, MRI, or PET. For the locoregional recurrence, there should be a pathology report for confirmation. In the study, the ipsilateral or contralateral locoregional region referred to the chest wall/breast, and four lymphatic drainage regions of breast (axillary, supraclavicular, subclavian, and internal mammary one). Patient's inclusion criteria included: (1) BC diagnosis at age $\geq$ 18 years and in 1997 or later (2) Immunohistochemistry (IHC) test results on HR and HER2 status from the primary tumor (3) HR+ HER2− subtype of primary tumor; HR+ was defined as ER+ or PR+ (both criteria were $\geq$ 1% by the IHC method); HER2− was defined as IHC 0 or 1+, or fluorescence in situ hybridization (FISH)-negative on the IHC 2+ tumor. Patient's exclusion criteria included: (1) inflammatory or bilateral primary BC (2) recurrence emerged before the completion of surgery, chemotherapy, and radiotherapy (RT) if the patient had (3) tumor recurrence likely from other malignant diseases.

In analysis, the primary tumor diagnosis date was defined as the baseline. The earliest date of first recurrence diagnosis was defined as the endpoint date. DFS in days was calculated as the result of the endpoint date minus the baseline + 1. Two specific events of ipsilateral or contralateral locoregional recurrence, and organ recurrence were also considered for the specified event-free Cox analysis. The final covariates were determined from the review of univariate analysis result and literature.

This study was approved by the Research Ethics Committee of the Fourth Hospital of Hebei Medical University (FHHMU # 2019-166). For this type of study, the written formal consent is not required. All sensitive health information of participants was excluded from the study dataset.

Endocrine therapy and its compliance

Patient's compliance status of aET was summarized from the chart records and supplemented by phone call to patient or her caregiver. Only oral aET drugs were taken and they included tamoxifen (TAM), toremifene, letrozole, anastrozole and exemestane. There were not the ovarian function suppression (OFS) drugs (goserelin, leuprolide) used for the primary disease. Neither were there nET, ovarian RT, and ovariectomy administered for the primary BC. After the careful review on the data, two compliance status of oral aET was categorized. The full compliance was assigned to the patients who had faithfully taken all of oral aET drugs as prescribed for at least 5 years or until the tumor recurrence. None or partial compliance was assigned to the remaining patients. The

specific reasons for none or partial compliance were also collected if available.

Statistical methods

Continuous and categorical variables were summarized by the descriptive statistics. Analysis of variance (ANOVA), Chi-square or Fisher's exact tests if appropriate were used for comparison. The Kaplan-Meier curve with log-rank test was utilized for survival data. Cox regression model was used to evaluate the hazard ratio (HR), its 95% confidence interval (CI) and p value. Two-sided p < 0.05 was considered the statistically significance level. All statistical analyses were performed with SAS 9.4 for Windows.

Results

Characteristics at baseline

In total, 258 patients were analyzed. The full compliance rate of aET was 54.3%. Table 1 showed that except for tumor grade, other characteristics were not associated with the compliance status. In patients with none (15%, 21/140) and partial (85%, 119/140) compliance, there were only 14 (66.7%, 14/21) and 33 (27.7%, 33/119) patients who had not the reasons available. The listed reasons for none compliance were the 'physician did not prescribe' (n =3), 'ignored as she believed that she was tumor-free' (n =3), 'was too concerned of side effects written in drug labels' (n =1). Only 83 patients with partial compliance had the reasons - 'early discontinuation due to the intolerable side-effects of drugs' (56/83, 67.5%), 'irregular or occasional use because of lowering faith of drug effectiveness over time' (17/83, 20.5%). No analysis on the poor compliance reasons was possibly pursued.

Characteristics of tumor recurrence or metastasis

Table 2 showed that they had average age 50.5 years and median DFS 31.7 months at tumor recurrence. Two top locoregional recurrences at ipsilateral sites were chest wall (11.2%) and supraclavicular LN while they at contralateral sites were the supraclavicular LN (12.4%) and axillary LN (7.7%) (data not shown). Top three metastatic organs were bone (46.1%), liver (24.0%) and lung (22.5%). A significant relationship of liver metastasis with the compliance status of aET was observed (p = 0.015).

Cox regression analysis

Figure 1 showed that the patients with full compliance of aET had a higher DFS median compared to none or partial compliance patients (p=0.009). Multivariate analysis indicated that the full compliance patients were still significantly associated with a 38.6% decreased risk of recurrence (HR 0.614, 95%CI 0.467 – 0.807, p<0.001) (Table 3). In the event-free survival analysis of recurrence at the ipsilateral/contralateral regions, multivariate analysis showed that the full compliance status of aET (vs. none/partial compliance, HR 0.491, 95%CI 0.327 – 0.739, p =0.001) and RT (HR 0.615, 95%CI 0.388 – 0.976, p =0.039) were associated with a better event-free survival (data not shown). However, in the event-free survival analysis of organ recurrence, the compliance status of aET,
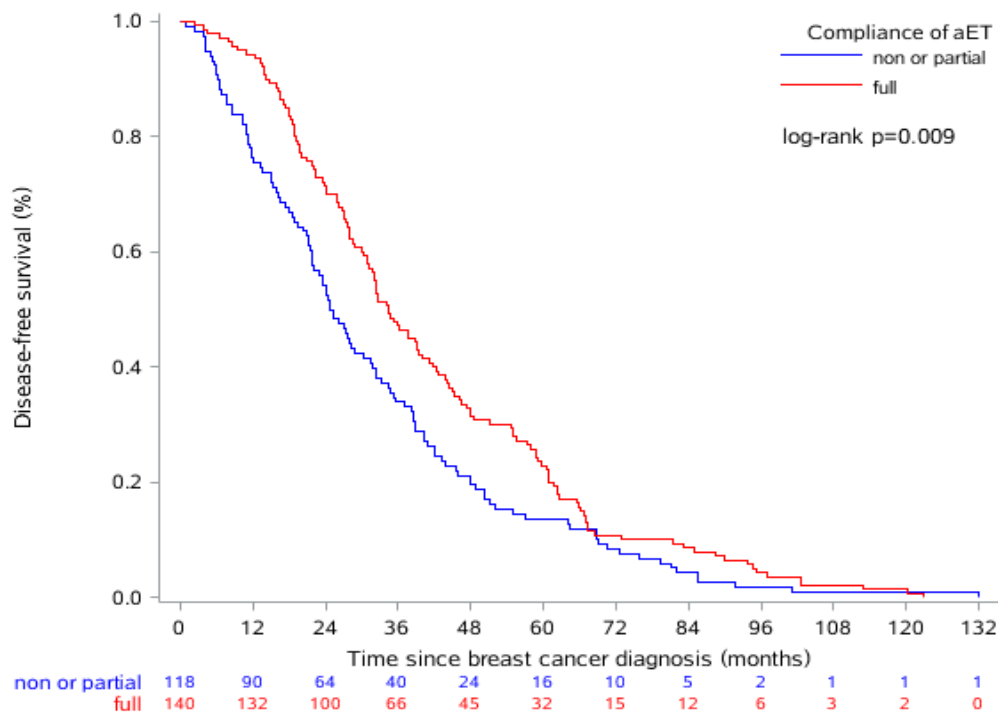
Figure 1. The Kaplan-Meier Disease-Free Survival Curves for Patients Grouped by Patient Compliance Status of Oral aET

chemotherapy and RT were not significantly associated with the event-free survival ($p = 0.213 – 0.265$) (data not shown). Last, the relationship of liver metastasis with the compliance status of aET was no longer significant at multivariate analysis ($p = 0.605$) (data not shown). In our review, the clinical diagnosis of organ recurrence by imaging could complicate the specified event-free survival analysis.

Discussion

Taking the aET drug for 5 to 10 years becomes one standard systemic therapy for HR+HER2− BC (Caparica et al., 2019; Burstein et al., 2019; Waks and Winer, 2019). However, like in many chronic diseases, low compliance of oral aET drug is a prevalent issue (Neugut et al., 2016; Paranjpe et al., 2019). In this retrospective study, we have analyzed 258 Chinese BC patients with first tumor recurrence over 11 years at a cancer center, and found that the full compliance rate of oral aET was only 54.3%. Through the multivariate analysis, the full compliance patients had a 38.6% decreased risk of tumor recurrence, compared to none or partial compliance patients. In our review, this finding could be used to empower the physician and patient to make greater efforts to improve the compliance of oral aET especially in Chinese BC patients.

HR+HER2− subtype approximately accounts for 70% BC patients (DeSantis et al., 2019). Because the ER signal pathway is the main driving force for tumor cell growth and survival, aET has been the most effective therapy for HR+HER2− BC (Prat et al., 2015). As mentioned before, recent studies have demonstrated that aET alone could be adequately reduce the tumor recurrence and its related death to the similar level as the aET plus chemotherapy in the low-risk patients (Sparano et al., 2019; Ahmed et al., 2020; Krauss and Stickeler, 2020). At present, tailoring aET with the OFS drugs are also proved to be able to further improve the DFS and OS of the premenopausal HR+HER2− patients with high-risk factors (Francis et al., 2018). In addition, more recent studies have suggested that aET combined with CDK4/6 inhibitors could significantly improve the prognosis for the relapsed or advanced-stage patients (Agostinetto et al., 2021). Taking into account these facts, it is so foreseeable that the optimal compliance of aET would become increasingly important to result in the best prognosis of HR+HER2− BC patients.

Low aET compliance of aET is also prevalent in BC patients with other races (Clancy et al., 2020; Peddie et al., 2021). Studies on the non-Chinese population demonstrated that the poor compliance of aET had negatively impacted on the tumor control in HR+ patients (Hershman et al., 2011; Chirgwin et al., 2016). Regarding the reasons for non-compliance, the BIG 1-98 trial data indicated that there were two measures of low adherence (early cessation of letrozole and a compliance score of < 90%) were both significantly associated with a reduced DFS with adjusted HR 1.45 ($p = 0.01$) and HR 1.61 ($p = 0.02$), compared to the counterparts (Chirgwin et al., 2016). In theory, there are two aspects of oral drug compliance. First, it is the adherence, which reflects the consistency of timing, dosage, and frequency of medication with the prescribed. Second, it is the persistence, which refers to the continuity of medication from the beginning to the end (Wassermann et al., 2019). In this study, we were not able to distinguish both aspects of the partial compliance for analysis.

Like other countries, oral aET drugs in China mainly

Table 1. Characteristics of Patient and Tumor at Baseline and Their Comparisions by Patient Compliance Status of aET

Variable	All (n, %)	Compliance status of aET (n, %)		
		Full	None or Partial	p[a]
Patients	258 (100.0)	118 (45.7)	140 (54.3)	
Age (years)				
mean ± std	47.4±10.2	47.7±11.2	47.1± 9.4	0.660
median(Q1-Q3)	47 (40 - 54)	47.5 (40 - 56)	46.5 (40 - 54)	0.687
<35	31 (12.0)	16 (11.4)	15 (12.7)	0.380
<45	75 (29.1)	42 (30.0)	33 (28.0)	
<55	89 (34.5)	50 (35.7)	39 (33.1)	
<65	49 (19.0)	28 (20.0)	21 (17.8)	
≥65	14 (5.4)	4 (2.9)	10 (8.5)	
Diagnosis year [b]				
1997~2010	110 (42.6)	59 (42.1)	51 (43.2)	0.862
2011~2016	148 (57.4)	81 (57.9)	67 (56.8)	
Tumor Laterality				
Left	141 (54.7)	70 (50.0)	71 (60.2)	0.102
Right	117 (45.3)	70 (50.0)	47 (39.8)	
Surgery				
Lumpectomy	8 (3.1)	1 (0.9)	7 (4.7)	0.087
Mastectomy	250 (96.9)	107 (99.1)	143 (95.3)	
LN dissections				
ALND	240 (93.0)	127 (90.7)	113 (95.8)	0.113
SLND	6 (2.3)	4 (2.9)	2 (1.7)	0.691
IMLND	7 (2.7)	2 (1.4)	5 (4.2)	0.252
T stage				
T1	60 (23.3)	30 (21.4)	30 (25.4)	0.729
T2	138 (53.5)	75 (53.6)	63 (53.4)	
T3-4	39 (15.1)	24 (17.1)	15 (12.7)	
Unknown	21 (8.1)	11 (7.9)	10 (8.5)	
N stage				
N0	103 (39.9)	63 (45.0)	40 (33.9)	0.349
N1	79 (30.6)	40 (28.6)	39 (33.1)	
N2	27 (10.5)	11 (7.9)	16 (13.6)	
N3	40 (15.5)	21 (15.0)	19 (16.1)	
Unknown	9 (3.5)	5 (3.6)	4 (3.4)	
Tumor pathology				
IDC	206 (79.8)	118 (84.3)	88 (74.6)	0.053
Other	52 (20.2)	22 (15.7)	30 (25.4)	
Tumor grade				
I	2 (0.8)	1 (0.7)	1 (0.8)	0.041
II	159 (61.6)	97 (69.3)	62 (52.5)	
III	57 (22.1)	25 (17.9)	32 (27.1)	
Not reported	40 (15.5)	17 (12.1)	23 (19.5)	
LVI				
Positive	83 (32.2)	42 (30.0)	41 (34.7)	0.703
Negative	56 (21.7)	32 (22.9)	24 (20.3)	
Not reported	119 (46.1)	66 (47.1)	53 (44.9)	

aET adjuvant endocrine therapy, std standard deviation, Q1 first quartile, Q3 third quartile, LN lymph node, ALND axillary LN dissection, SLND supraclavicular LN dissection, IMLND internal mammary LN dissection, IDC invasive ductal carcinoma, LVI lymphovascular invasion, NAC neoadjuvant chemotherapy, AC adjuvant chemotherapy, RT radiotherapy. [a] p value from ANOVA or Chi-square or Fisher's exact test if appropriate in patients with actual values. [b] Fluorescence in situ hybridization (FISH) test became mandatory for patients with HER2 IHC 2+ since 2011.

Table 1. Continued

Variable	All (n, %)	Compliance status of aET (n, %)		
		Full	None or Partial	pª
Chemotherapy				
NAC	57 (22.1)	28 (20.0)	29 (24.6)	0.377
AC	233 (90.3)	127 (90.7)	106 (89.8)	0.811
Any	247 (95.7)	135 (96.4)	112 (94.9)	0.549
RT				
No	150 (58.1)	79 (56.4)	71 (60.2)	0.544
Yes	108 (41.9)	61 (43.6)	47 (39.8)	

aET adjuvant endocrine therapy, std standard deviation, Q1 first quartile, Q3 third quartile, LN lymph node, ALND axillary LN dissection, SLND supraclavicular LN dissection, IMLND internal mammary LN dissection, IDC invasive ductal carcinoma, LVI lymphovascular invasion, NAC neoadjuvant chemotherapy, AC adjuvant chemotherapy, RT radiotherapy. ª p value from ANOVA or Chi-square or Fisher's exact test if appropriate in patients with actual values. ᵇ Fluorescence in situ hybridization (FISH) test became mandatory for patients with HER2 IHC 2+ since 2011.

included two categories - selective ER modulators (SERMs) and aromatase inhibitors (AIs). At each category, they have the similar efficacy in controlling BC but with slightly different side effects (Caparica et al., 2019; Sparano et al., 2019). Low compliance of TAM (the most commonly used SERMs) is primarily due to the menopausal-related symptoms including hot flashes, sleep disturbance, vaginal dryness, and loss of libido (Moon et al., 2017; Peddie et al., 2021). Because that TAM is also associated with the slightly increased odds of infertility, venous thrombosis, and endometrial cancer, the fear of these serious adverse was reported to be main reason for the non-taker of TAM (Sawesi et al., 2014).

For AIs drugs, their commonest side effects include the musculoskeletal symptoms like muscle pain, joint pain or stiffness and risk of bone fracture due to the reduced bone density (Sawesi et al., 2014; Tenti et al., 2020). These side effects have significant and negative impact on the continuation of AIs among the postmenopausal patients (Roberts et al., 2017). In this study, among 83 Chinese patients with reasons for partial compliance, the early withdrawal (67.5%) due to the side effects was found to be the commonest mode. Similarly, the BIG 1-98 trial data showed that adverse events were mostly accounted for the early discontinuation (82.7%) (Chirgwin et al., 2016). Therefore, it seems there is still a large room for the

Table 2. Characteristics of Patient and Tumor at Recurrence and Their Comparsions by Patient Compliance Status of aET

Variable	All (n, %)	Compliance Status of aET (n, %)		
		Full	None or Partial	pª
Patients	258 (100.0)	118 (45.7)	140 (54.3)	
Age (years)				
mean ± std	50.5±10.6	50.4±11.7	50.5± 9.7	0.926
median (Q1- Q3)	50 (43 - 58)	49 (43 - 59)	51 (44 - 57)	0.911
DFS (months)				
median (95%CI)	31.7 (27.8 - 35.0)	35.0 (31.3 - 40.6)	25.4 (22.0 - 31.8)	0.009
Recurrence site				
ipsilateral region	123 (47.7)	61 (43.6)	62 (52.5)	0.151
contralateral region	51 (19.8)	29 (20.7)	22 (18.6)	0.677
Involved organ at recurrence				
bone	119 (46.1)	69 (49.3)	50 (42.4)	0.267
liver	62 (24.0)	42 (30.0)	20 (16.9)	0.015
lung	58 (22.5)	35 (25.0)	23 (19.5)	0.291
brain	10 (3.9)	5 (3.6)	5 (4.2)	1.000
other	38 (14.7)	20 (14.3)	18 (15.3)	0.827
any	183 (70.9)	104 (74.3)	79 (66.9)	0.196
Recurrence pattern				
region only	54 (20.9)	24 (17.1)	30 (25.4)	0.213
organ only	135 (52.3)	79 (56.4)	56 (47.5)	
region and organ	69 (26.7)	37 (26.4)	32 (27.1)	

aET adjuvant endocrine therapy, std standard deviation, Q1 first quartile, Q3 third quartile, DFS disease-free survival, CI confidence interval. ª p value from ANOVA, Chi-square test, Fisher's exact test or log-rank test.

Table 3. Cox Regression Analysis of DFS on the Patient Compliance Status of aET and Select Ccovariates

Outcome	Variable	Class	Univariate			Multivariate [a]		
DFS	Tumor		HR	95%CI	p	HR	95%CI	p
	T stage	T1	1.000		ref.	1.000		ref.
		T2	1.033	(0.762- 1.400)	0.835	0.989	(0.712- 1.375)	0.948
		T3	1.351	(0.900- 2.028)	0.146	1.213	(0.776- 1.898)	0.397
	N stage	N0	1.000		ref.	1.000		ref.
		N1	1.230	(0.914- 1.655)	0.171	1.008	(0.725- 1.401)	0.962
		N2	1.134	(0.738- 1.743)	0.565	0.729	(0.447- 1.188)	0.205
		N3	1.894	(1.303- 2.755)	0.001	1.021	(0.657- 1.586)	0.926
	IDC	Yes	1.311	(0.960- 1.791)	0.088	1.205	(0.788- 1.842)	0.389
		No	1.000		ref.	1.000		ref.
	LVI	Yes	1.185	(0.844- 1.665)	0.327	1.281	(0.878- 1.871)	0.199
		No	1.000		ref.	1.000		ref.
		Unknown	0.999	(0.752- 1.328)	0.995	1.047	(0.747- 1.477)	0.795
	Treatment							
	NAC/AC	Yes	1.494	(0.771- 2.894)	0.234	1.559	(0.739- 3.291)	0.244
		No	1.000		ref.	1.000		ref.
	RT	Yes	1.114	(0.869- 1.429)	0.394	0.932	(0.689- 1.260)	0.646
		No	1.000		ref.	1.000		ref.
	aET	full	0.722	(0.564- 0.924)	0.010	0.614	(0.467- 0.807)	<0.001
		none/partial	1.000		ref.	1.000		ref.

aET, adjuvant endocrine therapy; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; IDC, invasive ductal carcinoma; LVI, lymphovascular invasion; NAC, neoadjuvant chemotherapy; AC, adjuvant chemotherapy; ref, reference; RT, radiotherapy; [a] Final covariates included diagnosis age of primary disease, T stage, N stage, pathology, grade, LVI, NAC/AC, RT, diagnosis year of primary disease was after 2010.

compliance improvement of oral aET drugs by optimally controlling their side effects.

Except the drug side effects, many other factors are also found to be associated with the low compliance of aET (Hadji et al., 2013; Sawesi et al., 2014; Cahir et al., 2015; Farias and Du, 2017). Given that the medication compliance is a complex and dynamic behavior, it is associated with many aspects such as patient demographic and socio-economic status, patient comorbidity, and patient daily performance, other therapy-related adverse or efficacy, and others (Sawesi et al., 2014; Chirgwin et al., 2016; Farias and Du, 2017; Moon et al., 2017; Paranjpe et al., 2019; Wassermann et al., 2019; Clancy et al., 2020; Hwang et al., 2020). Farias and Du (2017) analyzed 8,688 Medicare BC patients, and found that 36.8% patients were non-adherent to aET, and the racial/ethnic disparities in aET adherence could be largely explained by women's differences in socioeconomic status and out-of-pocket medication costs. Hadji et al., (2013) conducted a retrospective analysis over 17,000 BC patients, and found that age <50 (vs. >70) year (p < 0.001), treatment in the gynecologist (vs. general practitioner) practice (p < 0.001), presence of comorbidities like diabetes (p < 0.001) or depression (p < 0.002) were associated with the decreased risk of therapy discontinuation. In this study, the patient's age and age group at baseline were not found to be related to the compliance status (p = 0.380 – 0.687).

This study has strengths and weakness. The strengths included: (1) it was a large study of aET compliance in HR+HER2− Chinese BC patients with recurrence (2)

many covariates were adjusted in estimating the risk profile of compliance status on any or specified event-free survival (3) all patients were consistently followed up at one institution. The weakness included: (1) there was not different risk of tumor recurrence between the patients without aET and the patients with the partial compliance of aET presumably due to the smaller sample sizes of subgroups. (2) lack of adequate and high-quality reasons and side effect data for the necessary analysis in order to identify the factors associated with low compliance of oral aET (3) there could be a few HR+HER2− patients not included because of the absence of FISH test to determine their HER2 status before 2011.

There are some limitations in this study. The study was a retrospective study on a cohort of HR+HER2− Chinese patients with first tumor recurrence. There could have the unadjusted confounders, selection and recall bias being involved.

This study has several clinical implications. The study finding would empower the patient and physician in practice to enhance the adherence and persistence of oral aET use in Chinese HR+ patients. More studies are needed to identify the reasons and modifiable factor of low compliance for effective intervention in Chinese BC patients.

In summary, this study conclude that full compliance of aET was quite low in Chinese HR+HER2− BC patients. However, it was associated with a 38.6% lower risk of first tumor recurrence. To search for effective tools to improve the compliance of aET in this population should be stressed in future studies.

List of abbreviations

AC	Adjunct chemotherapy
aET	Adjuvant endocrine therapy
AIs	Aromatase inhibitors
ALND	Axillary lymph node dissection
ANOVA	Analysis of variance
BC	Breast cancer
CI	Confidence interval
DFS	Disease-free survival
ER+/PR+	Estrogen or progesterone receptor-positive
FISH	Fluorescence in situ hybridization
HER2−	Human epidermal growth factor receptor 2-negative
HR	Hazard ratio
HR+	Hormone receptor-positive
IDC	Invasive ductal carcinoma
IHC	Immunohistochemistry
IMLND	Internal mammary lymph node dissection
LN	Lymph node
LVI	Lymphovascular invasion
NAC	Neoadjuvant chemotherapy
nET	Neoadjuvant endocrine therapy
OFS	Ovarian function suppression
ref.	Reference
RT	Radiotherapy
SERMs	Selective ER modulators
SLND	Supraclavicular lymph node dissection
std	Standard deviation
TAM	Tamoxifen

Author Contribution Statement

Acknowledgements

Ethical Statement

This study was approved by the Research Ethics Committee of the Fourth Hospital of Hebei Medical University (FHHMU # 2019-166). For this type of study, the written formal consent is not required. All sensitive health information of participants was excluded from the study dataset.

Availability of Data

The de-identified analysis datasets can be available from the corresponding author once the manuscript has been accepted for publication with the approval of the Fourth Hospital of Hebei Medical University in China..

Conflict of Interest

All authors declare no conflict of interests.

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