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Long-Term Impact of Various Endocrine Therapy Regimens on Mortality, Local Recurrence, and Metastasis in Breast Cancer: A 25-Year Retrospective Study

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ABSTRACT

Background: This retrospective cohort study explores the long-term effects of different endocrine therapy regimens on mortality, local recurrence, and metastasis in breast cancer patients.

Methods: Data from the Referral Cancer Research Center of Shahid Beheshti University of Medical Sciences were analyzed. Records of 2262 histologically confirmed breast cancer patients with 25 years of follow-up were included. We collected patient data, including treatment modalities and details of the endocrine therapy, and conducted statistical analysis to assess treatment outcome associations.

Results: Patients had an average age of 49.45 years, and 99.1% were female. The average tumor size was 2.8 cm, with a 12.3% mortality rate. Positive expression of human epidermal growth factor receptor 2, progesterone receptor, and estrogen receptor was found in 17.3%, 71.8%, and 70.6% of patients, respectively. Tamoxifen was administered to 1,700 patients, letrozole to 715, and exemestane to 540, with an average endocrine therapy duration of 5.2 years. Letrozole treatment duration (P = 0.001) and lymph node involvement (P=0.028) were independent predictive variables for local recurrence, with longer letrozole therapy associated with lower recurrence.

Conclusion: Estrogen receptor expression and endocrine therapy duration are independent predictive markers for recurrence and mortality. Longer letrozole therapy predicts lower local recurrence. Endocrine therapy duration inversely relates to mortality, recurrence, and local recurrence.

INTRODUCTION

Early breast cancer is diagnosed only in the breast or, in cases of node-positive disease, in the breast and locoregional lymph nodes, and almost all diagnosed tumors can be surgically removed. However, undiagnosed disease deposits may remain locally or at distant places and if left untreated, they could develop into a life-threatening clinical recurrence over the next 5, 10, 15 years or more.[1] Breast cancer stands out due to its unique nature —while the highest

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risk of distant recurrence occurs in the initial ten years after diagnosis, there remains a significant risk throughout the second decade as well.[2] The primary objective of systemic adjuvant therapy is to control any remaining malignancy deposits, reduce the recurrence rate, and improve long-term survival.

Approximately 15–20% of individuals diagnosed with early-stage breast cancer show tumors with HER2 receptor or oncogene overexpression, .amplification, or bothThe current standard of care for these patients involves adjuvant trastuzumab. Four extensive randomized trials have demonstrated the substantial impact of trastuzumab on significantly decreasing the risk of recurrence and mortality in individuals with this specific form of early breast cancer.[3,4]

Adjuvant antiestrogen therapies have been a cornerstone of care for Hormone receptor-positive (HR+) breast cancer for over 40 years.[5] In present-day clinical practice, evaluating ER and PR expression is a standard method to identify hormone-responsive diseases. Although their prognostic significance is well-established, their capacity to predict the effectiveness of antiestrogen treatment is restricted within the HR+ population. Currently, there is a lack of dependable predictive biomarkers with robust clinical validation, hindering the optimization of patient selection and informed decision-making regarding prolonged endocrine therapy.[6]

Earlier findings from the Arimidex (Anastrozole), Tamoxifen, Alone or in Combination (ATAC) trial revealed a substantial extension in disease-free survival, reduced occurrences of both local and distant recurrences, and a marked decrease in contralateral breast cancer among patients receiving anastrozole in comparison to tamoxifen. Moreover, anastrozole demonstrated a notably lower incidence of severe adverse events compared to tamoxifen.[7] In light of these investigations and observations, the current study aims to assess the long-term effects of various endocrine therapy regimens on mortality, local recurrence, and metastasis in breast cancer patients.

METHODS

This retrospective cohort study was conducted from Oct 1998 to Sep 2023, at the Referral Breast Cancer Research Center of Shahid Beheshti University of Medical Sciences. Patient selection involved individuals with histologically confirmed breast cancer. Only patients with confirmed diagnosis were included. After a breast cancer diagnosis, we staged patients by integrating insights from the NCCN Guidelines for Breast Cancer Screening and Diagnosis, Version 1.2023, and the AJCC TNM system. Staging considered factors like tumor size, lymph node involvement, metastasis, hormone receptor and HER2 status, grade, and recurrence .scores, with stages ranging from 0 to IV By combining information from both references, we aimed to enhance the precision and reliability of our breast cancer diagnostic and staging processes for accurate and timely treatment planning.[8,9,10]

Immunohistochemical markers, such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), had been assessed for all patients before initiating any therapy. ER and PR receptors were positive in most patients, and according to ASCO (the American Society of Clinical Oncology) guidelines, endocrine therapy is still recommended for patients who are triple negative or HER2 negative. ASCO's guidelines for clinical practice offer evidence-supported suggestions and delineate suitable approaches to treatment and care for healthcare professionals. This manuscript follows the recommendations published by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines.

The study included all types of surgical interventions, with the specific surgical approach determined based on disease extent and personalized treatment plans. We included all patients who received adjuvant hormone therapy, such as Tamoxifen, letrozole, or anastrozole, following the completion of 5, 7, or 10 years of adjuvant therapy. Additionally, patients who underwent combination therapy involving other modalities, like chemotherapy or targeted therapy, were included if hormone therapy formed part of their treatment regimen. Men were not included in this study due to .their statistically low representation

Data collection involved a comprehensive review of patient records available at the Referral Breast Cancer Research Center registry. We used the complete set of recorded data from the referral cancer center at Shahid Beheshti Cancer Research Center over the past 25 years, ensuring it met our inclusion criteria. Sample size was not a limiting factor here, as we utilized all available data. Authors had access to the data of individual participants after data collection. The patients' basic demographics including age, tumor characteristics (size, grade, lymph node involvement), treatment modalities (surgery type, radiation therapy, chemotherapy, targeted therapy), and details of the endocrine therapy regimen (type, duration) were extracted from the patient's records. The duration of the follow-up period was 25 years. We regularly examined the patients

every three months and provided reminders through phone calls.

All recorded data underwent analysis using the new version of SPSS Statistics V22. Statistical methods, such as chi-square tests or logistic regression analysis, were employed to evaluate the associations between treatment variables and outcomes. Subgroup analyses based on tumor characteristics and treatment factors were conducted to explore potential associations and identify relevant prognostic factors. A significance level of $P \leq 0.05$ was considered statistically significant in the analyses.

Ethical approval was obtained from the ethical committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.CRC.RRE.1402.005), ensuring patient privacy and confidentiality through the blinding of the collected data.

RESULTS

In this comprehensive study, a total of 2,262 breast cancer patients were included. The mean age at diagnosis was determined to be 49.45 years. In the study, 279 patients (12.3%) succumbed to the disease during the follow-up period. The mean tumor size was found to be 2.8cm, with the majority of tumors classified as T1 or T2 (88.5%). Histopathological analysis revealed that invasive ductal carcinoma (IDC) was the most prevalent tumor type, accounting for 68.7% of cases. Lymphovascular invasion was observed in 29.7% of cases. Grade 2 tumors were the most common, representing 51.9% of the cases. Surgical procedures involved an average dissection of 8.36 lymph nodes, with 2.13 lymph nodes, on average, being involved by the tumor. Immunohistochemical analysis demonstrated positive expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) in 70.6%, 71.8%, and 17.3% of cases, respectively. Among the patients, 1,700 individuals received Tamoxifen for an average duration of 4.29 years, 715 patients received letrozole for an average duration of 3.53 years, and 540 patients received exemestane for an average duration of 3.51 years. Recurrence analysis revealed that recurrence was observed in 20% of cases, with local recurrence accounting for 5.7% (Table 1).

Prognostic Factors for Recurrence and Mortality:

Multivariate analysis revealed several variables that significantly impacted overall recurrence and mortality. Subsequent regression analysis identified the expression of ER, tumor location, lymph node involvement, type of surgical intervention, and duration of tamoxifen and letrozole therapy as independent prognostic factors for recurrence ($P<0.05$). Moreover, the incidence of recurrence, tumor location, expression of ER and HER2, type of surgical intervention, and duration of tamoxifen therapy were identified as independent prognostic factors for mortality ($P<0.05$) (Table 2).

Table 1. Basic data and demographics of cases

Baselines	Data
Patients, n	2262
Mean age (SD), y	58.68±12.11
Mean age at diagnosis (SD), y	49.45±11.49
Mean follow-up period (SD), y	5.40±4.85
Female, n (%)	2262 (100.0%)
Mortality, n (%)	279 (12.3%)
Family history (Positive), n (%)	582 (25.7%)
Receptor, n (%)	
ER Positive	1598 (70.6%)
PR Positive	16.24 (71.8%)
HER-2 Positive	392 (17.3%)
P53 Positive	272 (12.0%)
KI-67	
<10%	374 (16.5%)
10-14%	435 (19.2%)
14-25%	514 (22.7%)
>25%	617 (27.3%)
Radiotherapy, n (%)	2047 (90.5%)
Chemotherapy, n (%)	1654 (73.1%)
Endocrine therapy (SD), y	
Tamoxifen	4.29±2.73
Letrozole	3.53±2.68
Exemestane	3.51±2.73
Recurrence, n (%)	
No recurrence	1810 (80.0%)
Local recurrence	130 (5.7%)
Distant recurrence	322 (14.3%)

ER Positive: Estrogen Receptor-Positive, PR Positive: Progesterone Receptor-Positive, HER-2 Positive: Human Epidermal Growth Factor Receptor 2 Positive

Factors Associated with Local Recurrence:

Univariate regression investigations determined that several factors were associated with local recurrence in breast cancer patients and others were not. These factors included diagnosis age, tumor stage, histopathology, tumor grade, the presence of lymphovascular invasion, the type of surgery performed, expression of ER and HER2 receptors, the number of excised and involved lymph nodes, and the duration of endocrine therapy ($P<0.05$).

After performing multivariate regression analysis, it was found that the only independent predictor of local recurrence was the duration of letrozole treatment ($P<0.05$).

According to the multivariate analysis conducted after excluding the variables that were not significantly associated with outcomes, numerous variables were found to significantly impact overall recurrence and mortality (Table 3).

Table 2. Prognostic Factors and Outcome Measures

Conditions	Total	Local Recurrence			Recurrence			Mortality		
		(+)	(-)	P	(+)	(-)	P	(+)	(-)	P
Age (SD), y	58.68±12.11	56.31±13.32	59.05±11.87	0.00	56.43±12.88	59.29±11.82	0.00	57.41±12.27	58.76±12.09	0.16
Age at diagnosis (SD), y	49.45±11.49	50.10±13.19	49.35±11.21	0.59	47.75±12.24	49.89±11.24	0.00	46.72±10.99	49.62±11.50	0.00
Mortality, n (%)	279 (12.3%)	279 (100.0%)	0 (0.0%)	-	215 (77.1%)	64 (22.9%)	0.00	36 (12.9%)	243 (87.1%)	0.00
Family history, n (%)	582 (25.7%)	72 (12.4%)	510 (25.7%)	1.00	110 (18.9%)	472 (81.1%)	0.09	33 (5.7%)	549 (94.3%)	0.60
Size (SD), Cm	2.80±1.89	2.47±2.80	2.64±1.74	0.00	3.64±2.39	2.59±1.68	0.00	3.14±2.05	2.78±1.88	0.09
Side, n (%)				0.00			0.00			0.16
Right	775 (34.3%)	175 (29.2%)	600 (70.8%)		193 (24.9%)	582 (75.1%)		47 (6.1%)	728 (93.9%)	
Left	708 (31.3%)	15 (2.1%)	693 (97.9%)		73 (10.3%)	635 (89.7%)		30 (4.2%)	678 (95.8%)	
Bilateral	74 (3.3%)	0 (0.0%)	74 (100.0%)		12 (16.2%)	62 (83.8%)		6 (8.1%)	68 (91.9%)	
T, n (%)				0.00			0.00			0.03
T1	876 (38.7%)	57 (6.5%)	819 (93.5%)		110 (12.6%)	766 (87.4%)		41 (4.7%)	835 (95.3%)	
T2	841 (37.2%)	113 (13.4%)	728 (86.6%)		196 (23.3%)	645 (76.7%)		43 (5.1%)	798 (94.9%)	
T3	223 (9.9%)	59 (26.5%)	164 (73.5%)		79 (35.4%)	144 (64.6%)		20 (9.0%)	203 (91.0%)	
Pathology, n (%)				0.00			0.00			0.00
IDC	1521(67.2%)	232 (15.2%)	1289(84.8%)		338 (22.2%)	1183(77.8%)		87 (5.7%)	1434(94.3%)	
DCIS	82 (3.6%)	5 (6.1%)	77 (93.9%)		6 (7.3%)	76 (92.7%)		4 (4.9%)	78 (95.1%)	
IDC/DCIS	335 (14.8%)	20 (5.9%)	315 (94.1%)		53 (15.8%)	282 (84.2%)		16 (4.8%)	319 (95.2%)	
ILC	149 6.6%)	12 (8.1%)	137 (91.9%)		28 (18.8%)	121 (81.2%)		6 (5.4%)	143 (94.6%)	
ILC/LCIS	22 (1.0%)	0 (0.0%)	22 (100.0%)		4 (18.2%)	18 (81.8%)		3 (13.6%)	19 (86.4%)	
Not defined	32 (1.4%)	5 (15.6%)	27 (84.4%)		5 (15.6%)	27 (84.4%)		5 (15.6%)	27 (84.4%)	
IDC/ILC	46 (2.0%)	4 (8.7%)	42 (92.3%)		7 (15.2%)	39 (84.8%)		1 (2.2%)	45 (97.8%)	
LCIS	2 (0.1%)	0 (0.0%)	2 (100.0%)		1 (50.0%)	1 (50.0%)		1 (50.0%)	1 (50.0%)	
Histological grade, n (%)				0.00			0.00			0.00
1	275 (12.4%)	15 (5.4%)	260 (94.6%)		32 (11.6%)	243 (88.4%)		5 (1.8%)	270 (98.2%)	
2	1150(51.9%)	123 (10.7%)	1027(89.3%)		204 (17.7%)	946 (82.3%)		59 (5.1%)	1091(94.9%)	
3	534 (54.1%)	92 (17.2%)	442 (82.8%)		144 (27.0%)	390 (73.0%)		36 (6.7%)	498 (93.3%)	

Receptor, n (%)										
ER Positive	1598(70.6%)	97 (6.1%)	1501(93.9%)	0.00	247 (15.5%)	1351(84.5%)	0.00	79 (4.9%)	1519(95.1%)	0.01
PR Positive	1624(71.8%)	141 (8.7%)	1483(91.3%)	0.00	276 (17.0%)	1348(83.0%)	0.00	84 (5.2%)	1540(94.8%)	0.09
HER-2 Positive	392 (17.3%)	56 (14.3%)	336 (85.7%)	0.00	102 (26.0%)	290 (74.0%)	0.00	35 (8.9%)	357 (91.1%)	0.01
P53 Positive	272 (12.0%)	57 (20.9%)	215 (79.1%)	0.05	65 (23.9%)	207 (86.1%)	0.67	14 (5.1%)	258 (94.9%)	0.56
KI-67				0.99			0.23			0.65
<10%	374 (16.5%)	46 (12.3%)	328 (87.7%)		70 (18.7%)	304 (81.3%)		17 (4.5%)	357 (95.5%)	
10-14%	435 (19.2%)	51 (11.7%)	384 (88.3%)		94 (21.6%)	341 (78.4%)		27 (6.2%)	408 (93.8%)	
14-25%	514 (22.7%)	60 (11.7%)	454 (88.3%)		112 (21.8%)	402 (78.2%)		30 (5.8%)	484 (94.2%)	
>25%	617 (27.3%)	72 (11.7%)	545 (88.3%)		109 (17.7%)	508 (82.3%)		30 (4.9%)	587 (95.1%)	
LVI, n (%)	657 (29.7%)	114 (17.3%)	543 (82.7%)	0.00	184 (28.0%)	473 (72.0%)	0.00	45 (6.8%)	612 (93.2%)	0.02
Lymph node (SD), n										
Resected	8.36±6.04	11.65±6.17	7.91±5.8	0.00	10.82±6.30	7.75±5.81	0.00	9.11±5.21	8.31±6.08	0.03
Involved	2.13±3.98	5.17±5.96	1.7±3.43	0.00	4.58±5.81	1.52±3.09	0.00	3.23±4.75	2.06±3.92	0.00
Surgery type, n (%)				0.00			0.00			0.00
BCS	1519(67.2%)	114 (7.5%)	1405(92.5%)		212 (13.9%)	1307		63 (4.1%)	1456	
MRM	606 (26.8%)	143 (23.6%)	463 (76.4%)		196 (32.3%)	410 (68.7%)		43 (7.1%)	563 (92.9%)	
Subcut mastectomy	7 (0.3%)	0 0 (0.0%)	7 (100.0%)		2 (28.6%)	5 (71.4%)		2 (28.6%)	5 (71.4%)	
BCS/MRM	14 (0.6%)	4 (28.6%)	10 (71.4%)		13 (92.8%)	1 (7.8%)		13 (92.8%)	1 (7.8%)	
Radiotherapy, n (%)	2047(90.5%)	258 (12.6%)	1789(87.4%)	0.48	411 (20.1%)	1636(79.9%)	0.49	114 (5.6%)	1933(94.4%)	0.44
Chemotherapy, n (%)	1654(73.1%)	217 (13.1%)	1437(86.9%)	0.31	343 (20.7%)	1311(79.3%)	0.94	97 (5.9%)	1557(94.1%)	0.70
Endocrine therapy (SD), y										
Tamoxifen	4.29±2.73	3.31±2.50	4.41±2.73	0.00	2.92±2.02	4.59±2.77	0.00	2.92±2.14	4.37±2.74	0.00
Letrozole	3.53±2.68	2.76±2.00	3.61±2.73	0.02	2.42±1.76	3.81±2.80	0.00	2.15±1.40	3.60±2.71	0.00
Aromysin	3.51±2.73	2.84±2.01	3.70±2.87	0.01	2.77±2.21	3.83±2.87	0.00	2.25±1.63	3.65±2.79	0.00

P: P-Value, IDC: Invasive Ductal Carcinoma, DCIS: Ductal Carcinoma in Situ, ILC: Invasive Lobular Carcinoma, LCIS: Lobular Carcinoma in Situ, ER Positive: Estrogen Receptor-Positive, PR Positive: Progesterone Receptor-Positive, HER-2 Positive: Human Epidermal Growth Factor Receptor 2 Positive, LVI: Lymphovascular Invasion, BCS: Breast-Conserving Surgery, MRM: Modified Radical Mastectomy

Additionally, the incidence of recurrence, tumor location, expression of ER and HER2, the type of surgical intervention, and the duration of tamoxifen therapy were independent prognostic factors for mortality ($P < 0.05$).

Table 4 which is the endocrine therapy classification and outcome, presents data on 1077 patients completing 5 years of hormonal therapy and 900 patients completing therapy from 5 to 10 years. The impact of therapy duration is evident. It illustrates the positive impact of specific regimens, particularly the exclusive use of letrozole.

Table 3: Prognostic Factors and Outcomes

Conditions	Local Recurrence			Recurrence			Mortality		
	OR	UCI	LCI	OR	UCI	LCI	OR	UCI	LCI
Age (SD), y	0.96	0.99	0.93	0.76	0.80	0.73	-		
Age at diagnosis (SD), y	-			1.28	1.34	1.22	0.96	0.98	0.93
Size (SD), Cm	1.02	1.39	0.75	1.05	1.22	0.90	-		
Side, n (%)	0.87						-		
Right	ref			ref					
Left	1.44	1.62	1.20	1.10	2.54	0.47			
Bilateral	1.33	1.48	1.18	0.96	1.42	0.65			
T, n (%)									
T1	ref			ref			ref		
T2	0.99	2.48	0.39	1.33	3.71	0.47	0.96	1.76	0.53
T3	2.22	17.56	0.28	1.50	3.35	0.67	0.93	2.05	0.42
Pathology, n (%)									
IDC	ref			ref			ref		
DCIS	0.17	1.99	0.01	7.35	9.51	5.01	1.36	3.27	1.06
IDC/DCIS	0.38	1.83	0.08	2.39	4.01	1.46	1.70	2.45	1.33
ILC	1.37	2.88	0.16	6.22	7.92	4.27	1.64	3.57	1.16
ILC/LCIS	0.02	0.04	0.01	7.39	9.11	5.51	2.74	4.42	1.56
Not defined	0.01	0.03	0.00	7.66	9.82	4.93	1.02	1.82	0.73
IDC/ILC	0.91	4.86	0.01	6.21	8.41	4.12	1.06	1.45	0.96
LCIS	0.01	0.01	0.00	1.45	2.95	0.98	1.0	1.0	1.0
Histological grade, n (%)									
1	ref			ref			ref		
2	5.05	8.59	2.46	0.48	0.92	0.25	1.40	2.07	1.15
3	3.42	4.75	1.03	0.75	1.51	0.37	1.49	2.40	1.17
Receptor, n (%)									
ER Positive	7.96	14.43	3.63	1.61	1.89	1.42	1.69	2.21	1.39
PR Positive	1.04	2.25	0.47	3.01	5.41	1.35	-		
HER-2 Positive	7.82	12.43	4.63	1.99	3.74	1.06	1.90	3.41	1.05
P53 Positive	0.55	1.56	0.19	-			-		
LVI, n (%)	1.39	2.95	0.66	1.02	1.68	0.62	1.93	2.69	1.51
Lymph node (SD), n									
Resected	1.01	1.09	0.94	0.98	1.02	0.94	0.97	1.03	0.92
Involved	1.05	1.15	0.96	1.11	1.15	1.06	1.04	1.12	0.97
Surgery type, n (%)									
BCS	ref			ref			ref		
MRM	2.99	6.46	1.38	1.48	2.01	1.23	1.32	2.51	0.69
Subcut mastectomy	5.45	16.93	3.60	3.95	13.30	1.17	3.12	5.92	2.80
BCS/MRM	4.64	7.48	1.00	1.00	8.43	0.01	3.72	7.96	1.26
Endocrine therapy (SD), y									
Tamoxifen	1.55	2.67	1.02	1.85	1.92	1.78	0.83	0.93	0.74
Letrozole	1.60	2.27	1.24	1.82	1.95	1.71	1.66	1.94	1.46
Aromysin	1.64	1.93	1.41	1.93	2.02	1.84	0.69	0.86	0.55

P: P-Value, OR: Odds Ratio, CI: Confidence Interval, IDC: Invasive Ductal Carcinoma, DCIS: Ductal Carcinoma in Situ, ILC: Invasive Lobular Carcinoma, LCIS: Lobular Carcinoma in Situ, ER Positive: Estrogen Receptor-Positive, PR Positive: Progesterone Receptor-Positive, HER-2 Positive: Human Epidermal Growth Factor Receptor 2 Positive, LVI: Lymphovascular Invasion, BCS: Breast-Conserving Surgery, MRM: Modified Radical Mastectomy

The patients were also classified into seven groups based on treatment regimens, and the analysis was conducted within these groups (Table 5). Among the patients, about 15% using a tamoxifen and Aromasin combination showed significant impacts on mortality, recurrence, and local recurrence ($P<0.05$).

A key finding highlights the substantial influence of treatment modalities and duration on different clinical outcomes. These critical findings contribute to understanding how treatment duration and regimens affect outcomes in hormone receptor-positive breast cancer, potentially guiding endocrine therapy optimization.

Figure 1 illustrates the duration of endocrine treatment based on different treatment regimens. In most cases, a statistically significant relationship exists between mortality, recurrence, local recurrence, and treatment duration (P<0.05). However, there are some exceptions. For instance, the regimen of tamoxifen plus letrozole does not exhibit a statistically significant difference in mortality (P=0.72), and the regimen of the three drugs does not demonstrate a statistically significant difference in recurrence (P=0.17). Similarly, the three drugs regimen and the regimen of exemestane plus letrozole do not manifest a statistically significant difference in recurrence (P= 0.73 and 0.22 respectively)..

Table 4. The endocrine therapy classification and outcome

Endocrine therapy period	Total (Number of Patients)	Mortality		Recurrence		Local Recurrence	
		(+)	(-)	(+)	(-)	(+)	(-)
<5 y	1077(47.6%)	171(15.9%)	906(84.1%)	303(28.1%)	774(71.9%)	87(8.1%)	990(81.9%)
5 to 7 y	514(22.7%)	58(11.6%)	456(88.4%)	89(17.3%)	425(82.7%)	25(4.9%)	489(95.1%)
7 to 10 y	386(17.1%)	28(7.3%)	358(92.7%)	45(11.7%)	341(88.3%)	13(3.4%)	373(96.6%)
>10y	285(12.6%)	22(7.7%)	263(92.3%)	15(5.3%)	270(94.7%)	5(1.8%)	280(98.2%)
Total	2262(100.0%)	279(12.3%)	1983(87.7%)	452(20.0%)	1810(80.0%)	130(5.7%)	2132(94.3%)
P-value		0.00		0.00		0.00	

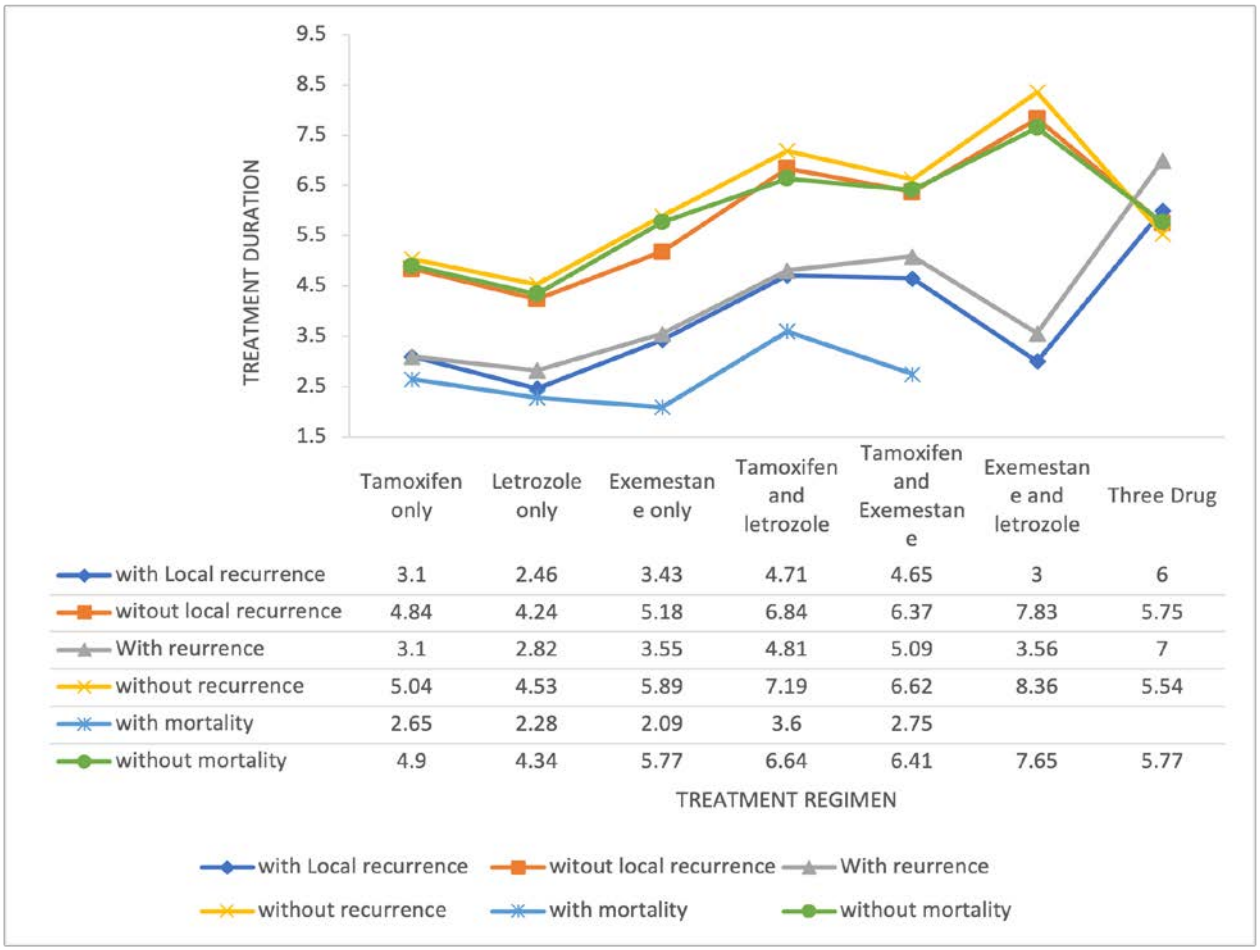

Figure 1. Illustrates the duration of endocrine treatment based on different treatment regimens.

Figure 1 illustrates the duration of endocrine treatment based on different treatment regimens. In most cases, there is a statistically significant relationship between mortality, recurrence, local recurrence and treatment duration (P<0.05).

However, there are some exceptions. For instance, the regimen of tamoxifen plus letrozole does not

Table 5. Treatment duration effect

Endocrine therapy regimen	Total		Mortality				Recurrence				Local Recurrence			
	N		N	(+)	(-)	P	N	(+)	(-)	P	N	(+)	(-)	P
Tamoxifen only	1043 (46.3%)	4.77 ±2.92	89 (32.2%)	2.65±2.92	4.90±2.91	0.00	147 (33.0%)	3.10±2.32	5.04±2.92	0.00	44 (34.1%)	3.10±2.66	4.84±2.91	0.00
Letrozole only	369 (16.4%)	4.18±2.95	37 (13.4%)	2.28±2.95	4.34±2.98	0.00	75 (16.8%)	2.82±1.86	4.53±3.08	0.00	11 (8.5%)	2.46±1.62	4.24±2.97	0.04
Aromysin only	156 (7.0%)	5.01±3.07	48 (17.4%)	2.09±3.07	5.77±3.13	0.00	59 (13.2%)	3.55±2.48	5.89±3.55	0.00	15 (11.6%)	3.43±2.14	5.18±3.11	0.03
Tamoxifen and Letrozole	300 (13.3%)	6.67±3.34	35 (12.7%)	3.60±3.34	6.64±3.31	0.72	65 (14.5%)	4.81±2.04	7.19±3.45	0.00	23 (17.8%)	4.71±1.90	6.84±3.39	0.00
Tamoxifen and Aromysin	337 (15.0%)	6.19±3.00	67 (24.3%)	2.75±3.00	6.41±3.03	0.00	96 (21.5%)	5.09±2.76	6.62±2.99	0.00	34 (26.4%)	4.65±2.31	6.37±3.03	0.00
Aromysin and Letrozole	27 (1.2%)	7.65±4.05	0 (0.0%)	0	7.65±4.05	1	4 (0.9%)	3.56±0.51	8.36±3.97	0.02	1 (0.8%)	3.00±0.00	7.83±4.02	0.22
Three Drug	19 (0.8%)	5.77±2.38	0 (0.0%)	0	5.77±2.38	1	3 (0.7%)	7.00±1.73	5.54±2.45	0.17	1 (0.8%)	6.00±0.00	5.75±2.44	0.73

exhibit a statistically significant difference in the occurrence of mortality (P=0.72), and the three drugs regimen does not demonstrate a statistically significant difference in recurrence (P=0.17). Similarly, the regimen of the three drugs and the regimen of exemestane plus letrozole do not manifest a statistically significant difference in local recurrence (P= 0.73 and 0.22 respectively).

Correlation Analysis:

The Spearman's rank correlation test demonstrated an inverse correlation between the duration of adjuvant endocrine therapy and the incidence of mortality, recurrence, and local recurrence. The correlation coefficients were -0.109, -0.212, and -0.103, respectively.

DISCUSSION

The long-term effects of different endocrine therapy regimens on mortality, local recurrence, and metastasis in breast cancer patients were investigated in this study. One of the key discoveries from our research is related to the duration of treatment, emphasizing its substantial influence on outcomes. This study specifically indicates that the length of therapy plays a significant role. Additionally, our exploration involved various regimens, revealing the positive impact of specific regimens on the study's outcomes. Notably, the exclusive use of letrozole also demonstrated significant differences. These critical findings, as highlighted in our results and tables, contribute to our understanding of how treatment duration and specific regimens can significantly affect outcomes in hormone receptor-positive breast cancer, potentially informing the optimization of endocrine therapy.

In a study on the effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival, 194 randomized trials of hormone treatment or adjuvant chemotherapy in 1995 underwent collaborative meta-analyses. The annual recurrence rate was almost cut in half and the breast cancer mortality rate was decreased by a third among women with ER-positive disease in the trials that sought to evaluate the effects of about 5 years of tamoxifen. Based on the results, longer treatment was more successful than shorter treatment for controlling breast cancer.[1]

This aligns with the present study's emphasis on the importance of endocrine therapy duration, indicating that longer treatment periods are more effective in controlling breast cancer. Barron, *et al.* discovered that women with stage I-III ER-positive early breast cancer had a considerably greater chance of breast cancer recurrence after hormone therapy was discontinued.[11]

The findings of their analysis were in line with information from randomized trials on the length of hormonal therapy treatment[1,12], with important implications for the development of treatments meant to improve devotion to hormonal therapy.[11] Pan, *et al*. reported that after adjuvant endocrine therapy for 5 years, breast cancer recurrences persisted continuously from 5 to 20 years throughout the study. Depending on the TN status and tumor grade, there was a considerable correlation between the risk of distant recurrence and the initial TN status, with risks ranging from 10 to 41%.[13] The findings of this study further emphasize the continuous risk of breast cancer recurrence from 5 to 20 years and the correlation between initial TN status and distant recurrence risk. Also, the previously mentioned studies by Barron *et al*., Pan *et al*., and Petrelli *et al*. reinforce the concept that extended endocrine therapy, beyond the recommended five years, is beneficial in terms of survival and preventing relapse. In patients with early breast cancer, a meta-analysis study evaluated the effectiveness of 5 years of hormone therapy alone with that of extra years of hormonal therapy. This study demonstrated that extending tamoxifen adjuvant endocrine therapy treatment beyond the recommended five years is beneficial for both survival and preventing relapse.[14] More studies confirmed that with about 5 years of endocrine therapy, a reduction in the incidence of second primary breast cancer was seen. These studies also confirmed the advantage of extended adjuvant endocrine therapy in patients.[4,15-18] A study was conducted in 2019 by Delshad *et al*. to compare the local recurrence rate and disease-free survival in patients with locally advanced breast cancer in breast-conserving therapy and modified radical mastectomy groups after neoadjuvant chemotherapy. In their study, 115 patients with an average age of 48.23 years were included. The status of hormone intake between the two surgical groups was significantly different, and 18.26% of patients showed local recurrence.[19] A study by Nichol *et al.* in 2017 aimed at the use of hormone therapy alone versus hormone therapy and radiation therapy for breast cancer in elderly women. In the endocrine therapy, alone group, endocrine therapy adherence was 75% at one year and 55% at four years. The 10-year local recurrence rate and disease-free survival was 90% with endocrine therapy, while the 10-year breast cancer survivors rate was 95% with endocrine therapy.[20] Studies by Delshad *et al.* and Nichol *et al.* underscore the importance of treatment adherence and its impact on local recurrence rates, disease-free survival, and overall survival. A study was conducted by Bense *et al*. with the aim of examining the biology of late recurrences in selecting patients for extended endocrine therapy in breast cancer. Patients who had higher expression of estrogen-responsive genes were associated with longer benefits from endocrine treatment. It was suggested that long-term intervention by extended endocrine therapy might reduce late recurrences in patients with tumors showing high expression of estrogen-responsive genes.[21] In a study on 20-year risks of breast cancer recurrence, it was found that breast cancer recurrences occur progressively from 5 to 20 years, with distant recurrence closely related to TN status. Tumor grade and Ki-67 status moderately predicted recurrence, while progesterone receptor and HER2 status did not. The study emphasized the importance of tumor features and endocrine therapy duration, such as letrozole, in reducing the chance of recurrence.[13] Another study explored the ideal duration and management approaches for adjuvant endocrine therapy in early breast cancer. It highlighted the advantages of anastrozole over tamoxifen and the potential benefits of longer-term treatment. Patient preferences, side effects, risk assessment, and molecular profiling should be considered in decision-making for personalized and prolonged treatment methods.[22] Extended adjuvant therapy with aromatase inhibitors, particularly letrozole, was found to be a successful choice for reducing recurrence risk in postmenopausal women in a study on overcoming recurrence risk by extended adjuvant endocrine therapy. Continuing hormonal therapy with letrozole after five years of tamoxifen use demonstrated significant advantages in reducing the risk of recurrence.[2] A study focused on the local recurrence of breast cancer in individuals who underwent breast-conserving surgery for stage I-II breast cancer. Risk factors for recurrence included premenopausal status, peritumoral vascular invasion, multifocality, and estrogen receptor deficiency. Lower overall survival was associated with a higher N stage, lack of estrogen receptors, and quick time to recurrence. The study emphasized the significance of personalized treatment considering unique patient features to decrease recurrence and increase survival.[24] A trial compared anastrozole and tamoxifen as adjuvant treatments for early-stage hormone-sensitive breast cancer. Anastrozole demonstrated higher efficacy in disease-free survival, recurrence, and distant recurrence after 120 months of

follow-up. For postmenopausal women with hormone-sensitive breast cancer, anastrozole was identified as a safe and highly effective treatment option.[7] A study conducted in the Netherlands found that breast cancer subtypes significantly affected 10-year recurrence rates. HER2-positive and triple-negative subtypes showed higher recurrence rates compared to luminal A, which had the lowest rates. Triple-negative illness also exhibited poorer 10-year overall survival. The study emphasized the importance of considering subtypes for individualized treatment and follow-up.[25] The study focused on phyllodes tumors of the breast and their local recurrence rates based on tumor grade. The risk of recurrence significantly increased in borderline and malignant tumors compared to benign tumors. Risk factors for recurrence included tumor necrosis, tumor boundaries, mitoses, surgical margin status, and breast-conserving surgery. The study highlighted the importance of adjusting management plans based on tumor grade to lower the likelihood of local recurrence.[25] The study aimed to improve adherence to adjuvant endocrine hormonal therapy (EHT) among breast cancer patients through an intervention involving an interactive smartphone application and patient navigator support. The goal was to increase communication, patient education, self-monitoring, and side-effect reporting. The study emphasized the potential benefits of improved adherence, such as raising overall survival rates, length of life, and quality of life, while reducing recurrence and healthcare costs.[26] Another study discussed the effectiveness of endocrine therapy with a standard duration of 5 years for endocrine-sensitive breast cancer. It highlighted the reduction in 15-year mortality rates and the potential benefits of prolonged therapy and ovarian suppression. The study emphasized the importance of recent data and considered the side effects of different treatment options.[27] In a study on how we treat HR-positive, HER2-negative early breast cancer, it was reported that local therapies, like breast-preserving surgery, aim to reduce aggressive treatment-related complications. Endocrine therapy is central to preventing breast cancer relapse, with adjuvant chemotherapy selectively used for high-risk cases identified through genomic assays. Bisphosphonates benefit postmenopausal women by lowering the risk of bone metastasis. The recent FDA approval of the CDK 4/6 inhibitor abemaciclib provides a new option for those at high risk of relapse.[28]

Despite the comprehensive nature of these studies, it is essential to acknowledge the limitations and variations in methodologies. However, the collective evidence supports the overarching theme that extended endocrine therapy, including letrozole, plays a crucial role in reducing recurrence risk and improving survival rates in breast cancer patients. Prognostic factors for recurrence and mortality, such as ER expression, lymph node involvement, and treatment duration, were identified in this study. These factors are crucial in predicting patient outcomes and can guide treatment decisions. The results also underscore the significance of adherence to endocrine therapy, as longer durations of therapy were associated with improved outcomes. This supports the notion that sustained treatment with hormone therapy can effectively lower the risk of mortality and recurrence in hormone receptor-positive breast cancer patients.

The results identified several independent prognostic factors for recurrence and mortality, including ER expression, and the duration of endocrine therapy. Notably, the length of letrozole treatment emerged as an independent predictor of local recurrence. This finding underscores the importance of considering the period of endocrine therapy when determining treatment regimens for breast cancer patients. It suggests that prolonged use of letrozole may help reduce the risk of local recurrence. Furthermore, correlation analysis demonstrated an inverse relationship between the time of adjuvant endocrine therapy and the incidence of mortality, recurrence, and local recurrence. This finding supports the notion that a longer length of hormone therapy is associated with improved outcomes in breast cancer patients. By identifying independent prognostic factors and highlighting the importance of treatment duration, this study provides valuable insights for clinicians in optimizing treatment strategies. Further studies involving multi-centric centers are needed to confirm the best results.

Limitations

Several limitations should be considered when interpreting the findings of this study. Being a retrospective study, the study suffers from inherent biases and limitations associated with retrospective data collection. Moreover, reliance on medical records introduces the possibility of missing or incomplete data, which may impact the analyses. Additionally, as the study was conducted at a single center, generalizability to other populations or healthcare settings may be limited. Despite these limitations, this study contributes valuable insights into the long-term effects of endocrine therapy regimens in breast cancer patients. Future prospective studies involving larger and more diverse patient populations are warranted to validate these findings and provide more robust evidence for optimizing endocrine therapy strategies in breast cancer management.

CONCLUSION

In conclusion, this 25-year retrospective cohort study provides insights into the long-term impacts of different endocrine therapy protocols on the mortality rates, local recurrence, and metastasis of individuals diagnosed with breast cancer. Despite the various regimens and modalities in treatments having positive effects on outcomes, the presence of letrozole in the treatment regimen can serve as a favorable prognostic factor for all three outcomes simultaneously. The results underscore the significance of considering tumor characteristics, including ER expression, lymph node involvement, and duration of treatment, in the process of treatment selection. This study makes a valuable contribution to the advancement of treatment strategies for breast cancer patients through the provision of evidence-based insights.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY

Data will be made available on request.

ETHICAL CONSIDERATIONS

Ethical approval was obtained from the ethical committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.CRC.RRE.1402.005), ensuring patient privacy and confidentiality through the blinding of collected data.

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