Study of Survival, Metastasis and Recurrence Rate of Breast Cancer in Comparison With Different Regimens of Endocrine Therapy

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Abstract In the early stages of breast cancer, malignancy is detected solely in the breast or, in the case of individuals with node-positive disease, the breast, and locoregional lymph nodes. All detected malignancies can be excised surgically. However, undetected deposits of malignancy may persist either locally or at distant sites that, if left untreated, could over the subsequent 5, 7, 10, or more years develop into a life-threatening clinical recurrence. The current systematic review was done based on the Strengthening the Reporting of Observationally Studies in Epidemiology and Meta-Analyses of Observational Studies in Epidemiology. The primary keywords were published in reliable databases such as Pubmed , Elsevier, SID, Wiley in English were searched until the end of 2022. Two authors independently examined the articles in terms of data extraction, inclusion criteria, and quality assessment of the articles. The age range from 496 samples was 57.3. Using the results of 5 published articles for MG and CESM, the overall specificity and sensitivity were 89% and 85%, respectively and for MRI, the overall specificity and sensitivity were 81% and 85%, respectively. In conclusion, the MRI method is the most sensitive tool for diagnosing BC in patients, but if a combination of new methods is used together, we will definitely achieve better results.

Key Words breast Cancer, Epidemiology, imaging diagnosis, multifocal, multicentric

1. Introduction

Breast cancer is the most common cancer in women and it is the second cause of death due to cancer after lung cancer [1], [2]. In Iran, it is considered the most common cause of death due to cancer [3]. About half of the patients with timely diagnosis of breast cancer, the rest of the life they live without recurrence and one third die due to the disease [4]. Therefore, it is clear that with extensive research and studies and complete knowledge of the course of the disease, ways of prevention, early diagnosis and appropriate treatment, this common disease can be cured to a large extent. Treatment is not definitive. Due to the prevalence of the disease, if it is possible to reduce the mortality caused by it even to a small extent, not only a large number of patients will be saved from death, but this issue will also be effective in improving the health of the society [5]. This cancer is the most common malignancy. It is among Iranian women and the main focus of attention in Iran.In recent years, the prevalence of the disease has been growing and the data shows that the survival rate of patients up to five years after diagnosis was 88% and 10 years after diagnosis was 80%. In fact, not all tumors are cancerous and may be benign or malignant.

Benign tumors grow abnormally but are rarely fatal. However, some benign breast masses can also increase the risk of breast cancer. Also, the risk of breast cancer has increased in some women with a history of biopsy of benign breast masses. On the other hand, malignant tumors are more serious and are considered cancer, but early detection of this type of cancer has increased the chances of successful treatment [4]. Predicting the recurrence of breast cancer is one of the most popular measures taken to develop data mining approaches. In addition, the life expectancy of patients with breast cancer is affected by various factors such as involvement of axillary lymph nodes, tumor size, the presence or absence of hormone receptors and the type of treatment method, and it is very important to know and examine each of them, especially in the patients of our country.

Incidence and death caused by this disease have undergone

many changes in the last few decades. There are many differences in terms of incidence and death due to this disease in different populations. Studies have shown that factors such as age, sex, race and ethnicity, time of diagnosis, socio-economic class, marital status and geographical location are effective in this diversity [6], [7]. Developed countries experienced an increase in the incidence of this disease from the 1980s, and its sharp increase continued until the 1990s, which is often associated with screening mammography [8]. Although the incidence rate in developed countries has always been higher than in developing countries, we have seen this trend of increasing incidence in developing countries as well. The increase in the incidence of breast cancer in people who migrated to developed countries confirms the influence of lifestyle in the development of this disease [3], [9], [10].

In the early stages of breast cancer, malignancy is detected solely in the breast or, in the case of individuals with node-positive disease, the breast, and locoregional lymph nodes. All detected malignancies can be excised surgically. However, undetected deposits of malignancy may persist either locally or at distant sites that, if left untreated, could over the subsequent 5, 7, 10, or more years develop into a life-threatening clinical recurrence [1]. Breast cancer is atypical in that although the risk of distant recurrence is greatest during the first decade post-diagnosis, it may still be substantial during the second decade [2]. The primary objective of systemic adjuvant therapy is to control any remaining deposits of malignancy, reduce the recurrence rate, and improve long-term survival. 15–20% of patients with early breast cancer have neoplasms that exhibit overexpression, amplification, or both, of the HER2 receptor or oncogene. The use of adjuvant trastuzumab is now the standard of care for these patients. Four large randomized trials have unequivocally demonstrated that trastuzumab has a significant effect in reducing recurrence and mortality in patients with this type of early breast cancer fields [3], [4].

Adjuvant antiestrogen therapies have been a cornerstone of care for Hormone receptor-positive (HR+) breast cancer for over 40 years. The selection of patients based on estrogen receptor (ER) and/or progesterone receptor (PR) expression marked a pivotal advancement toward modern precision oncology [5]. ER and PR expression are routinely measured in current clinical practice to indicate hormone-responsive disease. Their prognostic effect is well established; however, within the HR+ population, they have limited predictive value for selecting patients who derive benefit from antiestrogen treatment. To date, predictive biomarkers with robust clinical validation and utility to optimize patient selection and inform prolonged endocrine treatment have been lacking [6].

Previous reports from the Arimidex (Anastrozole), Tamoxifen, Alone or in Combination (ATAC) trial have shown significantly prolonged disease-free survival, lower rates of recurrence and distant recurrence, and significantly reduced contralateral breast cancer in patients treated with anastrozole compared with tamoxifen. Additionally, anastrozole was as-sociated with significantly fewer serious adverse events than tamoxifen [7]. In light of these investigations and observations, the objective of the current study is to ascertain the impact of alternative endocrine therapy regimens on mortality, locoregional recurrence, and metastasis.

2. Materials and Method

This retrospective case-series study aimed to assess the long-term effects of various endocrine therapy regimens on mortality, local recurrence, and metastasis in breast cancer patients. The study was conducted at the Referral Breast Cancer Research Center of Shahid Beheshti University of Medical Sciences. The patient selection involved individuals with histologically confirmed breast cancer, determined through clinical examinations, pathological examinations of tumor samples, and imaging modalities. Only patients with the confirmed diagnosis were included, and immunohistochemical markers, such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), were assessed for all patients before initiating any therapy.

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. The selection of the endocrine therapy regimen and duration is individuated by patient characteristics and treatment guidelines under the supervision of expert oncological surgeons and oncologists. 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, and they had no significant effect on study's findings after analysis. 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. Written informed consent was obtained from all patients.

Data collection involved a comprehensive review of patient records available at the Referral Breast Cancer Research Center registry. Information regarding patient demographics (age, gender), 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 collected data underwent analysis using new version of SPSS Statistics V22. Statistical methods, such as chi-square tests or logistic regression analysis, were employed to evaluate 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.

3. Results

In this comprehensive study, a total of 2,262 breast cancer patients were included in the study. Among them, 13 patients were male, accounting for 0.6% of the cases. The mean age at diagnosis was determined to be 49.45 years. Tragically, 279 patients (12.3%) succumbed to the disease during the follow-up period. The mean tumor size was found to be 2.8 cm, 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 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 17.7% 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 the bone was the most common site of recurrence, followed by local recurrence, lung, and liver. Overall, recurrence was observed in 20% of cases, with local recurrence accounting for 5.7% of cases (Table 1).

A. 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).

B. Factors Associated with Local Recurrence

Several factors were found to be significantly associated with local recurrence in breast cancer patients. These factors included diagnosis age, tumor stage, histopathology, tumor grade, presence of lymphovascular invasion, type of surgery performed, expression of ER and HER2 receptors, number of excised and involved lymph nodes, and duration of endocrine therapy (P<0.05) (Table 2). However, after conducting multivariate regression analysis, it was determined that the duration of letrozole treatment was the only independent predictor of local recurrence (P<0.05).

| Baseline	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 (%)	2241 (99.1%)
Mortality, n (%)	279 (12.3%)
Family history (Positive), n (%)	582 (25.7%)
Receptor	
ER Positive, n (%)	1598 (70.6%)
PR Positive, n (%)	1624 (71.8%)
HER-2 Positive, n (%)	392 (17.3%)
P53 Positive, n (%)	272 (12.0%)
KI-67	
<10%, n (%)	374 (16.5%)
10-14%, n (%)	435 (19.2%)
14-25%, n (%)	514 (22.7%)
>25%, n (%)	617 (27.3%)
Radiotherapy, n (%)	2047 (90.5%)
Chemotherapy, n (%)	1654 (73.1%)
Endocrine therapy	
Tamoxifen, y	4.29 (2.73)
Letrozole, y	3.53 (2.68)
Exemestane, y	3.51 (2.73)
Recurrence	
No recurrence, n (%)	1810 (80.0%)
Local recurrence, n (%)	130 (5.7%)
Distant recurrence, n (%)	322 (14.3%)

Table 1: Basic data and demographics of
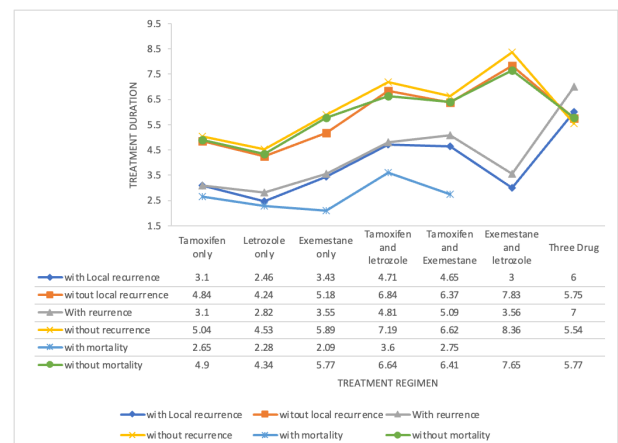
Figure 1: The duration of endocrine treatment based on different treatment regimens

C. 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 (Table 3).

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.

	Local Recurrence				Recurrence				Mortality				Total
	P2	P1	(-)	(+)	P2	P1	(-)	(+)	P2	P1	(-)	(+)	
Tamoxifen	0.79	0.00	4.37 (2.74)	2.92 (2.14)	0.00	0.00	4.59 (2.77)	2.92 (2.02)	0.00	0.00	4.41 (2.73)	3.31 (2.50)	4.29 (2.73)
Letrozole	0.02	0.00	3.60 (2.71)	2.15 (1.40)	0.01	0.00	3.81 (2.80)	2.42 (1.76)	0.99	0.02	3.61 (2.73)	2.76 (2.00)	3.53 (2.68)
Exemestane	0.07	0.00	3.65 (2.79)	2.25 (1.63)	0.57	0.00	3.83 (2.87)	2.77 (2.21)	0.13	0.01	3.70 (2.87)	2.84 (2.01)	3.51 (2.73)

Table 2: Prognostic Factors and Outcome Measure

Local Recurrence		Recurrence		Mortality		Total	Endocrine therapy period
(-)	(+)	(-)	(+)	(-)	(+)	(Number of Patients)	
990	87	774	303	906	171	1077	<5 y
489	25	425	89	456	58	514	5 to 7 y
373	13	341	45	358	28	386	7 to 10 y
280	5	270	15	263	22	285	>10y
2132	130	1810	452	1983	279	2262	Total
0.00		0.00		0.00			P-value

Table 3: The endocrine therapy classification and outcome

4. 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. The findings emphasize the necessity of individualized hormone therapy based on tumor features and patient considerations, as well as the importance of thorough monitoring and follow-up care to detect recurrence early. These findings help to improve treatment methods for hormone receptor-positive breast cancer.

In a study about 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 that started by 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 and longer treatment was more successful than shorter treatment for controlling breast cancer [1]. 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 [8]. The findings of their analysis were in line with information from randomized trials on the length of hormonal therapy treatment [1], [9], and they had implications for the development of treatments meant to improve devotion to hormonal therapy [8]. 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% [10]. 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 [11].

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], [12]–[15]. A study was conducted in 2019 by Akbari 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. 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 [16]. A study by Nichol et al., 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 [17].

A study was conducted by Bense et al. with the aim of 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 to 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 [18]. 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 [10].

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 [19]. 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: Extended Adjuvant Endocrine Therapy." Continuing hormonal therapy with letrozole after five years of tamoxifen use demonstrated significant advantages in reducing the risk of recurrence [20]. 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 [21]. 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 Fields [22].

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 [23]. 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 [24]. Another research 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 [25].

Our study aligns with these studies indicating that extended endocrine therapy, such as prolonged use of tamoxifen or letrozole, can significantly reduce the risk of recurrence and improve survival rates. Specifically, we observed the potential of letrozole in decreasing the likelihood of local recurrence, emphasizing the significance of considering treatment duration when designing breast cancer treatment plans. Prognostic factors for recurrence and mortality, such as ER expression, lymph node involvement, and treatment duration, were identified in this study. These factors play a crucial role in predicting patient outcomes and can guide treatment decisions. The study's 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 study's results identified several independent prognostic factors for recurrence and mortality, including ER expression, lymph node involvement, and the duration of endocrine therapy. Notably, the duration of letrozole treatment emerged as an independent predictor of local recurrence. This finding underscores the importance of considering the duration 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 duration of adjuvant endocrine therapy and the incidence of mortality, recurrence, and local recurrence. This finding supports the notion that a longer duration 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 needed to confirm the best results.

5. Conclusion

In conclusion, this 25-year retrospective descriptive 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. 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.

6. Limitations

Several limitations should be considered when interpreting the findings of this study. Being a retrospective study, inherent biases and limitations associated with retrospective data collection may be present. 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.

Authorship Contribution Statement

S Khoddam and M E Akbari conceptualized and designed the study. M E Akbari and B Wahidi wrote the draft, and M E Akbari data collection and curation, M Ghaderi and N Izadi data analysis, M E Akbari and S Khoddam edited the final draft. Finally, all authors had revised the manuscript.

Data Availability

Data will be made available on request.

Declaration

The authors declare that there is no competing interest.

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