Survival Rate of Breast Cancer and Related Factors in Iran: A 27-Year Follow-Up

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Abstract

Background: Several factors can affect the survival of patients with breast cancer (BC). We estimated BC patients' 5-, 10-, and 15-year survival rates and influential factors in a single medical center during the last three decades.

Methods: We enrolled patients diagnosed with BC managed in the Cancer Research Center of Shahid Beheshti University of Medical Sciences, Tehran, Iran from 1991 to 2018. All patients were followed to check the patients' status. The data were analyzed regarding demographic, clinical, pathological, and molecular biology characteristics. Descriptive and survival analyses were performed. Kaplan Meier and Cox proportional hazards regression models were used for survival analysis.

Results: Overall, 4, 429 women were included. The mean age was 49. 11 (±11. 98) yr. Nearly 70% of the patients had high school degrees. Totally, 35% of patients were diagnosed in the advanced stages of BC. Estrogen Receptor (ER), Progesterone Receptor (PR), and human epidermal growth factor receptor 2 (HER2) were positive in 72. 50%, 66. 90%, and 16. 20% of the cases, respectively. About 11. 6% of patients died. The overall 5-, 10-, and 15-year survival rates of BC were 90%, 83%, and 75%, respectively. In the Cox proportional hazard analysis, the survival rate was affected by literacy level, positive lymph nodes, lymphovascular invasion, ER, tumor size, and pathological grade.

Conclusion: This is the first report on the 15-year survival rate of BC and its influential factors, from a medical center in Iran. The results were acceptable and comparable with those of developed countries due to scientific protocols**,** teamwork, and effective follow-up in a developing country.

Keywords: Breast neoplasm; Disease management; Epidemiology; Survival; Iran

Introduction

Breast cancer is the most prevalent cancer and the leading cause of cancer-related death in women worldwide (1). In Iran, it is the most frequent cancer in both sexes, accounting for approximately 19, 559 new cases and the age-standardized rate (ASR) of 44. 34/10^5 in 2018 (2). There has been an increasing trend in BC incidence rates recently

(3). BC is one of the cancers with a favorable survival rate. The 5-year survival rate of BC in western countries were about 84-88% in 2018 (4). In Iran, the 5-, and 10-year survival rates were estimated at 80% and 69%, respectively in a nationwide study performed in 2019 (5).

Several factors, such as a developed healthcare system, public education, improvement in the availability of health services, early detection, and higher socioeconomic levels, increase the survival rate and prevent advanced disease manifestation (6). The inequality of socioeconomic factors is more effective at the stage of patient diagnosis than disease management (7). Survival is affected by factors such as the inequality of socioeconomic status (SES), demographic, clinical, and hormonal factors, and the type of surgery and management (8). During the last decade, cancer mortality continued to decline in all ages and sexes in the world and in Iran (9). It can be related to the early diagnosis of the disease and improving treatment protocols. The survival rate is an important indicator for determining diagnostic procedures and therapeutic methods in BC. Estimating cancer survival rates can help policymakers develop strategies for better healthcare services, improve patients' quality of life, reduce the cost of treatment, and plan cancer control programs (10).

This study was designed because of the high incidence rate of BC in women and its major impact on families and the community, as well as the importance of survival rate for evaluating treatment procedures and comparing to western communities. We aimed to estimate the 5-, 10-, and 15-year survival rates of patients with BC and evaluate their influential factors in a 27-year follow-up in a single medical center in Iran.

Material and Methods

In this observational retrospective cohort study, we included all patients diagnosed with BC managed in the Cancer Research Center (CRC) of Shahid Beheshti University of Medical Sciences, Tehran, Iran from 1991 to 2018. Patients with incomplete information in their records were excluded.

All precipitants were visited at least twice in the first two years after surgery and then at least once a year. An educated nurse followed the cases by phone contact and checked the patients' status (alive/dead) verbally or invited them to the clinic. Contact was repeated at different times to collect patients' information, if no one answered the call. Patients who were not available, were considered censored.

For survival estimation, death due to the cancer was considered the outcome, and the survival time was estimated from the time of cancer diagnosis to the time of death or the last follow-up. The data were analyzed in two parts: 1) Demographic characteristics such as age at diagnosis, sex, level of literacy, and 2) Clinical characteristics such as stage, type of surgery, pathological characteristics including type, tumor grade, lymphovascular invasion, number of positive lymph nodes, tumor size, Estrogen Receptor (ER), Progesterone Receptor (PR), human epidermal growth factor receptor 2 (HER2), and the type of case management. Univariate and multivariate analyses were done to show the real effect of variables on survival. We divided the duration of the study into four consecutive periods (<2003, 2004-2008, 2009-2013, and 2014-2018) for evaluating transitional changes such as age at diagnosis, tumor size, stage, level of literacy, and outcome of management during the study time.

Data analysis was performed using SPSS (ver. 26, IBM Corp. , Armonk, NY, USA). In the descriptive analysis, indices such as mean, Standard Deviation, median, frequency, and percentage were calculated. Statistical tests such as Chi-square and Analysis of Variance (ANOVA) were used to analyze demographic, clinical, pathological, and biological factors. We employed the Kaplan-Meier test for estimating the survival rate, the log-rank test for comparing the survival of different groups, and the Cox proportional hazards regression analysis for analyzing factors influencing survival. $P<0.05$ was considered statistically significant.

This study was approved by Ethics Committee of CRC (IR. SBMU. CRC. REC. 1401. 010). Written informed consent was obtained from participants.

Results

This study enrolled 4, 429 patients with BC managed during the last 27 years in CRC.

Demographic characteristics

Out of 4, 429 patients, 32 (0. 7%) were male. The mean and median age at diagnosis were 49. 11±11. 98 yr, and 48 yr (range 17-90). The mean age of male and female patients were 57. 58±14. 41 and 49. 06±11. 85 yr, respectively (Fig. 1).
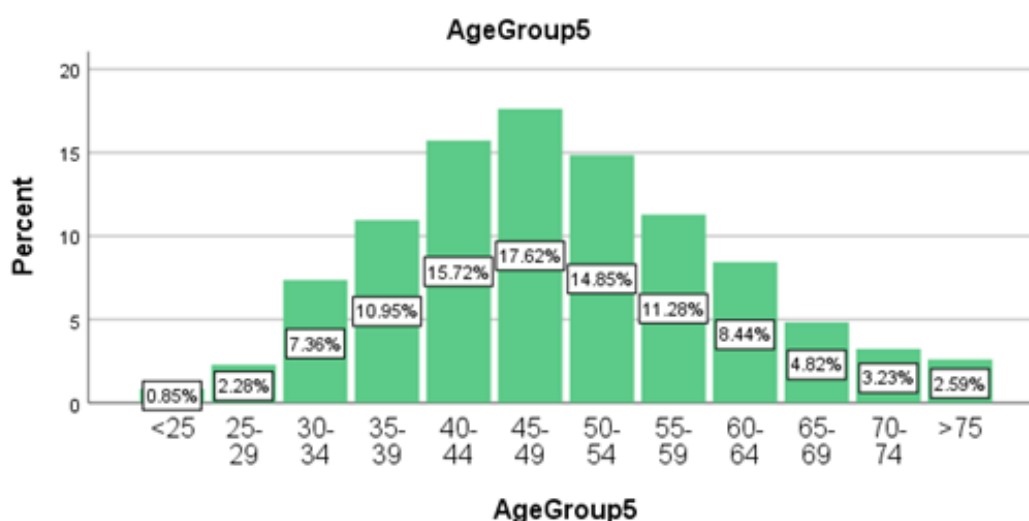

Fig. 1: Age distribution of patients with breast cancer managed in the Cancer Research Center for 27 yr

About 70% of the patients were graduated from high school or university; 28. 20% of educated patients were diagnosed with stage 1 and 4. 50% with stage 4, whereas in 11. 10% and 8. 60% of uneducated patients, the disease was manifested with stage 1 and stage 4, respectively (Table 1).

After dividing the study period into four groups (≤2003, 2004-2008, 2009-2013, and ≥2014), the mean ages were 47. 23, 48. 03, 49. 56, and 49. 48 yr in these periods. Hence, the mean age of patients at diagnosis had a significant difference between the first (≤2003) and the last (2014-2018) period (*P*=0. 007).

Clinical characteristics

More than half of the tumors (54. 88%) were 2 to 5 cm in diameter. The mass size was less than 2 cm in 31. 10% and more than 5 cm in 14. 20% of tumors. Changes in tumor size were significant during 27 yr; it was smaller than 2 cm in 20. 4% of

patients before 2003 and 35% in 2014-2018. Moreover, 16. 6% of tumors diagnosed before 2003 and 9. 8% between 2014 and 2018 were larger than 5 cm. The mean tumor sizes were 3. 6 (±1. 8), 3. 6 (±2. 1), 3. 22 (±1. 8), and 3 (±1. 7) cm, respectively, with no significant differences during the four periods. Most of the patients were in stage II and pathological grade II. Sarcoma and Lymphoma were observed in 32 and 16 cases, classified in the "others" subgroup. Steroid receptors were positive for ER in 72. 50% (negative in 27. 50%) and PR in 66. 90% of the patients (negative in 33. 10%). Overall, 28. 20% of the patients had LVI during this study. Most cases received breast-conserving surgery (BCS) (62. 70% vs. 37. 30%), and the rate of BCS from 2014 to 2018 was three times more than before 2003. In addition, the BCS rate from 2014 to 2018 was three times more than the MRM rate, whereas, before 2003, the MRM rate was three times higher than that of BCS.

Table 1: Baseline demographic and clinical characteristics of the patients

Variable	Sub-groups	Per-centage	Varia-ble	Sub-groups	Per-centage	Variable	Sub-groups	Per-centage
Sex			Stage			lympho-vascular invasion		
	Male	0. 70		0	4. 6		Positive	28. 20
	Female	99. 30		1	18. 2		Negative	41. 90
Age Group (yr)				2	42. 2		Missing	29. 90
	<30	3. 13		3	31. 1	HER-2		
	31-40	18. 31		4	3. 9		Positive	16. 20
	41-50	33. 34	Patho-logical Type				Negative	55. 40
	51-60	26. 13		invasive ductal carcinoma	78		Un-known	28. 40
	61-70	13. 26		ductal carcinoma insitu	3. 9	Surgery		
	>70	5. 82		invasive lobular carcinoma	6. 3		breast conserving surgery	62. 70
Literacy level				lobular carcinoma insitu	0. 3		modified radical mastectomy	37. 30
	University	34. 80		IDC/ILC	2. 1	Positive Lymph Node		
	Diploma	34. 50		others	9. 4		0	48. 90
	Middle school	12. 20	Grade				1-3	25. 90
	Elementary	12. 40		1	11. 45		4-10	17. 80
	Uneducated	6. 10		2	54. 62		>10	7. 40
				3	33. 93			

HER-2: human epidermal growth factor receptor 2

Survival Analysis

11. 6% of the patients passed away during this study period. The 5-, 10-, and 15-year survival rates of BC were 90%, 83%, and 75%, respectively (Fig. 2).
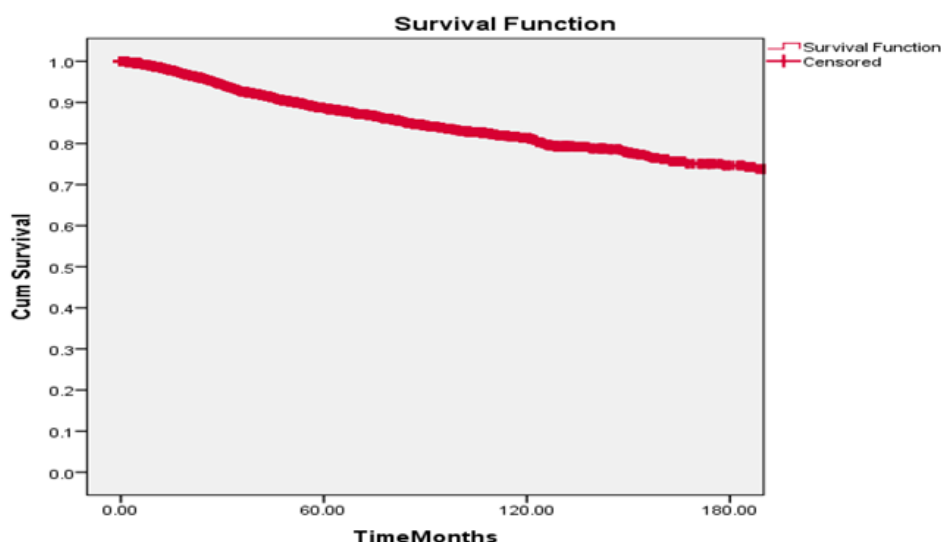
Fig. 2: Survival curve for patients with breast cancer managed in the Cancer Research Center

Furthermore, seven male patients died; therefore, the 5- and 10-year survival of male BC cases were 87% and 81%, respectively.

The age group of >70 yr had the worst survival, and all age groups of <60 yr had similar 10-year survival rates (83%), but in the 5-year survival rate, the age groups of 30 to 60 yr had similar rates (90%). There was a significant difference between >70 yr and other age groups (Fig. 3).
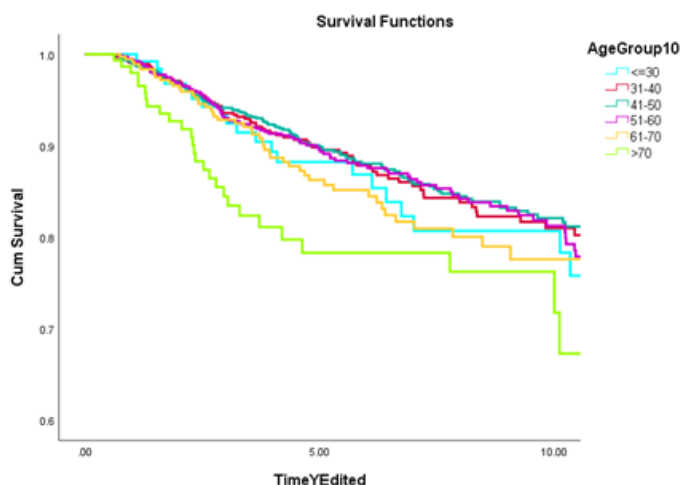

Fig. 3: Survival curve concerning the age groups

The 5- and 10-year survival rates were the highest in university-educated and the least in uneducated patients (10-year survival rate: 88% vs. 59%) (Fig. 4).

The five and ten-year survival rates of patients based on clinical characteristics are shown in table 2.
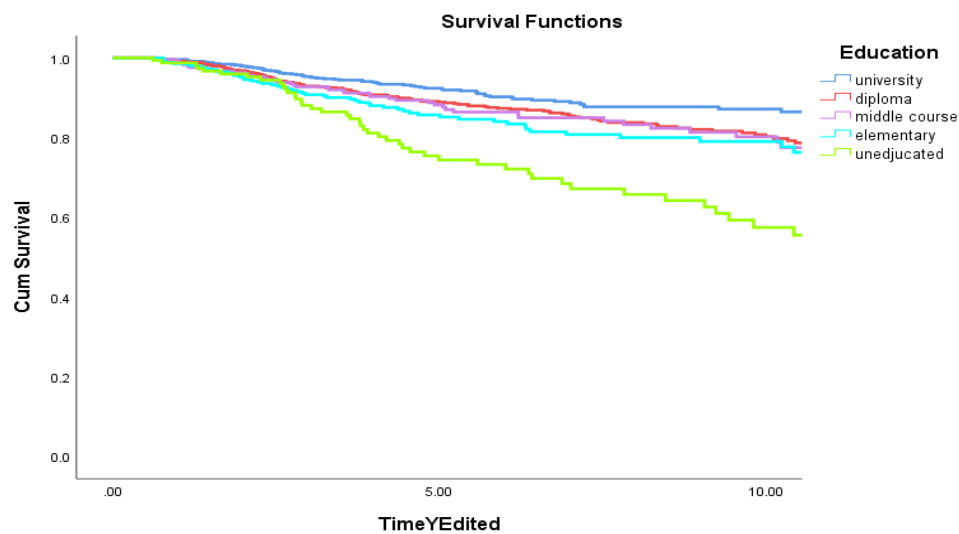
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Fig. 4: Survival curve concerning the level of patients' literacy

Table 2: Five and ten-year survival rates of patients with breast cancer

Clinical characteristic	Subgroups	5- ys survival (%)	10- ys survival (%)
Stage			
	1	98	92
	2	94	90
	3	90	70
	4	40	30
Grade			
	1	94	90
	2	90	83
	3	85	77
Pathological type			
	IDC	86	81
	ILC	91	83
Positive Lymph Node			
	0	97	93
	1-3	94	83
	4-10	82	63
	>10	70	60
Estrogen Receptor			
	Positive	90	81
	Negative	85	74
Progesterone Receptor			
	Positive	90	81
	Negative	85	74
HER-2			
	Positive	88	81
	Negative	91	84
Lymphovascular invasion			
	Positive	84	73
	Negative	95	90
Surgery type			
	BCS	93	86
	MRM	85	78

According to univariate analysis, variables such as age groups, literacy level, lymph node status, ER, PR, HER-2, tumor size, pathologic grade, type of surgery, and LVI showed a significant relationship with survival. In the Cox proportional Hazard model, variables such as literacy level, tumor size, pathologic grade, LVI, lymph node status, and ER affected the survival of patients with BC (Table 3).

Table 3: Cox proportional hazard analysis of variables affecting the survival of patients with breast cancer

Variable	Hazard Ratio (95% CI)
Tumor Size (cm)	
<2	1
2-5	1. 79 (1. 02- 3. 13)
>5	2. 86 (1. 50- 5. 45)
Grade	
1	1
2	1. 45 (1. 13- 1. 97)
3	2. 36 (1. 53- 3. 45)
LVI	
Negative	1
Positive	1. 92 (1. 34- 2. 91)
ER	
Positive	1
Negative	1. 29 (1. 08- 2. 15)
PR	
Positive	1
Negative	1. 37 (0. 84- 2. 24)
HER-2	
Negative	1
Positive	1. 40 (0. 92- 2. 12)
Surgery	
BCS	1
MRM	1. 38 (0. 94- 2. 01)
Positive Lymph Node	
0	1
1-3	1. 54 (0. 89-2. 66)
4-10	3. 88 (2. 33- 6. 47)
>10	5. 51 (3. 05- 9. 94)
Age Group (yr)	
<30	1
31-40	0. 58 (0. 26- 1. 26)
41-50	0. 71 (0. 33- 1. 53)
51-60	0. 41 (0. 18- 0. 94)
61-70	0. 89 (0. 37- 2. 15)
>70	1. 03 (0. 34- 3. 03)
Level of literacy	
University	1
Diploma	1. 18 (1. 02-1. 35)
Middle Course	1. 35 (1. 08- 1. 73)
Elementary	2. 09 (1. 12- 4. 04)
Uneducated	2. 36 (1. 35- 4. 42)

CI= Confidence interval, LVI: lymphovascular invasion, ER: estrogen receptor, PR: progesterone receptor, HER-2: human epidermal growth factor receptor 2, BCS: breast-conserving surgery, MRM: modified radical mastectomy

Discussion

In this study, the 5-, 10-, and 15-year survival rates for patients with BC were estimated at 90%, 83%, and 75%, respectively. Moreover, the survival rate was related to literacy level, positive lymph node, LVI, tumor size, pathologic grade, and ER status.

Disease management based on early detection, appropriate diagnosis, and comprehensive treatment is effective for timely disease

The 5-, 10-, and 15-year survival rates were 90%, 83%, and 75%, respectively. In a nationwide study in Iran (2019), 5-, and 10-year survival rates were estimated at 80% and 69%, respectively (5). In other studies, 5- and 10-year survival rates were reported as 77% and 65% (11). Five year survival rates in different studies performed in Iran were reported 70% (12), 51% (13). The survival rate differs worldwide, ranging from 80% in high-income countries to 40% in low-income countries (14). The 5- and 10-year survival in Turkey was 82% and 64%, respectively (15). The 5-year survival was reported at 83% in Canada (16).

In our research, the survival rate was nearly equal to the North American report (17), but patients referred for treatment in the late stages were more abundant (35% vs. 14%) while it was 65% in our study in early stages (0, 1and 2) compared to 74% (18). In the present study, the 15-year survival was 75%. The observed mortality rate after 15 years of diagnosis was very similar to the expected rates in the general female population, so it can be considered a cure.

The mean age at diagnosis was 49. 11 years. The mean age was 50. 68 yr in Iran in a national study (5), 51. 8 yr in Turkey (19), 49. 5 yr in Lebanon (20), 62 yr in the USA (17). The present study's mean age was almost equal to other studies in Iran and developing countries and lower than in Turkey and developed countries. Moreover, most patients were diagnosed in the age groups of 45 to 49 yr, about 10 yr younger than the report in western countries. The most prevalent age group is 40 to 49 yr in Malaysia (21), and 60 to 69 in the USA (22). The age distribution of women with BC shows that the age at diagnosis time was lower than in Western European and North American countries; confirmed by other studies conducted in the country (23). This result could be due to the countries' age pyramid shapes (24).

In the present study, age at diagnosis was a demographic variable that did not show any significant correlation with survival in multivariate analysis. Studies have shown different results for the effect of age on survival rate. In the United States, the survival rate of patients under the age of 41 is lower than that of older patients due to the more aggressive nature of the tumor at this age and a poorer response to treatment (25). In a study performed in Iran, the age of disease onset before and after 51 yr had no different effects on patients' lifespans (26). Comorbidities and poor health status in the elderly can explain their lower survival rate.

About 0. 7% of the patients were male. In Turkey, 1% of total patients were male (19). In other study, male BC was reported at 1% (27). Hence, our male patients with BC are similar to those in other countries. In this study, the mean age of male patients was 57. 58±14. 41 yr, about eight years higher than that of female patients. In northwest Iran, the mean ages of men and women were 54. 1±13. 6 and 48. 3±12. 8 yr (28), respectively. In another research the mean age of male BC was 57. 9±14. 7 yr and in females was 49. 1±12. 5 yr (23). Our estimation is in the range of reports from studies.

The 5- and 10-year survival rates for males were 87% and 81%, respectively. In an Iranian national study, the 5-year survival rate was 69% (5). In various studies from different parts of Iran, it was reported in the range of 60%-71% (29). Moreover, 5-year survival for male BC patients was estimated at 66% in Egypt (30), 76% in Italy (31), 83% in the USA (17), and 73. 9% in Turkey (32). In general, BC survival is worse in males than females because of diagnosis at older ages, advanced disease, and more abundance of triple-negative subtype (33). In this study, the survival of male cases was almost similar to that of male patients in developed countries.

One of the most important findings in this study was the relationship between survival rate and the level of patients' literacy. Early-stage breast cancers were more frequent in educated persons, and reversely, poor prognosis tumors were more frequent in uneducated patients. Tumors in advanced stages were inversely related to literacy level, with women who attended university having a fully adjusted OR of 0. 41 compared with those who had no formal education (34).

Some studies reported 5-year survival rates of 92. 2%, 84%, 73. 6%, and 56% for women with a higher literacy level, high school level, elementary level, and illiterate women, respectively (35). Levels of literacy are related to income and SES. Socioeconomic status is an important factor affecting the survival rate of women with BC. BC mortality correlates with socioeconomic factors and is associated with economic development, social factors, and lifestyle. The literature has documented survival inequality for many cancer types caused by socioeconomic factors, insurance, marriage, income, and literacy level (7). Patients' literacy levels have increased in recent periods. Increasing patients' awareness leads them to refer to a physician in the earlier stages of the disease. If a tumor is discovered early, it is more straightforward to perform BCS (36). Improving literacy makes information more accessible and causes higher levels of care, leading to healthier living. BC screening is performed more regularly and timely in women with higher literacy levels than in other populations (37).

In this study, the survival rate was affected by the level of literacy, positive lymph nodes, lymphovascular invasion, tumor size, pathologic grade, and ER. There was no significant difference between the two types of surgery in multivariate analysis. Methods of treatment can affect the survival rate. The comparable results for BCS and MRM in the multivariate analysis could have occurred because of the indirect effect of the higher level of patients' literacy and early-stage diagnosis. Several studies have shown equal or higher survival rates in BCS than in MRM (38). The result of this study was like many other studies. BCS makes patients more satisfied than MRM because of better body shaping (39).

Our findings showed that involvement of up to three lymph nodes did not change the survival; however, involvement of more than three lymph nodes affected the survival rate, as approved by previous trials (40). Despite different definitions of lymph node involvement, this finding is replicated in several studies (41). This point indicates the importance of BC screening and early detection in stages.

In Iran, the 5-year survival was reported at 82%, and influential variables included level of literacy, positive lymph nodes, and positive Estrogen receptors (42). In another study, age less than 35 yr, positive LVI, and stage 3 disease were influential variables (43). In our study, age was not effective in survival rate, and there was no difference between those above and below 40 yr old in multivariate analysis. Moreover, only ER affected survival among steroid receptors, while PR and HER-2 positivity did not affect it in the multivariate analysis. Except for the type of treatment, other prognostic factors were similar to our findings. In Iran, ER, positive lymph node, pathologic grade, and HER-2 affected the survival of BC (41). The first three mentioned factors were similar to our study.

In this study, negative estrogen receptors increased the risk of death from BC, as confirmed in similar studies (42). The status of estrogen receptors is essential to be identified for using the hormonal treatment for patients with positive hormone receptors, which increases the survival rate of these patients (43). PR was not a prognostic factor, unlike ER. In addition, multivariate analysis showed that HER-2 positivity did not affect the survival of patients, although it was influential in the univariate analysis by considering triple-negative cases (42).

Patients with lymph node invasion, ER negativity, lower level of literacy, advanced clinical stage, and high pathologic grade had lower survival rates. These prognostic factors can guide physicians in selecting appropriate and effective treatments for these groups. Many patients were referred for treatment at an advanced stage, which specified the need to inform women about a BC diagnosis in the early stages. Moreover, extensive efforts must be made to educate the community and equip healthcare centers to improve the diagnosis, treatment, and care process.

As for limitations of the study, the patients who visited our medical center were not similar to the national population and were referred to this center as a referral center. Also, we did not evaluate the impact of other socioeconomic variables, on BC survival because of the lack of information.

Conclusion

Breast cancer, the most prevalent female cancer, is under more consideration by health policymakers, healthcare workers, and researchers. The outcome of this single medical center during the last 27 yr was acceptable and comparable with developed countries and those with better socioeconomic status. This success may be due to some principles followed in this cancer research center, such as teamwork, respecting social determinants of health, close contact with patients during the process, trying to save the breast, limited chemotherapy as much as the science permits, and using radiotherapy for all cases who needed.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Conflict of interest

The authors declare that they have no conflict of interest.

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