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Prognostic factors influencing prognosis in early breast cancer patients

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Abstract

Aim of the study: The present study showed the clinicopathological characteristics and survival of early breast cancer (BC) patients.

Material and methods: A total of 236 patients were included in the study. The mean follow-up time was 59.5 months (range: 12-204 months). The inclusion criteria consisted of female patients aged > 20 years and early BC patients (stages I and IIA).

Results: The mean age at diagnosis was 51.2 years (range, 23-83 years), and 55.9% of patients were aged ≥ 50 years. Most patients (92.8%) did not have lymph node metastasis, and luminal B had the highest prevalence (54.2%) in patients. The eight-year overall survival (OS) and disease-free survival (DFS) rates were 98.3% and 92.3%, respectively. Stage IIA and Ki67 index ≥ 14% were more prevalent in the patients with tumour size of $2 \leq T \leq 5$ cm compared to another tumour size group and Ki67 index.

Conclusions: The mean age at diagnosis in this study was in agreement with other studies reported in various areas, but with a higher percentage for elderly patients compared to some previous studies. In addition, the survival rate in the present study was higher than the results of previous studies. Future studies need to investigate these factors in a higher number of patients and in different areas and should select similar stages for early BC.

Key words: early breast cancer, survival, recurrence, prognosis.

Introduction

Breast cancer (BC) is a heterogeneous disorder with different pathological and histological characteristics [1]. Based on the latest statistics from the International Agency for Research on Cancer (IARC), 1,677,000 women were diagnosed with BC in 2012 and 577,000 died [2]. According to the American Cancer Society (ACS), around 252,710 BC deaths occurred in 2017 in the United States [3]. In Iranian women, BC mortality of 3.93 per 100,000 people in 2006 increased to 4.92 per 100,000 people in 2010 [4]. The global incidence of BC in women is predicted to be approximately 3.2 million new cases per year by 2050 [5].

BC can be classified into different subtypes based on the diagnosis of oestrogen receptor (OR), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) [1]. Recurrence risk in BC changes during the follow-up time [6]. The prognosis of early BC depends on the patient and tumour characteristics [7]. Studies have reported that early BC detection with proper treatment can decrease BC death rates significantly in the long term [8]. Early BCs can be fully resected by surgery [2]. A BC patient experiences BC recurrence within 10 years following the achievement of initial treatment without adjuvant therapy [2, 9]. There was no early BC in Iran in the past due to the lack of screening studies. Nowadays, because of opportunistic screening and increasing of awareness of early BC among Iranian people, this study was performed to investigate the epidemiological features and survival of early BC (stages I and IIA), which is the first report in Iran.

Material and methods

This retrospective study was done on female patients referring to the Breast Cancer Research Centre, Tehran University of Medical Sciences, Tehran, Iran during 2008-2018. A total of 236 patients were included in the study. The clinicopathological factors (age at diagnosis, menopausal status, tumour size, lymph node metastasis, surgery, stage, grade, vascular invasion, lat-

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erality, OR, PR, HER2 status, Ki67 index, subtype, chemotherapy, and endocrine therapy) were obtained for each patient according to the pathological and clinical records. The mean follow-up period was 59.5 months (range: 12 to 204 months). The inclusion criteria consisted of: female patients aged > 20 years and early BC patients (stages I and IIA). The exclusion criteria included: male patients and patients without information about their OR, PR, or HER2 status. HER2 2+ detection by fluorescence in situ hybridisation (FISH) was considered HER2-positive. In addition, OR and PR were positive if staining was more than 10% of cells in the nucleus. Classification of tumours into four subtypes was done based on the study of Li *et al.* [10]. Overall survival (OS) was determined as the period from the date of BC diagnosis to the date of death due to any reason, and disease-free survival (DFS) was determined as the period from the date of BC diagnosis to the first local/regional recurrence, distant metastasis, or death due to any reason. The patients with tumour size greater than 1.2 cm were treated by chemotherapy because these patients had no lymph node metastasis. Chemotherapy regimens were AC4T4 (cyclophosphamide-adriamycin [AC]) used every three weeks for four cycles, followed by docetaxel (T) given every three weeks for four cycles, or anthracycline-based regimens and TC (docetaxel and cyclophosphamide) given every three weeks for four cycles, or non-anthracycline-based regimen. Anti-HER2 treatment was performed by trastuzumab in necessary cases for 17 sessions (one year) during or after chemotherapy. Hormone therapy regimens were aromatase inhibitors (letrozole and exemestane) or tamoxifen. In addition, in a number of patients, the tumour size was very small and the tumour was removed by excisional biopsy with a negative margin. Also, fine-needle aspiration (FNA) of axillary lymph nodes was negative; therefore, these patients did not undergo surgery. It is very common to use neoadjuvant chemotherapy to reduce the tumour size to make breast-conserving surgery possible in stage I-II breast cancer. Hence, many guidelines state that neoadjuvant chemotherapy should be used to reduce the size before surgery to make the surgeon more comfortable. All treatments (surgery, chemotherapy, and radiotherapy) were based on the National Comprehensive Cancer Network (NCCN) guidelines. Therefore, based on the NCCN, the size of the breast determines whether the patient requires neoadjuvant chemotherapy or not. When the size of the breast is small and even the size of the tumour is too small, it should be done first by neoadjuvant chemotherapy and then by breast-conserving surgery.

Statistical analyses

We used IBM SPSS (version 22) software (IBM Corp., Armonk, NY, USA) for the analysis of data. χ^2 test was used for the analysis of differences between the variables. A *p*-value (two-tailed) < 0.05 was considered statistically significant, with the confidence interval (CI) of 95%. DFS and OS curves were plotted by GraphPad Prism software (package version 5.0; GraphPad Software Inc., San Diego, CA, USA). The probability of OS and DFS over time was performed by applying Kaplan-Meier curves, and the comparison of OS and DFS between the subtypes of BC was performed by log-rank analysis.

Results

The mean age at diagnosis was 51.2 years (range: 23-83 years), and 55.9% of patients were aged ≥ 50 years. Table 1 shows the baseline characteristics of 236 patients with early BC. Tumour size was $2 \leq T \leq 5$ cm in 50.4% of patients and < 2 cm in 49.6% of patients (range: 0.1-5 cm). Most patients (92.8%) did not have lymph node metastasis. Out of all patients, 162 patients underwent surgery, 155 patients underwent chemotherapy, and 232 patients received endocrine therapy. Stages I and IIA were found in 128 and 108 patients, respectively; whereas, grades I, II, and III were observed in 45, 148, and 43 patients, respectively. Out of all patients checked for vascular invasion, 36 patients were positive. Laterality in 108 patients was found in the right side, and the rest of the patients were found to have laterality in the left side. The receptors showed that 80.1%, 73.3%, and 49.2% of patients were OR-, PR-, and HER2-positive, respectively. Out of 165 patients checked for Ki67 index, 45.5% had an index of less than 14%, with a mean of 20.7% in all patients. Most of the patients had tumours with luminal B (54.2%), followed by luminal A (27.1%) and HER2 overexpression (11%), and just 7.6% had triple-negative tumours.

Figure 1 illustrates the OS and DFS of early BC patients. The eight-year OS rate and mean OS were 98.3% and 57.2 months, respectively. In addition, the eight-year DFS rate and mean DFS were 92.3% and 55.4 months, respectively.

The prevalence rates of age, tumour size, and Ki67 index are shown in Figure 2. Most of the patients were between the ages of 40 and 60 years, and the number of young and elderly patients was very low. In addition, most of the patients with early BC had a tumour size of 1 to 3 cm, and the Ki67 index in most of the patients was ≤ 40%.

Table 2 shows the clinicopathological features of the patients with early BC grouped by mean age. Among the variables, there was no significant difference for all variables with mean age group, except for menopausal status ($p < 0.001$).

The clinicopathological features of the patients with early BC grouped by tumour size are shown in Table 3. Stage and Ki67 index had a significant difference with

Table 1. Characteristics of the patients with early breast cancer (n = 236)

Variable	Value
Age, *n* (%)	
Mean ±SD (range)	51.2 ±11.2 (23-83)
< 50 years	104 (44.1)
≥ 50 years	132 (55.9)
Menopausal status, *n* (%)	
Premenopausal	114 (48.3)
Postmenopausal	122 (51.7)
Tumour size, *n* (%)	
Mean ±SD (range)	1.85 ±0.69 (0.1-5)
< 2 cm	117 (49.6)
2 ≤ T ≤ 5 cm	119 (50.4)
Lymph node metastasis, *n* (%)	
Yes	17 (7.2)
No	219 (92.8)
Surgery, *n* (%)	
Breast-conserving surgery	99 (41.9)
Mastectomy	63 (26.7)
No	74 (31.4)
Stage, *n* (%)	
I	128 (54.2)
IIA	108 (45.8)
Grade, *n* (%)	
I	45 (19.1)
II	148 (62.7)
III	43 (18.2)
Vascular invasion, *n* (%)	
Positive	36 (15.3)
Negative	200 (84.7)
Laterality, *n* (%)	
Right	108 (45.8)
Left	128 (54.2)
OR, *n* (%)	
Positive	189 (80.1)
Negative	47 (19.9)
PR, *n* (%)	
Positive	173 (73.3)
Negative	63 (26.7)
HER2, *n* (%)	
Positive	116 (49.2)
Negative	120 (50.8)
Ki67, *n* (%) (*n* = 165)	
Mean ±SD (range)	20.7 ±17.2 (0-90)
< 14	75 (45.5)
≥ 14	90 (54.5)
Subtype, *n* (%)	
Luminal A	64 (27.1)
Luminal B	128 (54.2)
HER2 overexpression	26 (11)
Triple-negative	18 (7.6)
Chemotherapy, *n* (%)	
Yes	155 (65.7)
No	81 (34.3)
Endocrine therapy, *n* (%)	
Yes	232 (98.3)
No	4 (1.7)

HER2 – human epidermal growth factor receptor 2, OR – oestrogen receptor, PR – progesterone receptor, SD – standard deviation

tumour size groups (p < 0.001 and p = 0.006, respectively). Stage IIA and Ki67 index ≥ 14% were higher in the patients with tumour size of 2 ≤ T ≤ 5 cm compared to another tumour size group and Ki67 index.

Figure 3 shows the comparison of eight-year OS and DFS of the early BC patients based on molecular subtype. The OS rates were 98.4%, 98.4%, 96.2%, and 100% (p = 0.814) and DFS rates were 93.8%, 94.5%, 80.8%, and 88.9% (p = 0.108) in luminal A, luminal B, HER2 overexpression, and triple-negative groups, respectively. In pairwise comparison, the difference in OS and DFS rates between both subtypes was not significant: luminal A vs. luminal B, luminal A vs. HER2 overexpression, luminal A vs. triple-negative, luminal B vs. HER2 overexpression, luminal B vs. triple-negative, and HER2 overexpression vs. triple-negative.

Discussion

As in Iran, due to the onset of BC at an early age, early warning and screening programs are essential for early diagnosis despite the relatively high levels of survival compared to other cancers [11]. One study indicated that age-standardised incidence rates of BC in Central and Northern provinces of Iran were higher than elsewhere [12]. The present study evaluated some characteristics, including OS and DFS of the early BC patients (stages I and IIA) and correlation between the factors associated with it.

Based on NCCN guidelines, the size of the breast determines whether the patient needs neoadjuvant chemotherapy or not. When the size of the breast is small and even the size of the tumour is too small, it should be done first by the neoadjuvant chemotherapy and then by breast-conserving surgery. Out of 6248 early BC patients treated in neoadjuvant and adjuvant chemotherapy in a cohort, 57% showed OR positivity, 43% PR positivity, 17% HER2 positivity, 20% triple-negative, and 35% < 2 cm in tumour size [13]. In addition, another study on 1287 early BC patients in China (stage I-III) reported that 44.6%, 44.6%, 55.8%, 17.7%, and 23.5% of patients had tumour size < 2 cm, lymph node metastasis, grade III, triple-negative, and Ki67 < 14%, respectively [10]. The prevalence of these variables in the present study (stage I and IIA) was 49.6%, 7.2%, 18.2%, 80.1%, 73.3%, 49.2%, 45.5%, and 7.6% for tumour size < 2 cm, lymph node metastasis, grade III, OR positivity, PR positivity, HER2 positivity, Ki67 < 14%, and triple-negative, respectively. These differences can be due to the selection of different stages for early BC among studies.

The mean age at diagnosis in our study on BC patients with stages I and II was 51.2 years (55.9% had age ≥ 50 years), as in previous Iranian studies: 47.6 years [14] and 49.6 years [15]. Three studies [10, 16, 17] reported early BC patients (stages I to III or stages I

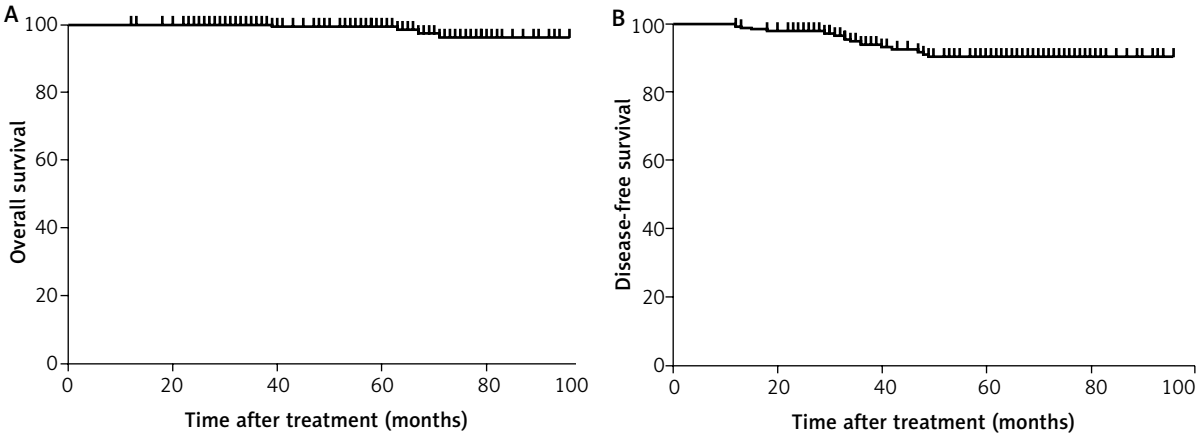

Fig. 1. The 8-year (**A**) overall survival and (**B**) disease-free survival in the early breast cancer patients

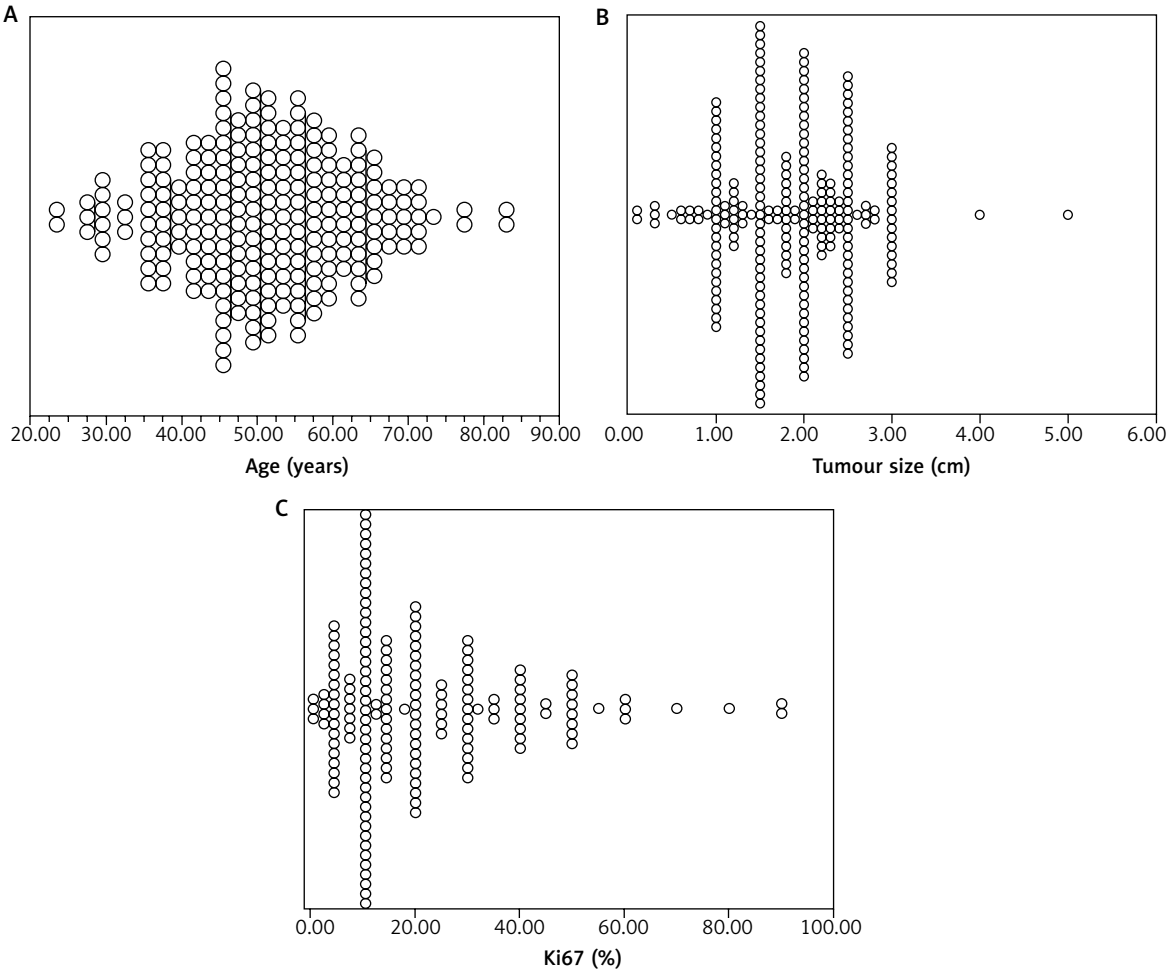

Fig. 2. The distribution of (**A**) age, (**B**) tumour size, and (**C**) Ki67 index in the patients with early breast cancer

and III), one study reported the median age of 50 years at diagnosis (age range: 42-59 years; 51.2% ≥ 50 years), another study reported the mean age of 48.2 years, and the last study reported the median age of 51 years (range: 28-92 years). One study [18] selected 36,340 Iranian women and reported the highest age-specific incidence rate (ASIR) for the age ranges 45-65 and 80-85 years, respectively. Therefore, almost mean age of BC patents in different areas is similar, but with a different percentage of elderly patients among studies.

Among Iranian women, BC is the third most common cause of death, and age at onset of BC has decreased from 40.0 to 30.0 years [19]. Of the 1500 Iranian BC patients, 36% had age ≥ 50 years, and the result

Table 2. Clinicopathological features of the patients with early breast cancer grouped by age at diagnosis (n = 236)

Variable	< 50 years	≥ 50 years	*p*-value
Menopausal status, *n* (%)			< 0.001
Premenopausal	104 (100)	10 (7.6)	
Postmenopausal	0 (0)	122 (92.4)	
Tumour size, *n* (%)			0.241
< 2 cm	47 (45.2)	70 (56.0)	
2 ≤ T ≤ 5 cm	57 (54.8)	63 (47.0)	
Lymph node metastasis, *n* (%)			0.126
Yes	4 (3.8)	13 (9.8)	
No	100 (96.2)	119 (90.2)	
Stage, *n* (%)			0.599
I	54 (51.9)	74 (56.1)	
IIA	50 (48.1)	58 (43.9)	
Grade, *n* (%)			0.057
I	18 (17.3)	27 (20.5)	
II	60 (57.7)	88 (66.7)	
III	26 (25.0)	17 (12.9)	
Vascular invasion, *n* (%)			0.365
Positive	13 (12.5)	23 (17.4)	
Negative	91 (87.5)	109 (82.6)	
Laterality, *n* (%)			0.360
Right	44 (42.3)	64 (48.5)	
Left	60 (57.7)	68 (51.5)	
Ki67, *n* (%) (*n* = 165)			0.492
Mean ± SD	21.8 ±17.1	19.9 ±17.3	
< 14	30 (41.7)	45 (48.4)	
≥ 14	42 (58.3)	48 (51.6)	

Table 3. Clinicopathological features of the patients with early breast cancer grouped by tumour size (n = 236)

Variable	< 2 cm	2 ≤ T ≤ 5 cm	*p*-value
Menopausal status			0.366
Premenopausal	53 (45.3)	61 (51.3)	
Postmenopausal	64 (54.7)	58 (48.7)	
Lymph node metastasis			0.515
Yes	8 (6.8)	9 (7.6)	
No	109 (93.2)	110 (92.4)	
Stage			< 0.001
I	117 (100)	11 (9.2)	
IIA	0 (0)	108 (90.8)	
Grade			0.197
I	23 (19.7)	22 (18.5)	
II	78 (66.7)	70 (58.8)	
III	16 (13.7)	27 (22.7)	
Vascular invasion			0.113
Positive	14 (12)	22 (18.5)	
Negative	103 (88)	97 (81.5)	
Laterality			0.151
Right	58 (49.6)	50 (42)	
Left	59 (50.4)	699 (58)	
Ki67, % (*n* = 165)			0.006
Mean ± SD	17.7 ±15.1	24.3 ±18.8	
< 14	49 (55.1)	26 (34.2)	
≥14	40 (44.9)	50 (65.8)	

showed a low number of elderly women with BC in Iran [20]. A nested cohort on 6248 early BC patients was in agreement with this research [13], whereas a cohort of 767 Brazilian BC patients showed the opposite results [21]. The percentage of elderly patients (≥ 50 years) in the present study was 55.9%. Many studies have reported that elderly women (≥ 70 years of age) have less aggressive BC, including a higher frequency of lower grade tumours and positivity for hormone receptor [22,

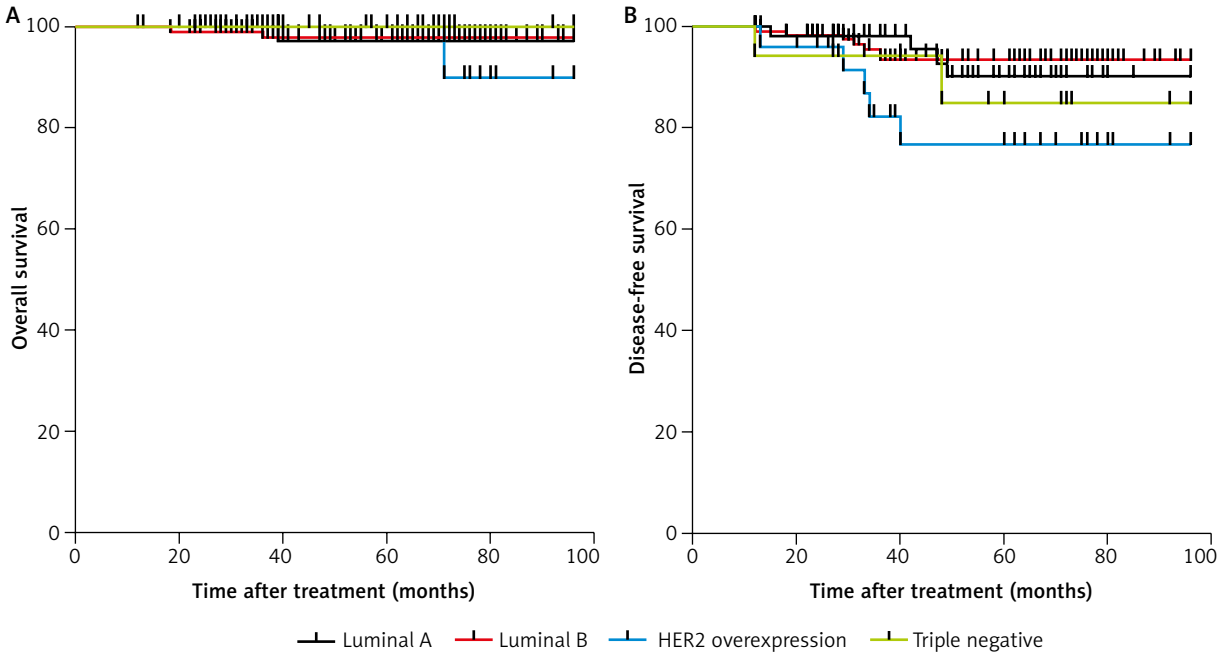

Fig. 3. The comparison of 8-year (**A**) overall survival and (**B**) disease-free survival of the early breast cancer patients based on molecular subtype

23]. In the present study, there was no significant difference between BC patients ≥ 50 years old compared to < 50 years old in terms of menopausal status, tumour size, lymph node metastasis, stage, grade, vascular invasion, laterality, and Ki67 index.

Much attention has been paid to small tumours in recent years, because T1a, bN0 tumours generally present with a good prognosis [10]. In particular, a patient with a tumour size of 2.1 cm can have a different prognosis than a patient with a 4.9-cm tumour [24]. A study [5] reported no correlation between the tumour size and Ki67 index (cut-off: 20%). In this study, large tumour size was significantly correlated with more advanced stage and Ki67 index (cut-off: 14%), and the difference in the results of Ki67 can be due to different cut-offs. However, the difference between two tumour size groups was not significant in other variables, but there was a lower lymph node metastasis, vascular invasion, and grade in the patients with small tumours.

In early BC patients with a median follow-up of 8.4 years, 5% of all patients had a local recurrence, whereas 28% had progressive metastasis [17]. The present study showed that the eight-year OS and DFS rates were 98.3% and 92.3%, respectively. A meta-analysis found that the one-, three-, five-, and 10-year OS rates of BC in Iran were estimated to be 95.8%, 82.4%, 69.5%, and 58.1%, respectively [25]. A study [17] on early BC patients indicated that OS rates at ages 5, 10, 15, 20, and 25 years were 82%, 62%, 49%, 39%, and 28%, respectively. A study on early BC with a median follow-up of 33 months showed the three- and five-year OS rates were 95.0% and 90.8%, respectively [10]. The mean five-year OS rate of women with BC was 71% in Iran in 2007 [26] compared to 92% in the United States [27]. In a cohort study including 1249 early BC patients (stages I to III) with a median follow-up of 73.7 months, there were 344 events (27.5%), including 272 cases with distant relapse, 64 cases with locoregional recurrence, and eight cases with contralateral neoplasms [6]. The results of one study showed that age, major diameter, tumoural volume, grading, and molecular subtype influenced DFS in univariate analysis [7]. The OS and DFS in the present study were better than in other studies including early breast cancer patients. This difference can be due to selecting different stages for early BC in the studies. Future studies should pay attention to selecting similar criteria for early stage of BC to obtain stronger and more accurate conclusion about early BC patients.

One research [28] included women aged > 65 years at BC diagnosis and found more early-stage neoplasms in the luminal subtypes. A study of 1287 early BC (stages I-III) patients [10] showed the five-year OS rate was 97.3% in luminal A, 94.1% in luminal B, 67.6% in HER2 overexpression, and 66.5% in triple-negative tumour ($p < 0.001$), which is in disagreement with the results of the present research (stages I and II). The difference between these two studies can be due to the selection manner of the early BC patients.

Conclusions

The present retrospective study investigated the clinicopathological features and survival of early BC patients, reflecting the situation of diagnosis and treatment in an area of Iran. The mean age at diagnosis in this study was in agreement with other studies reported in various areas, but with a higher percentage for elderly patients compared to some previous studies. In addition, the survival rate in the present study was higher than the results of previous studies. These differences can be due to the selection of different stages for early BC, which must be carefully considered in future research. Future studies need to investigate these factors in a higher number of patients and different areas, selecting similar criteria for early BC.

Disclosure

The authors report no conflict of interest.

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