

RESEARCH ARTICLE

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Long-Term Oncologic Outcome of Breast Cancer in Southern Iran: A Retrospective Cohort Study

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Abstract

Introduction: Breast cancer remains the most frequent and lethal cancer among women worldwide. This study aimed to investigate the characteristics, prognostic factors and outcome of breast cancer patient treated and followed-up in Shiraz, southern Iran from 2000 to 2005. **Methods:** In this retrospective study, 1,024 patients with breast cancer who were treated in Namazi hospital of Shiraz University of Medical Sciences between 2000 and 2005 were included. Survival analysis was performed to determine potential factors influencing disease free-and overall survival in these patients. **Results:** Median age of the patients at diagnosis was 47 (range 19-83) years. Median follow-up for surviving patients was 68 months. The majority of patients presented at stage II (42%) and stage III (41%). Additionally, most (61%) patients had positive axillary node. The 5-, 10- and 15-year overall survival rates were 83.8%, 61.5% and 56.6% respectively. On multivariate analysis for overall survival, histologic type, Tumor stage, node stage, disease stage, M stage, hormone receptor status, adjuvant radiotherapy, and chemotherapy regimen remained independent prognostic factor for overall survival. **Conclusion:** in this study, the poor long-term oncologic outcome of the patients with breast cancer may be due to the higher rate of locally advanced disease; as well as the lack of modern systemic therapies in the study period.

Keywords: Breast neoplasm- survival- neoplasm metastasis- Shiraz- Iran

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Introduction

Breast cancer follows lung cancer as the second most frequent cancer in overall and the first in women, with more than half a million deaths per year, one in 4 of the cancer cases among the women and nearly 2 million new case in 2018. As about two-third of the world population reside in Asia, it is estimated that the main mortality will occur here (Ferlay et al., 2019). Genetic factors like BRCA1 and BRCA2 mutation and positive family history along with non-hereditary variables, early age at menarche, late age at menopause, nulliparity, non-complete pregnancy, post-menopausal hormone therapy, smoking, obesity and alcohol consumption, are the known factors that increase the risk of breast cancer in a patient (Kamińska et al., 2015; McPherson et al., 2000a,b; Mersch et al., 2015).

Early diagnosis using mammography, breast sonography and MRI has decreased the disease associated mortality and morbidity (Kriege et al., 2004; Lehman et al., 2005) Estrogen(ER) and Progesterone(PR) receptor status, histologic subtype, age at presentation, gender, stage, number of positive dissected lymph nodes and metastasis location are considered as potential factors that

may influence the survival duration in different studies (de Boer et al., 2010; Metcalfe et al., 2019; Saad et al., 2019). In a study on more than 170,000 breast cancer patients in 2015, T-stage had reverse correlation with survival duration (Saadatmand et al., 2015). In females with BRCA2 mutation positive estrogen receptor causes shorter survival (Metcalfe et al., 2019). Regarding to an 18-year cohort study in 2016 (based on Danish cancer registry), lung, liver and brain metastasis respectively comes after bone metastasis as the most common sites of breast cancer metastasis. Patients with brain and liver metastasis had highest mortality rate during the first year after metastasis incidence (Ording et al., 2017). Radiotherapy and systemic treatments such as chemotherapy, hormone therapy, targeted therapy and immunotherapy are considered as non-surgical treatments for breast cancer (Chambers et al., 2019; Waks et al., 2019).

There is a paucity evidence regarding the long-term oncologic outcome and prognostic factors of patients with breast cancer in southern Iran. This study aimed to investigate the characteristics, prognostic factors and long-term oncologic outcome of 1,024 breast cancer patient referred to the Namazi hospital of Shiraz University of

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Medical sciences from 2000 to 2005.

Materials and Methods

This retrospective study performed on all women with pathologically proven invasive breast carcinoma referring to the Namazi hospital of Shiraz University of Medical Sciences. Study cases selected since January 2000 till January 2005 with follow up till January 2021. Patients had regular follow up records. We evaluate patients' status using their phone numbers and reviewing their medical records. In case of uncertainty about patients' status, we searched local databases such as insurance information. Noninvasive breast cancer such as "carcinoma in situ" and pathologies other than adenocarcinoma such as "lymphoma", "sarcoma", and "phyllodes tumor" were excluded. Tumor, Node, Metastasis (TNM) staging was defined using the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system (Amin et al., 2017).

Study variables were Age at presentation, TNM stage, histologic subtype, estrogen and progesterone receptor status, Her2-Neu receptor status, dissected lymph nodes and positive dissected LNs ratio, Chemotherapy regimen, radiation dose, metastasis location and time, overall survival (OS) and disease free survival (DFS). Patients categorized with age cut-off point of 40 years. Date of breast cancer pathology report considered as disease presentation time. Used chemotherapy regimens were, CMF (Cyclophosphamide, Methotrexate and Fluorouracil), CAF (Cyclophosphamide, Adriamycin and Fluorouracil), CAF followed by paclitaxel and TAC (Docetaxel, Adriamycin and Cyclophosphamide). Disease Free Survival considered as the time period between surgery and the first occurred metastasis.

Data inserted in SPSS version 21 and checked for repetitive data. In the statistical tests p-value under 0.05 assumed as statistical significance. Mean and standard deviation used for quantitative data description. Student t-tests and ANOVA or non-parametric substitutes used

for comparison between different groups. Kaplan-Meier survival analysis done for age groups, histology, hormone receptor status, chemotherapy, radiotherapy, M-Stage, N-Stage, stage group, positive dissected LNs. Overall and disease free survival duration compared between subgroups using Log-Rank test. Cox regression analysis assumptions met and it performed to evaluate the possible effect of mentioned factors on overall and disease free survival.

Results

January 2000 to January 2005, 1,059 patients with documented breast cancer referred to our center for nonsurgical treatments. Thirty five patients were excluded due to male gender and rare pathologic subtypes so we performed analysis on 1024 women in this study. Median age of the patients at diagnosis was 47 (range 19-83) years and 274 of them (26.8%) were under 40 years. Ductal carcinoma was the most frequent (88.6%) histologic subtype followed by medullary (5.2%) and lobular (4.5%) carcinoma. The majority of patients presented at stage II (42%) and stage III (41%). TNM staging frequencies are shown in figure 4. Additionally, most (61%) patients had a clinically positive axillary node at the time of diagnosis. In the current study, the rate of stage IV at presentation was only 1.5% which might be underestimated due to inadequate staging workup. Due to limited resources and financial problems, 27 percent of patients with stage III disease did not have CT scans or bone scans. Only 26 patients (2.8%) did not receive adjuvant chemotherapy in their treatment course. During the follow-up period, approximately one-third of the patients developed recurrences, of which, only 2% had local recurrences, and the rest having distant relapse. Bone (43%), lung (22%), brain (9%), and liver (8%) were the most common foci of the metastasis. Chemotherapy regimen of CMF including cyclophosphamide, methotrexate and 5-FU (60.1%) and CAF including cyclophosphamide, doxorubicin and 5-FU (31.9%) were the most frequent chemotherapy protocol

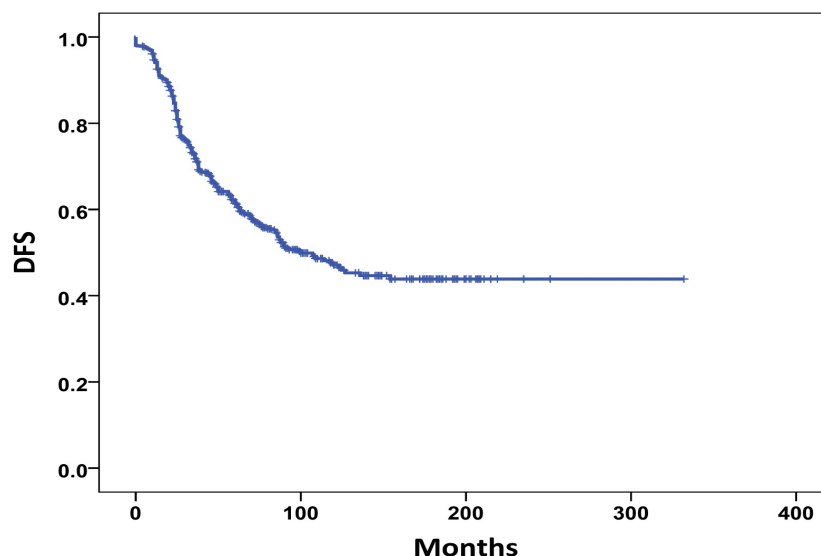


Figure 1. Kaplan-Meier Survival Curves for Disease-Free Survival (DFS) of 1024 Patients with Breast Cancer.

Table 1. Univariate Analysis of Prognostic Factors for the DFS and OS of 1024 Patients with Breast Cancer

Variables	Frequency (%)	OS months (95% CI)	P-value	DFS months (95%CI)	P-value
Age			0.212		0.043
<40	274 (26.8%)	176.6 (164.6-188.6)		115.6 (103.3-127.9)	
≥40	748 (73.1%)	233.5 (209.6-257.2)		171.7 (151.5-191.8)	
Histology			0.187		0.839
Ductal carcinoma	904 (88.6%)	188.5 (174.4- 202.6)		131.4 (122.5-140.2)	
Medullary carcinoma	54 (5.2%)	272.4 (228.3-316.6)		204.1 (125.8-282.4)	
Lobular carcinoma	46 (4.5%)	162.8 (116-209.6)		86.8 (62.7-110.8)	
Others	16 (1.5%)	141.7 (86.5-196.8)		114 (56.4-171.7)	
Relapsed site			<0.001		<0.001
No relapse	660 (64.5%)	296.3 (284.5-308.2)		292.955 (281.4-304.4)	
Bone	147 (14.3%)	178.9 (163.3-194.5)		35.591 (30.8-40.3)	
Lung	73 (7.1%)	107.4 (84.2-130.6)		32.849 (27.4-38.2)	
Liver	29 (2.8%)	95.3 (59.2-131.5)		23.069 (17.6-28.5)	
Brain	32 (3.1%)	69.8 (53.1-86.4)		32.802 (24.9-40.6)	
Multiple sites	51 (4.9%)	99.6 (77.9-121.3)		34.314 (26.6-41.9)	
Lymphatics	4 (0.4%)	158.7 (97.2-220.2)		41.250 (0.0-86.8)	
Local recurrence	20 (1.9%)	199.2 (178.7-219.6)		93.714 (16.4-61.5)	
others	7 (0.6%)	190.4 (171.8-208.9)		57.383 (35.5-79.0)	
Chemotherapy regimen			<0.001		<0.001
No chemotherapy	26 (2.5%)	213.4 (167.4-259.3)		172.6 (127.5-217.7)	
CMF	613 (60.1%)	255.7 (226.8-284.7)		186.5 (168-205)	
CAF or AC	326 (31.9%)	157.6 (144.5-170.7)		117.1 (104.5-129.7)	
AC followed by Taxol	40 (3.9%)	87.2 (63.1-111.2)		30.3 (21.7-38.8)	
TAC or Taxane-based	10 (0.98%)	82.6 (48.4-116.9)		30.7 (11.8-49.5)	
Others	4 (0.39%)	28.6 (9.8-47.5)		10.8 (3.3-18.4)	
Positive dissected LNs			<0.001		<0.001
<3	596 (58.4%)	260.4 (230.9-289.9)		216.2 (188.7-243.6)	
≥3	424 (41.5%)	152.6 (139.3-165.9)		78.4 (68.8-88.1)	
ER and/or PR			<0.001		<0.001
Positive	308 (27.4)	199.6 (186.2-213.0)		140.3 (125.8-154.9)	
Negative	281 (30.1)	118.4 (104.9-131.9)		115.7 (96.7-134.6)	
Unknown	435 (42.5)	148.7 (139.0-158.4)		135.1 (125.2-145.1)	
N-stage			<0.001		<0.001
0	401 (39.2%)	229.9 (220.1-239.8)		189.3 (173.2-205.3)	
1	273 (26.7%)	193.4 (152.3-234.4)		170.7 (136.6-204.8)	
2	206 (20.1%)	160.2 (142.9-177.6)		84.7 (70.3-99.2)	
3	142 (13.9%)	123.1 (102.1-144.2)		49.5 (39.1-59.9)	
M-stage			<0.001		<0.001
0	1004 (98.1%)	229.5 (204-255)		176.1 (163.3-189.0)	
1	19 (1.9%)	57.7 (39.8-75.6)		0.0 (0.0-0.0)	
Disease stage			<0.001		<0.001
1	153 (14.9%)	188.8 (172.2-205.4)		198.0 (187.0-209.1)	
2	432 (42.2%)	190.0 (177.2-202.8)		208.1 (187.9-228.3)	
3	419 (40.9%)	141.4 (126.8-156.0)		78.1 (67.9-88.2)	
4	19 (1.8%)	22.4 (17.0 - 27.7)		0.0 (0.0-0.0)	

DFS, disease free survival; OS, overall survival

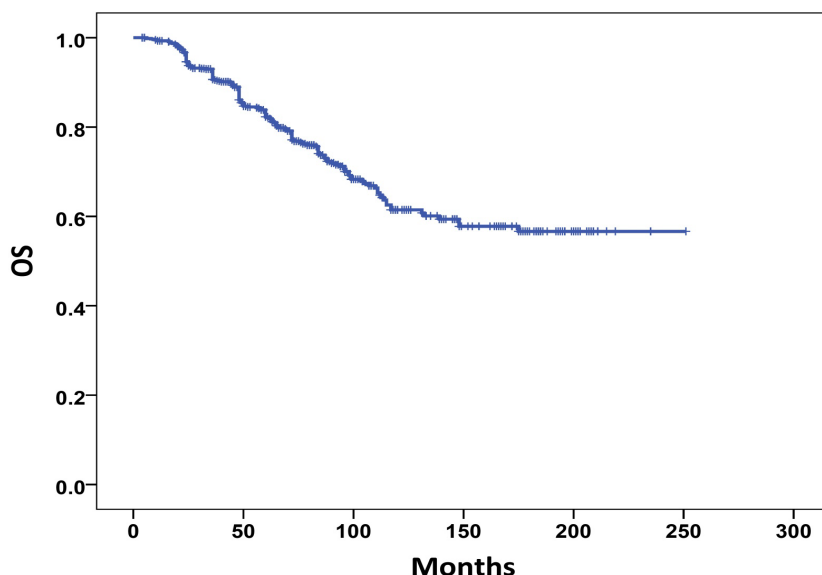


Figure 2. Kaplan-Meier Survival Curves for Overall Survival of 1024 Patients with Breast Cancer.

Table 2. Multivariate Analysis of Overall Survival of 1024 Patients with Breast Cancer.

Variables	Hazard Ratio ¹ (95 % Confidence interval)	P value
Histologic type		
Ductal carcinoma	ref	0.171
Medullary carcinoma	0.454 (0.211-0.976)	0.043
Lobular carcinoma	0.331 (0.116-0.947)	0.039
Others	0.515 (0.186-1.424)	0.201
Chemotherapy regimen		
No chemotherapy	ref	
CMF	0.049 (0.008-0.296)	0.001
CAF or AC	0.039 (0.009-0.161)	0
AC followed by Taxol	0.079 (0.019-0.328)	0
TAC or Taxane-based	0.221 (0.051-0.958)	0.044
Others	0.145 (0.020-1.036)	0.054
Neoadjuvant Radiotherapy		
No		
Yes	0.453 (0.253-0.812)	0.008
N-stage		
0	ref	
1	0.190 (0.119-0.303)	0
2	0.479 (0.314-0.729)	0.001
3	0.676 (0.445-1.026)	0.066
M-stage		
0	ref	
1	0.170 (0.083-0.348)	0
Disease stage		
1	ref	
2	0.316 (0.094-1.060)	0.062
3	0.13 (0.045-0.238)	0
4	0.060 (0.033-0.109)	0
Positive dissected LNs		
<3	ref	
≥3	0.386 (0.284-0.524)	<0.001

Table 2. Continued

Variables	Hazard Ratio ¹ (95 % Confidence interval)	P value
T-stage		
T1	ref	
T2	0.063 (0.025-0.157)	<0.001
T3	0.385 (0.237-0.626)	<0.001
T4	0.769 (0.505-1.162)	0.219
Radiotherapy		
Yes	ref	
No	0.285 (0.117-0.697)	0.006
ER and/or PR		
Positive	ref	
Negative	0.264 (0.164-0.420)	<0.001
Unknown	0.545 (0.344-0.862)	0.009

used in these patients. In addition, adjuvant radiotherapy with a median dose of 50 Gy was delivered to 915 patients (87.2%).

Median follow-up for surviving patients was 68 months. We had 178(17.3%) censored cases during survival analysis. The median DFS and OS was 47 and 56 months respectively. Age-related estimated overall survival comparing to expected life expectancy for Iranian females at the same time period are illustrated in table 3. The 1-, 2-, 3-, 5-, 10- and 15-year DFS rates were 94.7%, 84.7, 72.9%, 62.3%, 47.1% and 43.9% respectively (Figure 1). Likewise, the 1-, 2-, 3-, 5-, 10- and 15-year OS rates were 99.3%, 96.7%, 93%, 83.8%, 61.5% and 56.6% respectively (Figure 2). In the univariate analysis, age (P = 0.043), hormone receptor status (P <0.001), chemotherapy regimen (P <0.001), number of positive lymph nodes (P <0.001), node stage (P <0.001), and disease stage (P <0.001) were significant prognostic factors for disease-free survival. Likewise, Univariate analysis showed metastatic site (P <0.001), chemotherapy regimen (P <0.001), hormone receptor status (P <0.001),

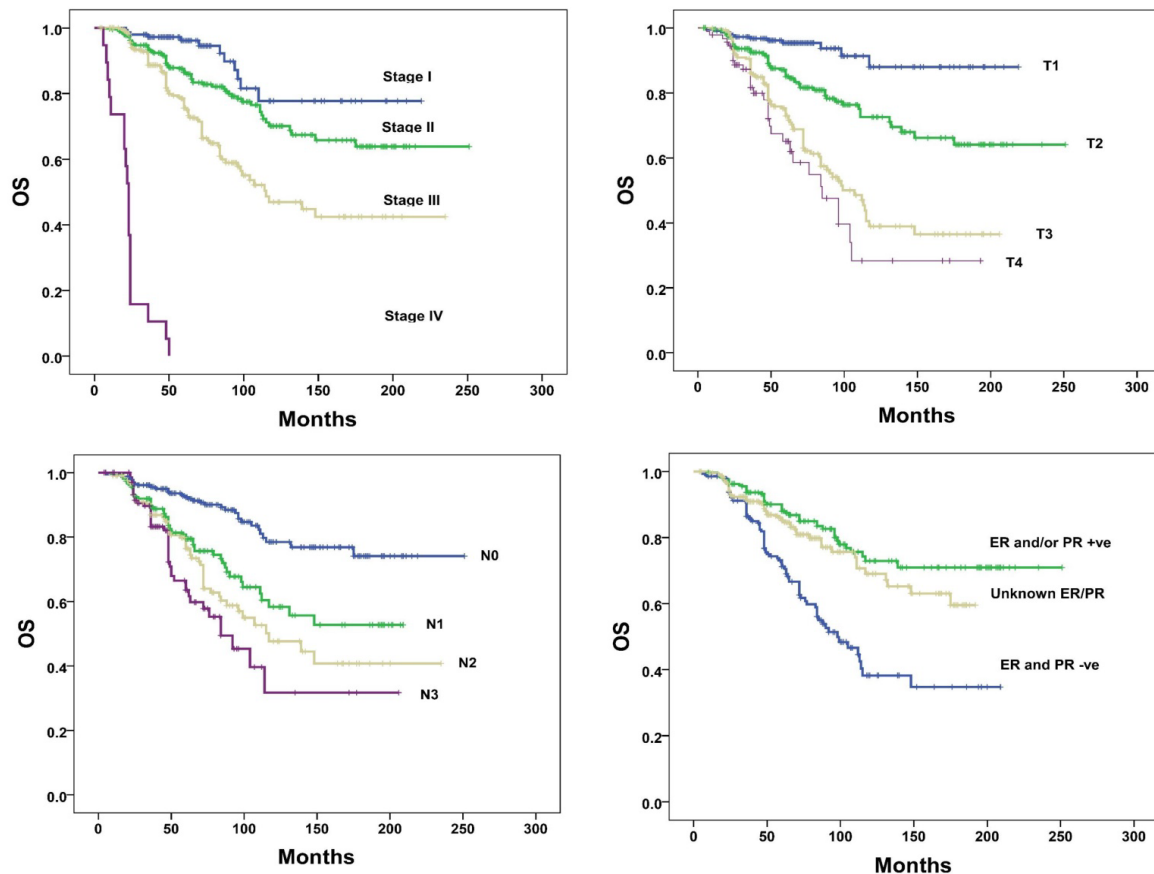


Figure 3. Prognostic Factors Impact of Disease Group, T-stage, N-stage, and Hormone Receptor Status on Overall Survival.

number of positive lymph nodes ($P < 0.001$), node stage ($P < 0.001$), and disease stage ($P < 0.001$) were significant prognostic factors for overall survival (Table 1). Figure 3 illustrates the impact of the most important prognostic factors including disease group, T-stage, N-stage, and hormone receptor status on overall survival. On multivariate COX-Regression analysis for overall survival, medullary and lobular carcinoma histology,

adjuvant radiotherapy, chemotherapy regimen, hormone receptor status, node stage, disease stage and more than 3 positive dissected lymph node had affect overall survival chance independently (Table 2). In multivariate analysis to find potential risk factors for visceral and bone metastasis, more positive dissected lymph nodes ($HR=1.1$, p -value= 0.001) and less dissected lymph nodes ($HR=0.94$, p -value=0.006) are risk factors for visceral

Table 3. Estimated Life Expectancy Comparing to the Expected Life Expectancy in Each Age Group

Age group (years)	Frequency	Estimated OS (months)	Expected life expectancy (months)	Percent live more than expected age related life expectancy
<25	6	.	.	.
26-30	30	151	448	0
31-35	87	187	388	0
36-40	148	173	328	0
41-45	186	240	268	0
46-50	213	174	208	0.95
51-55	160	167	160	10.6
56-60	96	187	112	12.6
61-65	44	130	52	44
66-70	24	138	76	33.3
71-75	17	72	36	58
76-80	7	43	12	85
>80	6	.	.	.

due to small sample size in two age groups, survival analysis were impossible to perform

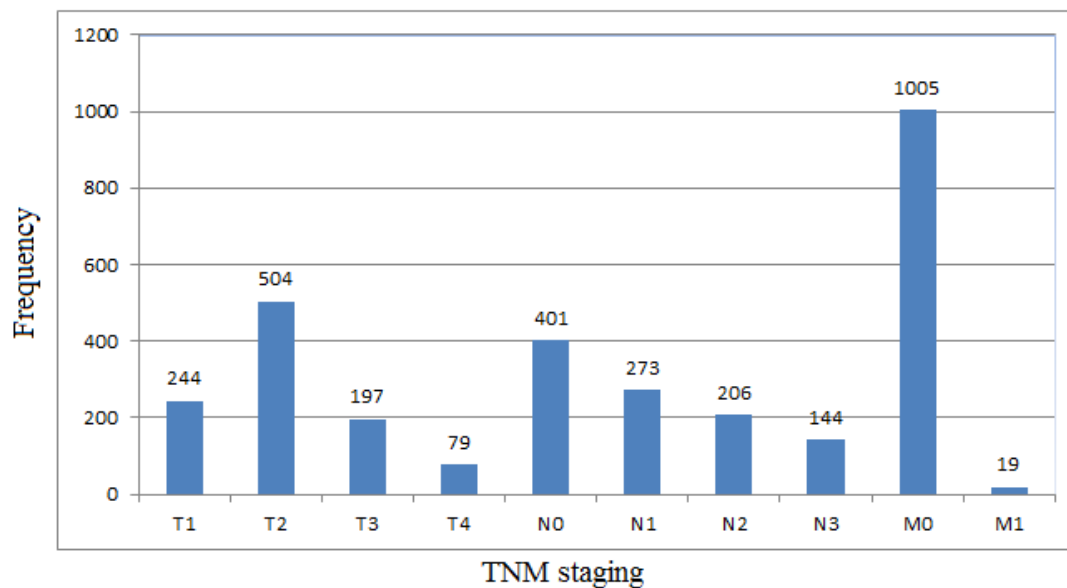


Figure 4. TNM Staging Frequencies

metastasis. Higher number of dissected lymph nodes (HR=0.9, p-value=0.01) and hormone therapy (HR=0.6, P-value=0.01) are protective against bone metastasis.

Discussion

In this retrospective study, we found a high rate of node positivity and locally advanced disease stage in patients with breast cancer treated in southern Iran. Higher node and disease stage, hormone receptor status, histologic subtypes, and adjuvant therapies independently have negative impact on disease-free and overall survival rates in these patients.

Breast cancer is one of the major health problems in developing countries with limited resources. In Iran, breast cancer imposes a heavy financial burden on patients and the insurance system (Farhood et al., 2018). Adjuvant treatments such as radiotherapy and systemic treatments include a significant portion of these costs. Patients with more advanced diseases incur a higher cost of treatment. Therefore, recognizing prognostic factors and early diagnosis of the disease can be very useful in saving patients' lives and reducing the cost of cancer treatment (Rezapour et al., 2021). Most major reports from Iran mainly investigated the incidence and prevalence of the disease and risk factors or clinical features of the patients and lack clinical information to fully evaluate the survival rate and prognostic factors; as well as, long-term follow-up of the patients with breast cancer (Shamshirian et al., 2020).

As far as we know, this is the second largest series with the longest follow-up period of the patients with breast cancer reported in southern Iran (Rezaianzadeh et al., 2009). In this study, the median age of the patients was 47 years old, which is about a decade younger than reports from developed countries. This finding and other clinical findings such as higher rate node positivity and locally advanced disease of this study is compatible with

other reported series from Iran (Ghasem Abedi et al., 2016; Foroozani et al., 2020).

In developing countries such as Iran in which there is no screening program for breast cancer detection, the presentation of the disease in advanced stages may be due to a delay in diagnosis (Dianatinasab et al., 2018). In a multi-center study by Foroozani et al, factors of delay in diagnosis and advanced stage at presentation were evaluated among Iranian patients with breast cancer. They found more than 3 months delay in diagnosis in one-third of patients. Older age, low family income, lack of health insurance, rural residency, never married, postmenopausal status, history of breast disease, unawareness of breast self-examination, asymptomatic tumors, obesity, and underlying comorbidities were associated factors with the delay in diagnosis (Foroozani et al., 2020).

In most studies, age is known as a prognostic factor. Young women tend to have higher rate of local recurrence and lower survival rate than older women (Bollet et al., 2007; He et al., 2017; Langman et al., 2021). In the present study, patients less than 40 years old had lower survival rates. This finding is compatible with the most reported series in the literature (Dai et al., 2019; Zhang et al., 2018). However, in contrary to our results, some reports found that patients less than 40 years old had a higher cure rate than older ones (Mojtaba Meshkat et al., 2020). In a recent study, Kadkhodaei et al reported treatment outcomes and prognostic factors among young patients with non-metastatic breast cancer in southern Iran. In the multivariate COX regression model, conserving breast surgery and higher disease stages remained independent prognostic factors for disease-free and overall survival. (Kadkhodaei et al., 2022).

In the current study, the histological type was recognized as the prognostic factor in both univariate and multivariate analysis. Histological typing is a known prognostic factor in breast cancer. College of American Pathologists has been considered histologic type as

Category I among all prognostic factors in breast cancer (Fitzgibbons et al., 2000). The extent of axillary lymph node involvement and disease stage are the most important and persistent prognostic variables in patients with breast cancer (Soerjomataram et al., 2008). The finding of the present study was consistent with most literature evidence and showed independent prognostic impact of the node and disease stage on DFS and OS in patients with breast cancer. In a similar study by Meshkat et al, found the number of involved lymph nodes and disease stage as independent prognostic factor in patients with breast cancer (Meshkat et al., 2020). In another study on 101 breast cancer patients, N-stage and perineural invasion were independent factors affecting disease free survival (Singh et al., 2022). In our study, higher number of dissected lymph nodes and less number of positive lymph nodes were independent risk factors for distant metastasis. In other studies factors such as histological subtype, negative hormone receptor, larger tumor size, older age and higher clinical stage mentioned as distant metastasis risk factors (Pulido et al., 2017; Slimane et al., 2004; Yao et al., 2019).

In addition, they found the overall 1, 5, 10, and 15-year survival rate were 95%, 75%, 60%, 47% respectively. Overall survival rates of the current study were consistent with study of Meshkat et al., (2020) and other reports from Iran (Ghasem Abedi et al., 2016; G. Abedi et al., 2016; Nafissi, 2008). Although there is a paucity regarding the state of DFS of breast cancer patients in Iran, DFS rates of the present study were in agreement with study of Mousavi et al they found 3- and 5-year DFS were 71.28 and 63.09 respectively (Mousavi et al., 2019).

In general, the cause of advanced stage presentation and poor survival of patients with breast cancer in our country is multifactorial and various factors such as socio-economic, cultural, nutrition, limited resource, and health behaviors determinants play an important contribution (Dianatinasab et al., 2018; Foroozani et al., 2020; Sobri et al., 2021).

Breast cancer decrease age-related life expectancy in our patients comparing to normal Iranian females with same age group (more dominant in younger cases). We followed our patients for 21 years but the expected life expectancy were far more than our follow up duration in younger age groups. Although none of our patients in younger age groups lived more than their expected life expectancy, significant number of them were alive at the end of study. On the other hand, more than half of the older patients had survival duration equal or more than their expected life expectancy. In conclusion, to determine the effect of breast cancer on life expectancy of younger patients longer follow up duration required.

Limitations of the study include the retrospective nature of the study, non-uniform pathologic reports of patients' medical records, the lack of data regarding some pathological features such as tumor grade, and the molecular status of the tumor, such as ER, PR and HER2.

Strengths of this study include large population sample size and long-term follow up, recognizing more evidence of prognostic factors, early diagnosis of the disease and reducing the cost of breast cancer treatment in southern

Iran.

Author Contribution Statement

All authors contributed equally in this study.

Acknowledgements

This study performed as the thesis of Ali Omidvari's MD-MPH degree at Shiraz University of Medical Sciences (SUMS). It was approved by Iranian National Ethics Committee in research (IR.SUMS.MED.REC.1401.108). We declare no conflict of interest. All of authors had active participation in data gathering, data analysis and manuscript revision. During this study we did not perform any additional paraclinic or treatment for the patients and minimal expenses were supported by research center of SUMS.

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