RESEARCH ARTICLE

Metastasis and its Related Factors in Female Breast Cancer Patients in Kerman, Iran

Behjat Kalantari Khandani[1], Leila Tavakkoli[2], Narges Khanjani[3]*

Abstract

Background: Metastasis is important in survival and the quality of life of female breast cancer patients. This study was run in order to investigate metastasis and its related factors in female breast cancer patients in Kerman province from 2005 to 2015. The aim of this study was to investigate the factors associated with secondary metastasis in female breast cancer patients in the largest province of Iran (Kerman). **Materials and Methods:** In this case-control study, medical records of women diagnosed with breast cancer between the years of 2005 to 2015 were studied. Among them, 200 breast cancer patients with secondary metastasis were randomly selected as cases and 400 patients without metastasis were selected as the control group. Backward logistic regression, chi-square test, t-test and Mann-Whitney-U test were performed for comparing the two groups in SPSS 22. **Results:** Disease stage at diagnosis was significantly associated with secondary metastasis (p<0.001). Female patients with stage III breast cancer at the time of diagnosis had a higher chance OR=9.11 (CI 95%=2.99-27.76) of metastasis than women with stage 0 and 1 at diagnosis. Also, patients from rural areas had a higher chance for metastasis OR=1.89 (CI 95%=1.04-3.41). Other factors such as age, tumor size, tumor grade at diagnosis, hormone receptor status of estrogen and progesterone and Her-2 showed no significant association with metastasis (p>0.05). **Conclusion:** Stage at diagnosis and the residential location of patients were the most important factors related to secondary metastasis. These results emphasize the importance of early diagnosis, adequate education and awareness for breast cancer screening.

Keywords: Metastasis- breast neoplasm- Kerman- Iran

Introduction

Breast cancer includes 25% of all new cancer cases and 15% of all cancer deaths globally and is the most common cancer among women in the world and East Mediterranean region (International-Agency-for-Research-on-Cancer, 2012, Parkin et al., 2005, World-Health-Organization, 2009). In 2012, GLOBOCAN published a report about the worldwide cancer statistics that showed breast cancer was the leading cause of death among women with cancer in not only developing, but also developed countries (Torre et al., 2015).

Breast cancer incidence is different from region to region. The highest rates of breast cancer have been reported from North America and the lowest rates from Africa and Asia (Porter, 2009). According to the World Health Organization report in 2014, 14.2% of 23,300 deaths among Iranian women were due to breast cancer (World-Health-Organization, 2014). Breast cancer is also the most common cancer among Iranian women (Harirchi et al., 2011) with an incidence rate of 23.65 cases per 100,000 and a death rate of 3.3 cases per 100,000 (Mousavi et al., 2009). Meanwhile, in Iran, the average

age of female breast cancer diagnosis is approximately 10-15 years lower than developed countries (Vostakolaei et al., 2012, Mousavi et al., 2007) and also most of them are diagnosed at advanced stages (Harirchi et al., 2011).

Depending on its extent of spread, breast cancer can be categorized as in situ carcinoma, invasive carcinoma and metastatic carcinoma which spreads from the breast to other parts of the body such as the bones, lung, liver and brain (Haghighat and Yavari, 2014-2015). According to research done up to now, one of the factors related to survival in breast cancer patients may be metastasis (Faradmal et al., 2014, Atashgar et al., 2016).

Research has also showed that the number of involved lymph nodes, number of pregnancies (Mokarian et al., 2012), socioeconomic status, age (Lord et al., 2012), tumor size, hormone receptor status (Hosseini et al., 2012) and the status of Her2 (Gohari et al., 2013) were related to secondary tumors or metastasis in breast cancer patients.

Considering the importance of breast cancer and lack of studies that have specifically examined the factors related to secondary metastasis in Iran, the aim of this study was to investigate the clinicopathologic factors associated with secondary metastasis in female breast

[1]*Department of Internal Medicine, School of Medicine,* [2]*Department of Epidemiology and Biostatistics, School of Public Health,* [3]*Neurology Research Center, Kerman University of Medical Sciences, Kerman, Iran. *For Correspondence: n_khanjani@kmu.ac.ir*

cancer patients in Kerman province, Iran.

Materials and Methods

This was a case-control study. Data were inquired from the cancer registry of Kerman University of Medical Sciences from 2005 to 2015. The Kerman cancer registry records age, diagnosis date, pathological type, grade and sometimes stage at diagnosis and also residential addresses of cancer cases diagnosed in the province. The Medical records at the Department of Oncology were used for completing the cancer registry data.

Study population and Data collection

Two hundred female breast cancer patients with secondary metastasis were randomly selected from the available files as cases and 400 patients without metastasis were selected as the control group.

Data extracted from the medical records included metastasis status, age at diagnosis, tumor size, pathological type, type of treatment, Estrogen and Progesterone hormone receptors status (ER and PR), Human epidermal growth factor receptor 2 (Her2) status and also grade and stage at diagnosis. Grade shows how different the cancer cells look from normal and healthy breast cells (BreastCancer.org, 2017a). Stage is based on characteristics including, tumor size, whether cancer is invasive or non-invasive, whether lymph nodes are involved or not and whether the cancer has spread to other parts of the body (metastases) (BreastCancer.org, 2017b).

Statistical analysis

Descriptive statistics, backward logistic regression, chi-square, t-test and Mann-Whitney-U were performed in SPSS 22.

Results

Demographic characteristics of participants

All patients were female and the mean age of breast cancer patients with secondary metastasis was 47.88±11.23 and the mean age of patient without secondary metastasis was 47.89±11.34 years and the difference was not significant (p=0.958). Among all patients, the youngest was 22 and the oldest was 84 and more than half were from urban areas. Estrogen and Progesterone receptor status and Her2 status were positive in 39.3%, 37.8 % and 52.6% of the patients with metastasis, respectively (Table 1).

The mean size of tumor at diagnosis in patients with metastasis was 4.09±1.95 cm and in the patients without metastasis was 3.44±1.83 cm, respectively (p=0.945). The most common pathological type of tumor was invasive ductal (in more than 80% of all patients) and also, the most common type of treatment was adjuvant (in more than 70% of all patients). The stage and grade at diagnosis in 41.3% and 21.9% of patients with metastasis were III and II, respectively and also the most common metastasis location was the bones (Table 1).

Univariate and Multivariate results of Logistic Regression

The results showed that, stage at diagnosis was

Table 1. The Frequency of Different Variables in the Breast Cancer Patients

Variable		Female breast cancer patients with secondary metastasis	Female breast cancer patients without secondary metastasis	P-value of Chi-square
		Frequency (%)	Frequency (%)	test
Hormone receptors status				
ER	Positive	79 (39.3)	244 (61)	
	Negative	92 (45.9)	152 (38)	0.082
	Unknown	29 (14.8)	4 (1)	
PR	Positive	78 (37.8)	236 (59)	
	Negative	75 (39.9)	158 (39.5)	0.057
	Unknown	45 (22.9)	6 (1.5)	
Her2 status	Positive	105 (52.6)	235 (58/8)	
	Negative	56 (27.6)	152 (38)	0.323
	Unknown	40 (19.9)	13 (3.3)	
Pathologic type of tumor				
Invasive ductal		159 (81.1)	347 (86/8)	
Invasive lobular		14 (1.7)	16 (4)	
Insitu ductal		1 (0.5)	11 (2.8)	
Insitu lobular		0 (0)	1 (0.3)	
Invasive ductal-lobular		2 (0.8)	-0.8	0.055
Medullary		2 (0.8)	8 (2)	
Carcinoma		2 (0.8)	0 (0)	
Unknown		20 (8.8)	13 (305)	
Stage at diagnosis				
0		0 (0)	9 (2.3)	
I		5 (2.6)	53 (13.3)	<0.001
II		35.2 (69)	200 (50)	
III		81 (41.3)	87 (21.8)	
Unknown		41 (20.9)	51 (12.8)	
Grade at diagnosis				
I		20 (10.2)	59 (14.8)	
II		39.8 (78)	207 (51.8)	0.335
III		43 (21.9)	85 (21.3)	
Unknown		55 (28.1)	49 (12.3)	
Location				
Urban areas		101 (51.5)	230 (57.5)	
Rural areas		39 (19.9)	61 (15.3)	0.115
Unknown		56 (28.6)	109 (27.3)	
Metastasis location*				
Lung		56 (28.8)	---	
Liver		50 (25.5)	---	
Brain		12 (6.1)	---	
Bones		106 (54.1)	---	---
Neck lymph-node		7 (4.6)	---	
The opposite breast		3 (0.5)	---	
Skin and other areas		3 (1.2)	---	
Total		200 (100)	400 (100)	---

* Some patients had metastasis to more than one area

Table 2. Factors Related to Secondary Metastasis in Female Breast Cancer Patients

Variable	Odds Ratio (Crude)	CI (Crude)	P-value (Crude)	Odds Ratio (Adjusted)	CI (Adjusted)	P-value (Adjusted)
ER						
Positive	1.00	---	---	---	---	---
Negative	0.62	0.27-1.43	0.264	---	---	---
PR						
Positive	1.00	---	---	---	---	---
Negative	1.45	0.61-3.31	0.412	---	---	---
Her2						
Positive	1	---	---	---	---	---
Negative	1.27	0.66-2.42	0.469	---	---	---
Tumor size	0.88	0.73-1.07	0.198	---	---	---
Stage at diagnosis						
0 and I	1.00	---	---	---	---	---
II	2.06	0.63-6.79	0.232	2.82	0.94-8.45	0.064
III	7.76	2.10-28.72	0.002	9.11	2.99-27.76	<0.001
Grade at diagnosis						
I	1.00	---	---	---	---	---
II	1.45	057-3.71	0.436	0.86	0.42-1.78	0.693
III	2.29	0.80-6.52	0.121	1.58	0.71-3.54	0.261
Type of treatment						
Adjuvant	1.00	---	---			
New-adjuvant	0.64	0.12-3.28	0.592	---	---	---
Location						
Urban areas	1.00	---	---	1.00	---	---
Rural areas	1.82	0.86-3.87	0.118	1.89	1.05-3.41	0.035

significantly associated with secondary metastasis (p<0.001). Patients with stage III at diagnosis had a higher chance OR=9.11 (CI 95%=2.99-27.76) of metastasis in comparison with patients whose stage at diagnosis was 0 and I. Also, patients from rural areas showed a higher chance of metastasis OR=1.89 (CI 95%=1.04-3.41) in the adjusted model (Table 2).

Discussion

This study was one of the first studies to investigate metastasis and its associated factors in female breast cancer patients in the south east of Iran. According to the results of this study, stage at diagnosis was significantly associated with secondary metastasis and patients with stage III, at diagnosis had a higher chance of metastasis.

In Australia, Lord et al's population based cohort showed that in female invasive breast cancer patients, those with no lymph node involvement had a lower chance for secondary tumors or metastasis (Lord et al., 2012). Hosseini et al in Isfahan showed that, the number of involved axillary lymph nodes had a direct correlation with the risk of metastasis (Hosseini et al., 2012). Also, Mokarian et al in Isfahan showed that in patients with more involved lymph nodes, metastasis was more likely (Mokarian et al., 2012).

Yaghmaei et al., (2008) study showed that survival in breast cancer patients with stage I and II was similar, but survival in patients with stage III and IIII was low. This shows the importance of diagnosing breast cancer patients at an early stage. Studies in Iran have shown that because of lack of knowledge many breast cancer patients do not visit physicians early (Rastad et al., 2012, Khanjani et al., 2012). Therefore, adequate education and awareness seems necessary to encourage women to see their physicians on time; and consequently, appropriate actions help to improve the prognosis and quality of life in breast cancer patients (Haghighat, 2013, Safaee et al., 2008, Fouladi et al., 2011).

In the present study, one of the factors related to metastasis was patients residential location and patients from rural areas had a higher chance to develop metastasis in comparison with patients who were from urban areas. As noted before, low literacy and knowledge, late referral (Rastad et al., 2012, Khanjani et al., 2012), and also lack of access to proper diagnosis and treatment facilities can be the cause of this association. Lord et al showed that, one of the determining factors in metastasis was living in low socioeconomic areas (Lord et al., 2012). Also, bad follow up and non-compliance in rural women, may also be related to secondary metastasis. Further studies are necessary to find out the reasons for more metastasis in rural women.

In the present study, age did not show a significant

association with metastasis. In MoghadamiFard et al`s and Gohari et al`s studies in Tehran age was not related to metastasis in breast cancer patients (Gohari et al., 2013, Moghadami et al., 2011) either, but in the Lord et al`s study from Australia women younger than 50 years were at a higher risk of metastasis (Lord et al., 2012); and in Germany, Hietz et al showed that younger breast cancer patients have an higher risk of developing cerebral metastasis (Heitz et al., 2011). In the present study, the non-existence of a relation between age at diagnosis and secondary metastasis may be due to the large number of patients aged under 50 years at diagnosis.

The most common place of metastasis in the present study was the bones and this was similar to Coleman and Rubens; and also Kennecke et al`s studies in Canada and also Ghavam Nasiri et al`s study in Mashhad, Iran (Coleman and Rubens, 1987, Kennecke et al., 2010, Ghavam Nasiri et al., 2014), but different from Gohari et al`s study from Tehran, Iran that showed the most common organs involved in metastasis were the liver and brain (Gohari et al., 2013).

In the present study, grade at diagnosis and the status of Her2 did not show a significant association with metastasis and these results are similar to the results of MoghadamiFard et al`s study from Tehran that showed Her2 was not related to metastasis in breast cancer patients (Moghadami et al., 2011), but in contrary to the results of Gohari et al`s study in Tehran that showed Her2 and grade were prognostic factors for breast cancer metastasis (Gohari et al., 2013). Sirati and Yadegari in Tehran, Iran investigated the association of Her-2 and axillary lymph node involvement in breast cancer patients and noted that, Her2 positivity is highly related to the invasiveness of breast cancer and its metastasis to lymph nodes (Sirati and Yadegari, 2004).

Although the average size of tumors in patients with secondary metastasis was more than patients without metastasis in our study, but logistic regression did not show a significant association between tumor size and metastasis and this was in contrary with Hoseini el al., (2012) study in Isfahan that showed patients with a tumor size more than 2 cm had a higher chance of metastasis. In Japan, Koisumi et al., (2010) showed that one of the important factors for bone metastasis in breast cancer patients was tumor size. In the present study, tumor size in both groups was between 2 to 5 centimeters and there was no significant difference.

Also, in this study ER and PR receptors did not have any significant association with secondary metastasis and these results are in agreement with MoghadamiFard et al., (2011) and Gohari et al., (2013) studies done in Tehran, Iran.

A limitation of this study was the missing data that some was not fulfilled even by checking the medical records. Also, the authors only enrolled patients who were listed at the Kerman Cancer Registry and unlisted patients did not have a chance to enter the study.

In conclusion, stage at diagnosis and residential location of patients were the most important factors related to secondary metastasis in breast cancer patients. These results emphasize the importance of early diagnosis, adequate education and awareness for women to take periodical screening. Also, more attention should be paid to breast cancer screening in rural populations.

Acknowledgments

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