Original Article

Multicentricity in Different Molecular Subtypes of Breast Cancer: A Cross-sectional Study in Isfahan

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Abstract

Background: Breast cancer is the most common cancer leading to death in women. Women with multicentric breast cancer were reported more likely to have poor prognosis. Here, we decided to study and compare the frequency distribution of multicentricity in different subtypes of breast cancer.

Materials and Methods: This is a cross-sectional study that was performed in 2019–20 on medical records and breast pathology reports of 250 patients who undergone mastectomy due to breast cancer. Demographic data of all patients including age, along with other medical data such as menstruation condition, breast cancer grade, multicentricity status, stage, and expression of estrogen receptor (ER), progesterone (PR), and human epidermal growth factor receptor 2 (HER2) receptors were collected from medical records. Samples were divided into four subtypes of Luminal B, Luminal A, HER2 expressing, and basal-like.

Results: The mean age of patients was 50.21 ± 11.15 years. Ninety-five patients (38%) had multicentricity and HER2 expressing (48.5%) and Luminal A (41.4%) were most common in patients with multicentricity. In addition, basal-like group presented with least multicentricity (13.5%) among the subtypes (P = 0.008). We also showed significant increased chances of multicentricity in Luminal B (odds ratio [OR] = 3.782) (P = 0.033), Luminal A (OR = 5.164) (P = 0.002), and HER2-expressing group (OR = 5.393) (P = 0.011).

Conclusions: Taken together, we showed significantly increased chances of multicentricity in patients with HER2-expression, Luminal A, and Luminal B groups compared to basal-like group or triple negative. These results were in line with most previous studies; however, we showed higher rates of multicentricity among our population compared to some previous reports.

Keywords: Breast neoplasms, immunohistochemistry, mastectomy, multicentricity

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Introduction

Breast cancer is the most common malignancy and the most common cancer leading to death in women. In the United States, 100,000 new cases of the disease are diagnosed each year, and about 30,000 patients die from this cancer.[1] The prevalence of breast cancer accounts for about one-third of all female cancers and is the second most common cancer after lung cancer and the most common cause of cancer death among women. In Iran, breast cancer accounts for 32% of all female cancers. The annual incidence of this cancer in women is 10,000 and the age of breast cancer is 10–12 years less than in developed countries.[2,3]

The average age of the disease in Iran is between 45 and 55 years, while in western countries, it is between 50 and 60 years. Many factors such as geography, family history, menstrual status and pregnancy, proliferative breast lesions, and history of radiation have been considered as risk factors for breast cancer.[4,5] One of the factors that has been

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discussed in the prognosis and treatment of breast cancer is the status of hormones and hormone receptors. About 5%–10% of breast cancer cases are inherited, including the BRCA1 and BRCA2 mutations, which are the most common known genetic factors involved in this cancer.[6] Being a woman is the most important risk factor for breast cancer. Although men are vulnerable to this type of cancer, women are 100 times more likely to get the disease. Breast cancer can manifest as a lump in the breast tissue, breast deformity, dimples, discharge from the nipple, or scaling of the breast skin.[7] In a patient whose disease has spread to other parts of the body, these symptoms can include bone pain, swollen lymph nodes, and shortness of breath. Currently, sampling of suspicious breast masses is mostly done by two methods: core-needle biopsy and surgical excision. Common treatment options include surgery, radiation therapy, chemotherapy, and molecular therapies.[8,9]

One of the easy and economical methods for classifying breast cancer that is used in most medical centers is the use of immunohistochemical (IHC) staining. In this method, cancer cells are examined for the expression of four molecules: human epidermal growth factor receptor 2 (HER2), estrogen receptor (ER) and progesterone (PR) receptors, and ki-67 protein. Based on these expressions, breast tumors can be divided into four groups: Luminal B, Luminal A, HER2 expressing, and basal like.[10,11] Breast cancer specimens are also examined for various features in pathology, such as multicentricity, perineural invasion, vascular invasion, and nipple and skin invasion.

Multicentricity means the presence of two or more separate invasive tumors in different quadrants of the breast. Women with multicentric breast cancer were reported to be more likely to develop lymph node metastasis and to have a worse prognosis and survival.[12,13] However, these relations are not consistent, and therefore, multicentricity is still not used as a factor in determining the stage or prognosis of the disease. Examining and comparing the frequency of multicentricity in four breast cancer subtypes based on IHC staining, considering the stage and grade of the tumors, can lead to a better understanding of the behavior and nature of these subtypes.[14,15]

Considering that there are few studies conducted in Iran, and to our knowledge, no studies in Isfahan, we decided to study and compare the frequency distribution of multicentricity in different subtypes of breast cancer based on IHC staining. It will help us better understand the nature of this cancer among the females in our population.

Materials and Methods

This is a cross-sectional study that was performed in 2019–20 in Al-Zahra Hospital affiliated to Isfahan University of Medical Science. The current study was conducted on medical records and breast pathology reports of 250 patients who undergone mastectomy due to breast cancer in our medical center in 2013–2018. The study protocol was approved by the Research Committee of Isfahan University of Medical Sciences and the Ethics Committee has confirmed it (REC number: IR.MUI.MED.REC.1398.254).

The inclusion criteria were female patients, diagnosis of breast cancer by expert oncologists and surgeons, undergoing mastectomy in 2013–2018, and complete medical records. The exclusion criteria were incomplete data of the patients' medical records and neoadjuvant chemotherapy before surgery. Due to the fact that all samples were eligible for inclusion criteria, the sample size was not calculated, and all samples within the study period were included by the census.

Demographic data of all patients including age, along with other medical data such as menstruation condition, breast cancer grade (based on Nottingham modification of Scarff–Bloom–Richardson grading system), multicentricity status, stage (determined by the American Joint Committee on Cancer (AJCC) and in the TNM classification), and expression of ER, PR and HER2, and ki-67 were collected from medical records.

Samples were divided into four groups based on their molecular expressions:

1. Luminal B (HR+/HER + and ki-67 expression >14%)
2. Luminal A (HR+/HER − and ki-67 expression <14%)
3. HER2 expressing (HR−/HER+)
4. Basal like (HR−/HER−).

HR + was considered as ER + and/or PR + and HR − was considered as ER − and PR−. Hormone receptors (ER and PR) were considered positive if they were reported more than 1% expressed on the surface of tumor cells. In addition, the status of multicentricity was obtained from pathology reports and preoperative imaging studies.

To analyze the data, demographic and baseline clinical characteristics of patients were described using the descriptive statistics including Mean and Standard deviation for quantitative variables and Number (N) and percentage for qualitative variables. Chi-square and logistic regression tests were used to measure relations. All analyses were performed using SPSS software version 18 (SW Statistics for Windows, Chicago, Illinois, USA: SPSS, Inc.) and the significance level in all tests was considered to be 0.05. In this study, age, stage, and grade were considered as possible confounding variables that were adjusted by logistic regression test.

Results

A total number of 250 pathology reports were evaluated in the present study. The primary analysis of baseline characteristics of patients showed that the mean age of patients was 50.21 ± 11.15 years with a range from 21 to 83 years, and the mean tumor size was 2.32 ± 1.02 mm. Based on our results, 111 patients (44.4%) were menopause and partial mastectomy was the most common surgical procedure among the study population (201 patients [80.4%]). The frequency of the involved side was almost the same in the right or left breasts,

and invasive ductal carcinoma was the most common tumor type among patients (222 patients [88.8%]).

Furthermore, based on our results, grade 2 tumors (68.4%), and stage 2A (37.2%) were most common and 95 patients (38%) had multicentricity.

Moreover, 145 patients (58%) were included in Luminal A group, 37 patients (14.8%) in basal-like group, 35 patients (14%) in Luminal B group, and 33 patients (13.2%) in HER2-expressing group. These data are summarized in Table 1.

Furthermore, we compared tumor grade, stage, and tumor subtypes among patients with or without multicentricity. These data indicated significant differences between patients regarding tumor stage and tumor subtypes. Based on our results, stage 2A was the most prevalent tumor stage in both groups of patients (31.6% versus 40.6%). Furthermore, we showed that among patients with 3B and 3C stage, multicentricity was more prevalent ($P < 0.001$ for stage).

We showed that HER2 expressing (48.5%) and Luminal A (41.4%) were most common in patients with multicentricity. In addition, basal-like group presented with least multicentricity (13.5%) among the subtypes ($P = 0.008$) [Table 2].

We also assessed the association between the IHC subtypes and multicentricity. Our data showed significant increased chances for Luminal B (odds ratio [OR] = 4.267) ($P = 0.014$), Luminal A (OR = 4.518) ($P = 0.003$), and HER2-expressing group (OR = 6.024) ($P = 0.002$) based on crude model and compared to basal-like group. After adjusting the results by stage, grade, menopause status, and age, we showed significant increased chances of multicentricity in Luminal B (OR = 3.782) ($P = 0.033$), Luminal A (OR = 5.164) ($P = 0.002$), and HER2-expressing group (OR = 5.393) ($P = 0.011$). These data are indicated in Table 3.

Table 1: Characteristics of the 250 study subjects

Variables	Mean±SD/*n* (%)
Age (years)	50.21 (11.15)
Tumor size (cm)	2.32 (1.02)
Menopause	
Negative	139 (55.6)
Positive	111 (44.4)
Surgery type	
Partial mastectomy	201 (80.4)
Complete mastectomy	44 (17.6)
Modified radical mastectomy	3 (1.2)
Breast-conserving surgery	1 (0.4)
Skin-sparing mastectomy	1 (0.4)
Breast side	
Right	123 (49.2)
Left	126 (50.4)
Both	1 (0.4)
Tumor cell types	
Invasive ductal carcinoma	222 (88.8)
DCIS	14 (5.6)
Invasive lobular carcinoma	10 (4.0)
Invasive mucinous carcinoma	1 (0.4)
Metaplastic carcinoma	1 (0.4)
Medullary carcinoma	1 (0.4)
Colloid carcinoma	1 (0.4)
Grade	
1	9 (3.6)
2	171 (68.4)
3	70 (28.0)
Stage	
0	14 (5.6)
1A	63 (25.2)
2A	93 (37.2)
2B	46 (18.4)
3A	10 (4.0)
3B	10 (4.0)
3C	14 (5.6)
Multicentricity	
No	155 (62)
Yes	95 (38)
Group	
Luminal B (HR +/HER +)	35 (14.0)
Luminal A (HR +/HER −)	145 (58.0)
HER2 expressing (HR −/HER +)	33 (13.2)
Basal like (HR −/HER −)	37 (14.8)

DCIS: Ductal carcinoma *in situ*, HER: Human epidermal growth factor receptor, SD: Standard deviation, HR: Hormone receptors

Discussion

Here in the present study, we evaluated the pathologic reports of 250 patients with breast cancer and showed that invasive ductal carcinoma and grade 2 and stage 2A tumors were the most common histological tumor type, grade, and stage, respectively. We also showed that 95 patients had multicentricity. HER2 expressing and Luminal A were the most common subtypes in patients with multicentricity and basal-like group presented with least multicentricity among the subtypes. Our data also showed significantly increased chances for multicentricity in Luminal B, Luminal A, and HER2-expressing subtypes compared to basal-like group.

Previous studies have also evaluated different IHC subtypes and their correlations with multicentricity in breast cancer. As mentioned, the main point of the current study was increased chances of multicentricity in Luminal B, Luminal A, and HER2-expressing subtypes. It has been described that various subtypes of breast cancer could have different clinical outcomes, and therefore, recognizing the invasive types and groups of tumors based on pathological and IHC studies has high importance. Based on the evidence, evaluation of ER, PR, and HER-2 receptors could be more practical and cost-effective than DNA assessments of tumors.[16] Goldhirsch *et al*. also declared that distinguishing different tumor subtypes including Luminal A and Luminal B could be performed by IHC and might predict the risks of multicentricity.[17]

A study was performed by Chuthapisith *et al*., in 2012, on pathologic reports of 321 women with breast cancer. It was indicated that invasive ductal carcinoma was the most common tumor type and HER2-expressing group was related with a higher chance of multicentricity.[18] Another study by Wiechmann *et al*., in 2009, investigated the features of breast cancer differ by molecular subtypes. It was shown that HER-2 (Luminal B, HER-2) subtypes were significantly more likely to manifest multifocality.[19] They also reported greater risks for having metastatic lymph nodes and multicentricity for tumors with HER-2-overexpression. Our findings were in line with the results of the mentioned studies.

In 2016, a study was conducted by Vasconcelos *et al*., in Germany, on 2984 breast tumors. They evaluated the risks of multicentricity and invasion in different subtypes of tumors and reported that Luminal B HER2-neu positive and nonluminal HER2-neu positive basal-like tumors were significantly correlated with increased risks for multicentricity.[20] Our data are consistent with these findings emphasizing the importance of Luminal B HER2-neu tumors. Prado-Vázquez *et al*. emphasized on the clinical importance of these classifications and showed that triple-negative breast cancer classification or basal-like group has the lowest chance of multicentricity.[21]

It has been documented that IHC staining for breast cancer lesions could be a useful technique in determining the possibility of multicentricity and invasive behavior of the tumor. Based on our results, those tumors with HR−/HER+ that were known as HER2 expressing had higher chances of multicentricity compared to triple-negative tumors. Luminal A and Luminal B had also higher chances afterward. These data were in line with the findings of previous studies. Swain *et al*. also reported higher chances of multicentricity for tumors with HER2-expressing classification.[22] The same results were also supported by Huober *et al*. and Xu *et al*.[23,24] Researchers believe that such classifications could indeed have high clinical values in determining the treatment strategies.

To the best of our knowledge, no previous studies have compared IHC characteristics of breast tumors in Isfahan city, and here, we reported higher rates of multicentricity compared to previous studies[20] that could also be due to differences in both number and characteristics of the study population. As a result, we believe that further studies on larger samples seem appropriate and necessary. Furthermore, we recommend similar studies on populations in other provinces in the country.

Table 2: Association between the immunohistochemical subtypes, grade, and stage with multicentricity

Variables	Multicentricity		*P*
	Yes (*n*=95)	No (*n*=155)	
Grade			
1	2 (22.2)	7 (77.8)	0.130
2	72 (41.2)	99 (57.9)	
3	21 (30)	49 (70)	
Stage			
0	12 (85.7)	2 (14.3)	<0.001
1A	19 (30.2)	44 (69.8)	
2A	30 (32.3)	63 (67.7)	
2B	18 (39.1)	28 (60.9)	
3A	1 (10)	9 (90)	
3B	6 (60)	4 (40)	
3C	9 (64.3)	5 (35.7)	
Group			
Luminal B (HR +/HER +)	14 (40)	21 (60)	0.008
Luminal A (HR +/HER −)	60 (41.4)	85 (58.6)	
HER2 expressing (HR −/HER +)	16 (48.5)	17 (51.5)	
Basal like (HR −/HER −)	5 (13.5)	32 (86.5)	

HER: Human epidermal growth factor receptor, HR: Hormone receptors

Conclusions

Taken together, we showed that Luminal A and HER2 expressing were the most common subtypes in patients with multicentricity and basal-like group presented with least multicentricity among the subtypes. Based on our results, we observed significantly increased chances of multicentricity in patients with HER2-expression, Luminal A, and Luminal B groups compared to basal-like group or triple negative. These results were in line with most previous studies; however, we showed higher rates of multicentricity among our population compared to some previous reports.

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Conflicts of interest

There are no conflicts of interest.

Table 3: Association between the immunohistochemical subtypes and multicentricity using logistic regression

Group (reference: Basal like (HR−/HER−)	Crude model			Adjusted model (adjusted by stage and age group)		
	OR	CI (OR)	*P*	OR	CI (OR)	*P*
Luminal B (HR +/HER +)	4.267	1.33-13.61	0.014	3.782	1.11-12.85	0.033
Luminal A (HR +/HER −)	4.518	1.66-12.26	0.003	5.164	1.79-14.89	0.002
HER2 expressing (HR −/HER +)	6.024	1.88-19.28	0.002	5.393	1.46-19.92	0.011

HER2: Human epidermal growth factor receptor 2, OR: Odds ratio, CI: Confidence interval, HR: Hormone receptors

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