Risk Factors, Clinical Features and Treatment Outcomes of Male Breast Cancer in Saudi Arabia: A Single Center Study

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Abstract

The aim of this study was to determine the risk factors, clinical features and treatment outcomes of Male Breast Cancer (MBC) patients in Saudi Arabia. This retrospective-cohort study was conducted in Princess Nora Oncology Center at King Abdulaziz Medical City in Jeddah, Saudi Arabia. By using consecutive sampling, all male patients who were diagnosed with breast cancer based on the pathology results that were collected from the medical records from January 1998 to December 2017 and treated in Princess Nora Oncology Center at King Abdulaziz Medical City, Jeddah, Saudi Arabia were included in this study. Excel was used to encode all the patients' data, while SPSS was used for the analysis. A descriptive statistic was used to find the minimum, maximum, and mean of age at the time of diagnosis. On the other hand, frequencies and percentages were utilized to summarize all other clinical features of the patients including the pathological type, stage at time of diagnosis, metastasis, risk factors, performance status, treatments and relapse. The mean age of all the 15 patients was 58 +/- 16.5 SD at the time of diagnosis, whereas the maximum was 91 and the minimum was 36. The most predominant type of male breast cancer was Invasive Ductal Carcinoma IDC, which affected 14 patients out of 15 (93.3%).

Key words: Male breast cancer; Ductal carcinoma; Clinical features; Risk Factors; Treatment.

Introduction

Breast cancer in men is a very rare disease, accounting for less than 1% of all cases of breast cancer and less than 1% of all cancers in men(1). Presentation includes palpable breast mass, which may be associated with nipple retraction or overlying skin changes and few cases have the initial presentation as abscess(2,3). Although breast cancer occurs predominantly in females and shares many similarities with male breast cancer, there are also some important differences(4). The etiology and pathogenesis of this disease have been linked in multiple factors. Of all the causes involved, BRCA2 mutations is found to be a related factor that clearly increases the chance of men to be affected with breast cancer(5). Apart from this factor, Klinefelter's syndrome, (6) life style and environmental factors including radiation and heat exposure, smoking, alcohol consumption, obesity , and the lack of physical activity, (5,6) and hepatitis (7,8) were also reported.

There are few cases of breast cancer among men that have been reported in the literature, however, the mortality rate is increasing worldwide. This could be due to the fact that men do not typically undergo routine clinical or self-evaluations for breast changes unlike females who are constantly advised to perform an early check-up to recognize the early signs of breast cancer and therefore perform prompt intervention when necessary(2). Particularly the disease is usually discovered in its late stages, which lowers the patients' survival rate. Although breast cancer treatment has improved significantly over time, the exact utility in adaption of this guideline in the management of breast cancer among men is still unknown.

The National Comprehensive Cancer Network (NCCN) guideline is one of the most established guidelines in the management of Female Breast Cancer FBM and is also used to treat male breast cancer.(9). The diagnosis of male breast cancer depends on several procedures and modalities besides the physical examination. Therefore, a combination of various diagnostic tests is essential for the diagnosis, grading, and staging of male breast cancer. The initial diagnostic tool is mammography, which is used to measure the symptoms of male breast cancer(5). However, to have an accurate result of the grading and the specific type of male breast cancer, a biopsy is the gold standard(10). On the other hand, PET/CT F-18 FDG is an excellent imaging procedure that determines the stage and the effectiveness of a therapy of breast cancer in males since it has a 100% sensitivity and an 89% accuracy for the detection of metastasis(11). Additionally, it is highly recommended to have BRCA genetic testing, especially for those individuals who have relatives with the history of breast cancer(5).

Treatment for male breast cancer varies from single or combination modalities based on many criteria including the type and the stage of the cancer. A mastectomy was considered the standard treatment years ago, but lumpectomy has raised in significance since it has shown 82.9% ten-year breast cancer survival compared to mastectomy that had only 77.3%(12). In order to avert the regrowth of cancer, Post-Mastectomy Radiation Therapy PMRT is highly considered to improve the overall survival rate(13). A hormonal therapy such as tamoxifen is very effective in patients with positive estrogen receptors(5). Moreover, chemotherapy is a systematic therapy that is suitable especially for patients with advanced stages and metastasis(5). Besides chemotherapy, there is also systematic targeted therapy including anti-HER and CK4,6 inhibitors in adjuvant and metastatic settings.

In this study, we investigated the risk factors, clinical characteristics and treatment outcomes of breast cancer among male Saudi patients, which may provide evidence that will help to improve the patient's prognosis and selection of proper treatment. Moreover, we tested for the association between several clinical and treatment factors to treatment outcomes for breast cancer among men. Finally, we identified the overall survival rate of male breast cancer patients in Saudi Arabia.

Methods

Study Design and area and settings

This retrospective-cohort study was conducted in Princess Nora Oncology Center at King Abdulaziz Medical City in Jeddah, Saudi Arabia. All male patients who were diagnosed with breast cancer based on the pathology results that were collected from the medical records of January 1998 to December 2017 and treated in Princess Nora Oncology Center at King Abdulaziz Medical City, Jeddah, Saudi Arabia were included in the study.

Identification of study participants

The sample size was calculated by using the Raosoft software from the website www.raosoft.com/samplesize.html. The total number of male breast cancer patients from January 1998 to December 2017 was 15. The required sample size was estimated at the 95 percent confidence level with an estimated 0.7% (14) prevalence of male breast cancer patients and margin of error of +/- 5%. The required minimum sample size was determined to be 10. As the sample size was small, we included all the 15 patients in our study during the above mentioned period. The selection of the sample was through consecutive sampling which involved recruiting all male patients diagnosed with breast cancer. Consecutive samples were collected retrospectively based on the medical records from January 1998 to December 2017.

Data collection process

Patients' data with the diagnoses of male breast cancer were collected form the database of the pathology lab in Princess Nora oncology center. All data dated before 2012 were verified with the data provided by the medical records, while data dated 2012 and later were verified with the institutional patient's database (Best Care) to ensure the accuracy of the data. Information was then collected into a hard copy data collection sheet. Required information included patient's date of birth, date of diagnosis, type of breast cancer, treatment provided, clinical features

including stage, pathology results, serology results, and laboratory workup and current status of the patient. Data were then transferred into an Excel sheet and all hard copies were safely discarded. All the three investigators were involved in collecting the data in both hard copy and soft copy. Anonymity and confidentiality of any information or data pertaining to the patients was assured by shredding all hard copy data and deletion of all soft copies that were used.

Data analysis

Excel was used to encode all the patients' data. The encoded data was then transferred into SPSS for analysis. A descriptive statistic was used to find the minimum, maximum, and mean of age at the time of diagnosis. On the other hand, frequencies and percentages were utilized to summarize all other clinical features of the patients including the pathological type, stage at time of diagnosis, metastasis, risk factors, performance status, treatments, and relapse.

Results

Here are the results of the clinical features of the patients. The mean age of 15 patients was 58 +/- 16.5 SD at the time of diagnosis, whereas the maximum was 91 and the minimum was 36. The most predominant type of male breast cancer was invasive ductal carcinoma, which affected 14 patients out of 15 (93.3%). However, one patient had an intraductal papilloma (6.7%). 40% of the patients presented with metastasis (6/15), while 33.3% had a locally advanced stage of the disease (5/15) and 26.6% had an early stage of the disease (4/15). Out of the six patients who presented with a metastatic disease, three of these patients had multiple metastasis in different organs including bone, lungs, liver, axillary lymph nodes. One patient had metastasised into the liver and left axillary lymph node, while another patient had metastasised in both bone and lungs. The last one out of the three 'multi-mets' had the spread into the liver, bone, and lungs. However, for the single organ involvement, two patients had metastasised into the axillary lymph nodes only and one patient had bone metastasis only. Accordingly, here the results of metastasis are stated based on the organ of involvement. Two patients had liver metastasis (13.3%), two patients had lung metastasis (13.3%), three patients had bone metastasis (20%), and three patients had axillary lymph nodes metastasis (20%). The ECOG performance status was 0 zero in two patients, 1 in two patients, 2 in two patients, 3 in one patient, and the remaining 8 patients had unknown scores.

Several risk factors were observed. The genetic testing of positive receptors was 46.7% (7/15). A single patient had only an ER+, while 5 patients had both ER and PR positive. The last patient had a triple positive of ER, PR, and HER-2. Another risk factor is a testicular disease, specifically benign prostatic hyperplasia, which accounted for 13.3% (2/15). Other risk factors that were detected in the patients are smoking in 3 patients, and obesity in 2 patients. Additionally, 2 patients had a positive family history of female breast cancer. One patient had a sister diagnosed with breast cancer, while the other one had an aunt.

In this part of the paper, the treatment results will be discussed. The majority of the patients had undergone surgical removal of cancer, while only 2 out of 15 (13.3%) had no surgery. 80% of the patients had a modified radical mastectomy MRM (12/15). On the other hand, only a single patient had a breast conservative surgery BCS (6.7%). Another therapeutic modality that the patients received was chemotherapy. 26.7% of the patients were treated with adjuvant chemotherapy (4/15). On the other hand, 6.7% had received both adjuvant and neoadjuvant (1/5). Lastly, 1 patient had palliative chemotherapy (6.7%). The third method of treatment is radiation therapy. 26.7 % of the patients had curative radiation therapy (4/15), while 20% had palliative radiotherapy (3/15). The last therapeutic modality was hormonal therapy. 53.3% of the patients had been given tamoxifen (8/5). In contrast, 6.7% had received letrozole (1/15). Finally, only 1 patient had a combination of tamoxifen, letrozole, and megace accounting for 6.7%.

The last part of the results is the relapse of the cancer. Only 2 patients (13.3%) had a recurrent distant metastatic disease. Both of these patients were treated with radiation and hormonal therapies (13.3%), while only one of them had received chemotherapy at the time of relapse (6.7%). Unfortunately, 80% of the patients were lost to follow up. One case had died (6.7%) and 2 were known to be alive (13.3%).

Table 1: Age at diagnosis

Variables	N	Minimum	Maximum	Mean ± SD
Age at diagnosis	15	36	91	58.33 ± 16.513

Table 2: Clinical features of study participants

Clinical Features	Percentage % (n/N)
Cancer pathology	
Invasive ductal carcinoma	93.3 (14/15)
Others	6.7(1/15)
Stage of cancer	
Early	26.6 (4/15)
Locally Advanced	33.3 (5/15)
Metastatic	40 (6/15)
Metastasis	
Liver	13.3 (2/15)
Lung	13.3 (2/15)
Bone	20 (3/15)
Other metastasis	20 (3/15)
Multi-organ metastasis	
Liver + axillary lymph node	6.6(1/15)
Bone + lungs	6.6(1/15)
Bone + lung + liver	6.6(1/15)
ECOG	
ECOG 0	13.3 (2/15)
ECOG 1	13.3 (2/15)
ECOG 2	13.3 (2/15)
ECOG 3	6.7 (1/15)
N/A	53.3 (8/15)
Family history	
Positive (Yes)	13.3 (2/15)
Negative (No)	86.7 (13/15)

Table 3: Risk factors of study participants

Risk Factors	Percentage (n/N)
Genetic testing risk	
Positive (Yes)	46.7 (7/15)
Negative (No)	53.3 (8/15)
Out of +ve genetic test 7	
ER	14.3 (1/7)
ER + PR	71.4 (5/7)
ER + PR + HER-2	14.3 (1/7)
Testicular disease	
Positive (Yes)	13.3 (2/15)
Negative (No)	86.7 (13/15)
Other risks (smoking, obesity, family hx.)	
Positive (Yes)	26.7 (4/15)
Negative (No)	73.3 (11/15)

Table 4: Treatments of study participants

Treatments	Percentage (n/N)
Surgery	
None	13.3 (2/15)
MRM	80 (12/15)
BCS	6.7 (1/15)
Chemotherapy	
Neoadjuvant	60 (9/15)
Adjuvant	26.7 (4/15)
Palliative	6.7 (1/15)
Adjuvant & neoadjuvant	6.7 (1/15)
Radiation therapy	
None	53.3 (8/15)
Curative	26.7 (4/15)
Palliative	20 (3/15)
Hormonal therapy	
None	33.3 (5/15)
Tamoxifen	53 (5/15)
Letrozole	6.7 (1/15)
Tamoxifen & Lentozole & Megace	6.7 (1/15)

Table 5: Relapse of study participants

Relapse	Percentage (n/N)
Distant metastasis	
Positive (Yes)	86.7 (13/15)
Negative (No)	13.3 (2/15)
Treatment at relapse	
Chemotherapy	6.7 (1/15)
Hormonal therapy	13.3 (2/15)
Radiation therapy	13.3 (2/15)
Status of patient at last follow up	
Alive	13.3 (2/15)
Died	6.7 (1/15)
Loss of follow Up	80 (12/15)

Discussion

Based on the results of the study, the most prominent type of male breast cancer was ductal carcinoma, which accounted for a total of 93.3%. That finding was very similar to data from more than 2,000 male cancer patients in the Surveillance, Epidemiology, and End Results (SEER) cancer registry in which ductal carcinoma accounted for 93.7% out of all the other remaining types of breast cancer in the male (6). Other research that had been done at the Sheri-i-Kashmir Institute of Medical Sciences also had 93.7% of invasive ductal carcinoma as the most common type of male breast cancer (15). The mean age at diagnosis was 58 with the range from 36 to 91 years, and these values were very comparable to a clinicopathological study in Nigerians that had a mean of 64 years and a range of 35 to 90 years (16). According to this paper 73.3% of the patients, unfortunately, presented to the clinic with an advanced stage of the disease. 40% of these patients had a metastatic disease, which was consistent with another study with stage IV disease accounting for 43% (16). Half of the patients with stage IV had multi-organ metastasis and there are two causes, which can explain that. First, there is a stereotype that breast cancer is a disease of females only. Therefore, lack of education and knowledge among males specifically will lead to a delay in the diagnosis and management of male breast cancer. A study on 28 adult men had shown that 80% of its participants lack the knowledge of the high risk of developing male breast cancer regardless of positive family history of a maternal blood relative with breast cancer (17). On the other hand, the second major reason behind the late presentation of the disease is the absence of an early screening program with mammography, unlike females. Therefore, lack of education and absence of early screening both contributed to the development of the advanced metastatic disease.

Many risk factors are associated with male breast cancer including family history, genetic disposition, testicular diseases, and other risks such as obesity and smoking. In a study, they found 9.3% of patients had undescended testes and infertility, whereas 6.2% had orchitis. In our study, 13.3% of the patients had benign prostatic hyperplasia. Besides, obesity is a risk factor accounting for 12.5% due to the increase in converting androgens to estrogen by peripheral aromatization (15). Obesity also doubles the risk of male breast cancer (18). In this study, two patients were obese. One study had shown a positive Estrogen Receptor (ER) and Progesterone Receptor (PR) on 39 participants, which accounted for 64% of the total patients (19). Similarly, in this study around half of the patients had positive outcomes in the genetic testing. Five patients were positive for both PR and ER, one patient was positive for only ER, and one patient was a triple positive of PR, ER, HER-2. Family history is also another important risk factor that has been mentioned in the literature. There is a 2.5 times increase in developing male breast cancer with a female relative who had breast cancer (6). As in our study, two patients were found to have a female family member with a history of breast cancer.

Treatment options for MBC followed the NCCN guidelines for FBC (9). In male patients, however, surgical treatment has been noted to be less conservative (20). Nevertheless, instead of a radical mastectomy, the surgical approach has been replaced with modified radical mastectomy which is less invasive (21). In our study, out of all male patients who underwent surgical intervention, 92% had an MRM. On the other hand, only 8% of our male patients used the BCS procedure. Chemotherapy was another modality used for MBC treatment. Although only 40% of our male patients received chemotherapy, most had received the treatment following a surgical intervention, while only 1 patient received the chemotherapy treatment without surgical involvement. 33% of the patients who underwent MRM received chemotherapy whether it was only adjuvant or both adjuvant and neoadjuvant. With histological findings,

radiotherapy is preferred. These findings can be nodal involvement, multifocality, or high proliferation (22). However, Radiotherapy is tended to be favored in high-risk patients (21). In Meguerditchian et al., 50 articles corresponding with the key word "male breast cancer" were reviewed, which found that "Most papers have indicated no net overall survival benefit of radiotherapy." (23). On the other hand, in a study done by Schuchardt et al., 8 out of 9 patients who received radiotherapy were alive and cancer-free, and they determined that "radiation therapy should play an important role in the management of male breast cancer."(24). In our study, where only 47% of our male patients received radiotherapy, detecting the survival rate was not plausible due to losing follow up with 86% of those patients. 67% of our male patients received hormonal therapy, and 60% of them were estrogen-receptor positive. Tamoxifen, which is an anti-estrogen, has shown to improve the survival rate in female patients. In males, however, there are no clinical trials that assessed the use of tamoxifen (5). Even though tamoxifen has not yet been assessed in male patients, the administration of this treatment in male patients has shown improved survival rate with an overall disease-free outcome, which places tamoxifen as an important treatment in most cases of male breast cancer (25).

Lastly, there were several limitations to this study. Male breast cancer is an uncommon disease. Therefore, it was very challenging to collect the proper sample size. The minimum required sample was 10 individuals, however, we collected the data of 15 patients. That challenge was not preventable because the rarity of this disease is out of our control. Another limitation was the collection of ECOG performance status scores of the patients. We observed that 8 patients out of the 15 had on ECOG score recorded. And one reason that could explain the lack of ECOG score documentation is the objectivity of this assessment method. The ECOG score will mainly depend on the objective evaluation of a physician and it may vary between one another. Therefore, not all treating physicians give focused attention to report the score. The last limitation was the inability to find the survival rate in this study due to loss of follow up. The dates of the last appointment at the hospital to find whether the patient was still alive or dead were missing for 12 patients out of the 15.

Conclusion

The main recommendation for any future studies is the involvement of multi-centers to improve the sample size since male breast cancer is a rare disease. Another recommendation is spreading awareness among males, especially those with known risk factors, regarding breast cancer and clarifying the misconception of it being a female-disease only. Hopefully, this can contribute to early presentation to the clinics. Accordingly, an early stage of the disease will be managed better than an advanced metastatic one.

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