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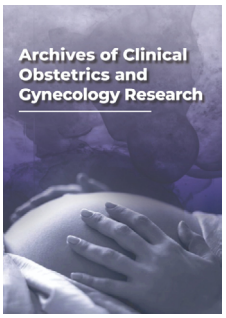
Original Article



Male breast cancer: A North African Center for cancer treatment's experience, and systematic review of literature

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Keywords

Male Breast Cancer, female breast cancer, treatment, prognosis

Abstract

Background: Male breast cancer is a rare disease that accounts for less than 1% of all male cancers and 1% of all incident breast cancers.

Materials and methods: We conducted a descriptive, observational, retrospective study of 92 cases of male breast cancer treated at our center between 2000 and 2020.

Data were collected on the basis of a standardized data sheet after literature analysis.

Objectives: Our research focused on the clinicopathological features, treatments, and prognostic factors in a Moroccan cohort of 92 men with breast cancer, and compared these results with those found in the literature.

Interventions: The data collection lasted for 3 months, from January 2021 to March 2021.

For patients treated before 2014, we had to retrieve their paper files from the archives of our center to collect the necessary information.

We were able to select more recent files using the ENOVA file computerization system. To find the files of interest, we selected the breast as the main organ, then limited ourselves to the files of male patients, and finally, we limited the period of file research from January 2014 to January 2020.

Results:

Epidemiological data: The median age was 71.3 years, and the primary reason for initial consultation was periareolar nodule self-examination. Patients consulted 12.1 months after the first clinical signs. Infiltrating ductal carcinoma (88.3%) was the most common histological type of carcinoma. The most common immunohistochemical profile (55.5%) was Luminal B.

Treatment: The treatment plan included radical mastectomy with axillary lymph node dissection, followed by adjuvant radiotherapy with or without adjuvant chemotherapy. Tamoxifen has been suggested to be effective for all patients with hormone receptors.

Follow-up: The evolution was marked by complete remission (62%), local relapse (7%), progressive disease (7%), metastatic relapse (14%), and death (10%) over a median follow-up period of 42 months (8-156 months).

Conclusion: Although breast cancer in men is very similar to breast cancer in women, it has distinct characteristics. Future prospective studies on a global scale are required to improve the management and prognosis of such patients.

Introduction and objectives of the study

Male breast cancer is still infrequent, accounting for approximately 1% of all cancers in men [1], and it is an entity with no clear treatment guidelines.

The rise in its prevalence over the last two decades has prompted several trials and reviews to focus on it with the goal of obtaining international recommendations [2-3].

Between 2000 and 2020, we examined the clinicopathological features, treatments, and outcomes of 92 men treated for breast cancer at Mohamed VI Center for Cancer Treatment in Casablanca, Morocco.

Materials and methods

This was a single-center, descriptive, monocentric retrospective observational study of 92 men treated for breast cancer at the Mohamed VI Center for Cancer Treatment between January 2000 and December 2020.

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We were able to select more recent files using the ENOVA file computerization system. To find the files of interest, we selected the breast as the main organ, restricted the research to male cases, and limited the file research period from January 2014 to January 2020.

The inclusion criteria were as follows :

- Any man over the age of 18 with breast cancer, regardless of the stage

The exclusion criteria were as follows :

- Any incomplete or unusable file
- Any patient who refused treatment after being diagnosed
- Any patient who was lost to follow-up before the first 5 years of post-therapeutic monitoring

We thus selected 92 usable and complete files.

The results were obtained after completing a previously established chart review.

Breast carcinoma was identified either by biopsy or surgical treatment. The disease was staged using the most recent TNM classification (8th edition of the UICC for International Cancer Control).

The Scarf Bloom and Richardson (SBR) nuclear grade was determined histopathologically, and nuclear staining greater than 10% was considered positive. Complementary immunohistochemical staining revealed the presence of hormone receptors (ER: estrogen receptors, PR: progesterone receptors) and Herceptest.

Statistical analysis

Statistical analyses were performed using SPSS. The results are presented as percentages.

Values of $p < 0.05$ were considered significant in all analyses of the study.

Objectives

Our research focused on the clinicopathological features, treatments, and prognostic factors in a Moroccan cohort of 92 men with breast cancer, and compared these results with those found in the literature.

Results

Clinical features

Ninety-two men who were treated for breast cancer between January 2000 and December 2020 were evaluated in terms of epidemiological, clinicopathologic, therapeutic, and prognostic factors.

The median age was 71.3 years, range, 18–88 years).

In 93.7% of the cases, the primary reason for the initial consultation was self-examination of a periareolar nodule. In addition, 17.9% of the patients had inflammatory symptoms. Nipple discharge was present in 77% of the cases.

Patients consulted an average of 12.1 months after the onset of their first symptoms, with extremes ranging from 3 to 26 months.

We classified the various tumors using the 2018 AJCC TNM classification and then regrouped them into stages, as shown in Table 1.

The predominant histological type was infiltrating ductal carcinoma in 88.3% of cases. We classified the other histological types as follows:

- Carcinoma in situ in 3.1% of cases, medullary carcinoma in 7.5% of cases, and mucosal colloid carcinoma in 1.1% of cases

The most representative histological prognostic grade was SBR (38 %).

The predominant immunohistochemical type was luminal B (55.5%) followed by luminal A (19%). Overexpression of the Her2 protein was identified in 17% of the cases. Finally, "basal-like" tumors represented 8.5% of the panel.

Treatment

Surgical treatment consisted of radical mastectomy with axillary lymph node dissection in all patients who underwent surgery.

We indicated chemotherapy following two main protocols (AC60 and FEC100), including 13% of cases before surgery, 57% after surgery, and 30% with palliative intent.

Tamoxifen was prescribed for all cases expressing hormone receptors for at least five years, and in a single case, we combined hormonotherapy with chemical castration.

Treatment with HER-2 targeted therapy was offered for 69.9% of patients over-expressing the HER2 protein, at a rate of 18 cycles in total.

We should note that the unavailability of the product influenced this rate at our center, especially before 2008.

External radiotherapy was administered to all patients with curative intent on the chest wall. The irradiation schedule was as follows:

-Classic fractionation: Total dose of 50 Gy, in 25 fractions of 2 Gy, at the rate of 5 weekly sessions

-"Classic" hypo fractionated regimen according to the START B Trial: Total dose of 40 Gy, in 15 fractions of 2.67 Gy, at the rate of 5 weekly sessions

The mean spread was 37.7 days, with extremes ranging from 27 days to 53 days.

The therapeutic modalities used in this study are summarized in Table 2.

With a median follow-up of 42 months (8-156 months), the evolution was marked as follows:

- Complete remission in 62% of cases
- A local relapse in 7% of cases
- An evolutionary pursuit in 7% of cases
- Metastatic relapse in 14% of cases
- Death in 10% of cases

The main metastatic sites were the pleura (60%), bones, and liver (40%).

The 5-year-old and 10-year-old survival rates were respectively 65% and 50% (Figure1).

Discussion

Male breast cancer is a rare disease. Although it has many similarities with cancers in women, it still has its own distinct characteristics.

This increase in its incidence has motivated several studies to focus on identifying its epidemiological and clinical features.

It accounts for nearly 1% of male cancers in European countries [1,4]. Its frequency rate compared to women's is around 1% [5]. The incidence of male breast cancer in Morocco according to the national cancer registries of Rabat and Great Casablanca is estimated at 0.8-1%. [6] However, much higher incidences are found in sub-Saharan African countries, which can be explained by the prevalence of infectious diseases responsible for liver damage leading to hyperestrogenism [4,15].

The mean age at initial diagnosis is generally higher in men than in women (68 vs. 62 years) [16].

A family history of breast cancer confers a relative risk of 2.5, and 20% of men with breast cancer have a first-degree relative with breast cancer [4,6].

In addition, cases of male breast cancer have been reported in families with Cowden syndrome and hereditary nonpolyposis colorectal cancer syndrome, although the risk in these cases is low to moderate [22].

Genetic susceptibility to develop male breast cancer may result from mutations in high penetrance genes such as BRCA1 and BRCA2, which rarely occur but confer a high risk of developing breast cancer, or mutations in low penetrance genes such as CHECK 2, which occur more frequently but confer a lower risk of developing breast cancer [20].

Male breast cancer is more common in BRCA2 families than in BRCA1 families.

Currently, BRCA2 mutations are considered the main genetic risk factor for male breast cancer, with an earlier age at diagnosis in people with this mutation (median:58.8 years) than in non-carriers (median:63.4 years) [21].

Individuals with Klinefelter syndrome, characterized by the addition of at least one X chromosome to the normal XY karyotype (usually 47XXY), exhibit testicular dysgenesis, associated with low serum testosterone concentrations and increased gonadotropins. The risk of breast cancer in these individuals is 20–50 times higher than that in men with the classic 46XY karyotype [7].

Moreover, cases of breast cancer have been reported in transgender men receiving repeated estrogen injections.

Endogenous causes of hyperestrogenism include obesity, cirrhosis, mumps orchitis, testicular malformation, cryptorchidism, and orchiectomy [4,8,17].

Case reports suggest excessive production of prolactin in the carcinogenesis of breast cancer [23]. However, other case-control studies have demonstrated no difference in serum prolactin levels between affected male patients and controls.

Moreover, previous thoracic irradiation may be associated with male breast cancer. Indeed, there have been several reports of thymomas and supradiaphragmatic Hodgkin's disease, which develop into adult breast cancer [9,10]. The relative risk of developing breast cancer after irradiation was 7.2, especially in the interval of 20–35 years after initial exposure. This risk decreased three to four decades after the last exposure [20].

The first clinical sign is an isolated lump [4], axillary lymph node invasion is rarely found.

Breast lumps were the main clinical signs in our patients.

Mastodynia, signs of inflammation, and nipple discharge are rare.

Bilaterality (synchronous and/or metachronous) seems less frequent in mec than in women. Crichlow reported an overall rate of 1.4% [29].

The rarity of male breast cancer, and therefore the low suspicion of patients and their physicians, is largely responsible for diagnostic delays [4]. In the 1990s, the average duration before the first consultation was 21 months in the European population. More recently, this duration has been reduced to 6–10 months [12].

Unfortunately, in Moroccan society, this duration remains high because of numerous taboos related to the body. Indeed, given the rarity of male breast tissue, thoracic extension occurs much more quickly, and we also observe secondary lymph node involvement earlier [13, 17].

Mammography has a sensitivity and specificity of > 90% in men. The malignancy criteria were identical to those found in women: spiculations, calcifications, and presence of a mass eccentric to the nipple. Ultrasound visualizes a hypoechoic mass with irregular margins [24].

As the male breast does not have lobular elements, the predominant histological type remains infiltrating ductal carcinoma in > 90% of cases [4]. Infiltrating lobular carcinoma, spinal cord lesions, and tubular or neuroendocrine tumors are exceptional [17].

The immunohistochemical profile very frequently shows overexpression of hormone receptors, with a large predominance of luminal cancers, and a very small proportion of breasts with overexpression of HER2 (Human Epidermal Growth Factor Receptor 2) or basal-like cancers (not expressing neither hormone receptors nor HER2). [4, 17] These results agree with those found in our study.

In general, the most frequent surgical procedures are modified radical mastectomy, axillary lymph node dissection, and sentinel lymph node biopsy. Conservative surgery is often considered inappropriate in men [24]. Indeed, the results of several series agree on a much higher local recurrence rate in patients who have undergone surgery [25, 26].

However, conservative and/or nipple- or skin-sparing mastectomy can also be performed in selected cases. Oncoplastic techniques should be used whenever possible because of the psychological impact of such surgeries on patients.

Men are more likely to receive adjuvant radiotherapy than women are, as they are often diagnosed at a more advanced stage [17,24,31].

Overall, the standard radiation dose was 50 Gy, delivered in 25 fractions of 2 Gy. The target volume includes the chest wall (which includes the mastectomy scar, skin, and underlying muscles). Regional lymph node irradiation should include the axillary, supraclavicular, and internal mammary nodes, depending on the number of invaded lesions and the possible existence of capsular rupture.

In the particular case of left breast cancer, very particular attention should be paid in radiotherapy planning to limit the heart dose constraint, especially if an HER-2 targeted therapy is already initiated, to reduce the cardiotoxicity risk [4].

Adjuvant hormone therapy based on antiestrogen (tamoxifen) has been shown to increase survival rates in female patients with breast cancer and luminal cancer. To

date, and based on this observation, Tamoxifen is the standard treatment for hormone-dependent male breast cancer [4]. Aromatase inhibitors, on the other hand, should not be used alone, as they can cause a partial decrease in estrogen, but also an increase in androgen levels by loss of the negative feedback of estradiol on gonadotropins at the level of the hypothalamic-pituitary axis [18].

Moreover, 80% of estrogen production in men is ensured by peripheral aromatization, and the remaining 20% by direct testicular production. Therefore, chemical or surgical castration is recommended in association with the use of anti-aromatases [19]. This combination is reserved only in a few cases of locally advanced or metastatic luminal cancer.

Further studies would be necessary to determine the duration of this adjuvant hormone therapy because an extended duration - as proposed in women - is responsible for a considerable rate of treatment abandonment due to the rise of side effects (thromboembolic complications, hot flushes and decreased libido).

As for adjuvant chemotherapy, it has shown a benefit in terms of overall survival and progression-free survival in N+ patients [4] or in the case of RH -, or SBR III cancer, with variable objective responses depending on the series, but with a preference for CMF, AC or EC regimens, and taxanes may be considered when lymph nodes are involved. [27].

This was a single prospective study of 24 cases of male breast cancer who received chemotherapy according to the CMF protocol (cyclophosphamide, methotrexate, and fluorouracil) and whose main objective was to evaluate the overall survival rate. This was evaluated at more than 80% at five years, and was significantly greater than that in a similar cohort [32].

As for treatment with anti-HER monoclonal antibodies, although it is a mainstay in the treatment of HER+ breast cancers in women, its role in men is less clear, because HER2 receptors seem to be less overexpressed. However, it seems reasonable to systematically propose it for all HER2+ male breast cancers according to the same protocol as that for women [24].

For metastatic luminal cancer (the most common cancer), the preferred first-line metastatic treatment is tamoxifen. If progression occurs, other treatment options such as aromatase inhibitors may be offered. Hormonal castration was proposed in this specific case in our study.

Over the past five decades, hormone therapy has remained the mainstay of treatment for metastatic cancer. The first hormone therapies were ablative, including orchiectomy, adrenalectomy, and hypophysectomy [4-14].

These approaches were effective in 55–80% of cases, but they were traumatic and led to morbidity [24].

Combinations of endocrine agents and targeted therapies, such as mTOR pathway inhibitors and anti-CDK4, can be used in these patients, following the same indications as those for metastatic female luminal breast cancer.

Chemotherapy should be reserved for symptomatic visceral or bone metastases. In this case, we can use the same agents and regimens recommended for metastatic cancer in women [17].

As in the neoadjuvant or adjuvant situation, the benefit of HER-2 targeted therapy treatment is not clear. Indeed, there is only one reported case of good response to trastuzumab in the treatment of HER+ metastatic male breast cancer [28]. However, in the absence of studies supporting the benefit of anti-HER treatment in metastatic situations, it would be preferable to prescribe it systematically [33].

Some studies have suggested that breast cancer has a worse prognosis in men than in women. However, if we compare the results according to age and disease stage, there is no difference between the sexes. The overall 5- and 10-year survival rates of male breast cancer patients are around 60 and 40%, respectively

The less favorable prognosis in men is due to a more advanced stage of the disease at the time of diagnosis and, above all, to older age, which leads to higher levels of comorbidity.

In univariate analysis, hormone receptor negativity and tumor grade were associated with poorer prognosis and reduced survival [30].

Through our research, we found an impressive retrospective cohort study of 169,278 cases of breast cancer, including 1,123 males, which showed differences in clinical and pathological characteristics between males and females. The results showed that male breast cancer has a worse overall prognosis compared to female breast cancer, which corroborates with what we have discussed throughout our discussion. We have gathered the most significant differences in the disease characteristics of male versus female breast cancer seen in this review are presented in Table 3 [34].

Conclusion

The incidence of male breast cancer is increasing because of the aging population. It is often discovered at an advanced stage due to the lack of knowledge about it, particularly its risk factors. Thus, any patient undergoing hormonal treatment (especially those treated for prostatic neoplasia) must be aware of the serious side effects associated with the development of male breast cancer.

Therefore, any breast complaints of these patients should be fully and thoroughly evaluated.

The number of invaded lymph nodes, tumor size, advanced age at the time of diagnosis, and the presence of comorbidities limit certain therapeutic choices.

It is necessary to undertake randomized prospective studies on a larger scale to improve the management and prognosis of this condition, the psychosocial impact of which is considerable.

Supplementary material

Table 1: Tumors' Clinicopathologic features

Table 2: Therapeutic modalities according to tumors' stage and immunohistochemical profile

Table 3: Main features from Nan Yao's review

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Author contributions

FO wrote the article after conception of the study design and acquisition of data, analysis, and interpretation; SS, TC, MB, ZB, NB, HJ, NT, and AB made critical assessments of the article.

SS supervised the work.

All authors agreed on submission to this journal

Institutional Review Board Statement

Ethical review and approval were waived for this study because of the lack of application or existence of an ethics committee concerning scientific work in Morocco, except for the Ethics Committee for Biomedical Research, which did not apply to us.

Ethics approval and informed consent

Written informed consent has been obtained from the patient(s) to publish this paper.

Data availability

The data presented in this study are openly available in the tables published in this work

Competing interests

The authors declare no conflict of interest

Article Summary: Strengths and Limitations

Our study is valuable because we were able to gather a significant number of cases, even though it is a rare disease.

We confirmed that the characteristics found in our cohort did not differ from those reported in the literature.

However, this was a retrospective study, with all the limitations implied. A larger prospective trial is required to confirm our results.

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Supplementary Data

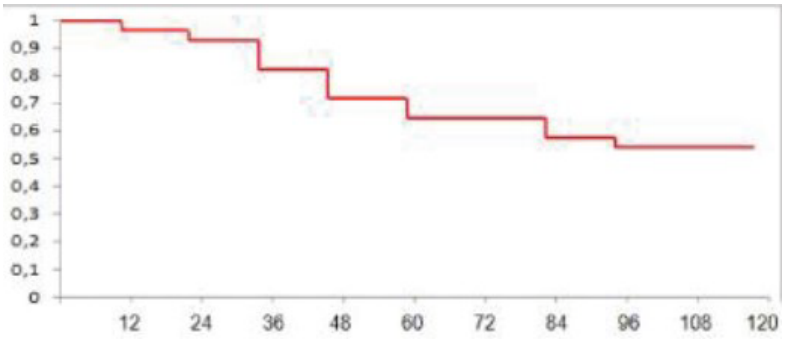

Figure 1. *Estimated overall survival in our study*

Table 1. *Tumors' Clinicopathologic features*

Features	Number of cases concerned		%
Size T	X	0	0
	0	0	0
	1	13	14.1
	2	25	27.3
	3	21	22.8
	4	33	35.8
Lymph node status N	X	5	5
	0	18	19.3
	1	40	42.5
	2	22	25.5
	3	7	7.7
Presence/Absence of metastases M	M0	61	66.8
	M+	31	33.2
Staging	Stage I	4	4
	Stage IIA	10	11.3
	Stage IIB	13	14
	Stage IIIA	13	14
	Stage IIIB	12	13
	Stage IIIC	9	10.5
	Stage IV	31	33.2
SBR-Grade	I	5	5.8
	II	52	56.2
	III	35	38
IHC profile	Luminal A	17	19
	Luminal-B	51	55.5
	Her overexpresses	16	17
	Triple negative (Basal like)	8	8.5
Histological type	ICC	81	88.3
	Medullary carcinoma	7	7.5
	C. in situ	3	3.1
	C. mucosal colloid	1	1.1

Table 2. *Therapeutic modalities according to tumors' stage and immunohistochemical profile*

Stage	IHC profile	Therapeutic means				
		Surgery	Chemotherapy	Hormone therapy	anti HER treatment	Radiotherapy
Stage I N=4	Luminal A 2	2	0	2	0	1
	Luminal B 2	2	0	2	0	1
	Her + 0	0	0	0	0	0
	Basal Like 0	0	0	0	0	0
Stage IIA N=10	Luminal A2	2	2	2	0	2
	Luminal B 8	8	8	8	0	8
	Her + 0	0	0	0	0	0
	Basal Like 0	0	0	0	0	0
Stage IIB N=13	Luminal A 6	6	6	6	0	5
	Luminal B 5	5	5	5	0	5
	Her + 1	1	1	1	1	1
	Basal Like 1	1	1	0	0	1
Stage III N=34	Luminal A 5	5	5	5	0	4
	Luminal B 19	19	7	7	0	7
	Her + 8	8	8	3	5	8
	Basal Like 2	2	2	0	0	2
Stage IV N = 31	Luminal A 2	0	2	2	0	0
	Luminal B 17	8	17	5	0	2
	Her + 7	3	7	0	5	2
	Basal Like 5	3	5	0	0	1

Table 3. *Main features from Nan Yao's review*

	Male	**Female**	**p**
Number of patients	1123	169278	
Age	63.45 (+/-10.81)	58.96 (+/-12.14)	<0.001
T3 T4	10.51%	8.75%	<0.001
N0	56.90%	68.48%	<0.001
M+	5.25%	3.14%	<0.001
SBR I	11.67%	22.82%	<0.001
Ductal	84.86%	77.81%	<0.001
Lobular	0.62%	8.14%	<0.001
RE	97.42%	82.72%	<0.001
RP	91.63%	72.46%	<0.001
HER	11.04%	14.68%	<0.001