**CLINICAL AND PATHOLOGICAL CHARACTERISTICS, MANAGEMENT AND PROGRESSION OF MALE BREAST CANCER IN URUGUAY. A RETROSPECTIVE ANALYSIS OF A CASE SERIES.**

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**Abstract**

Male breast cancer (MBC) is a rare condition that, while sharing some similarities with breast cancer (BC) in women, has a unique disease profile of its own. Objective: To understand the characteristics of MBC and its management in our area. Material and Methods: Retrospective observational study that included patients diagnosed with MBC in 3 centres in Uruguay over a period of 14 years. Results: The study included 22 patients, with a median age at diagnosis of 62.5 years. Of these, 27% (6 patients) had relevant family history. Clinical-pathological characteristics: All cases were infiltrating ductal carcinomas (IDC); 90.9% (20 patients) were classified as final histological grade (FHG) 2-3, 68.1% (15 patients) were stage (S) I-II, and 68.1% (15 patients) had axillary metastases. Three biological subtypes were defined: 73% (16 patients) were HER2- ER/PR+, 23% (5 patients) were HER2+, and one patient was triple negative. Patients with localised disease underwent a mastectomy, most patients were treated with chemotherapy (CTx), and all ER/PR+ patients received adjuvant hormone therapy, mostly with good adherence and tolerability. Nineteen percent of patients treated with curative intent (4 out of 21 patients) relapsed. Discussion: On a national and international level, the median age at diagnosis for MBC is higher than for female BC, which was also reflected in this study. As reported on a national and international level, the predominant histological type was IDC; however, most tumours were FHG 2-3, while on a national and international level it is well-differentiated tumours that are reported most frequently. It is common for these patients to initially present with S III or S IV BC, but in our study 68.1% of patients initially presented with S I-II. In accordance with what is documented in the literature, most of the tumours were HR+. Twenty-three percent of our patients were HER2+, which is similar to the figure reported for women internationally (20%) and somewhat lower than the figure reported nationally (27%). Conclusion: We present a case series of patients with MBC. In accordance with what has previously been reported, most cases were ER/PR+ and HER2-. However, in this series, the median age at diagnosis was similar to that of BC in women, and a higher proportion of the patients initially presented with localised stages and high-grade tumours when compared to what has previously been described in the literature.

Keywords: breast neoplasm, ductal carcinoma, male, diagnosis, treatment.

**Introduction:**

Male breast cancer (MBC) is a rare condition. Much of what is known about the disease is based on non-randomised retrospective studies, as well as on the greater understanding we have of breast cancer (BC) in women. However, although MBC has some similarities to female BC, it is a condition that has a unique disease profile of its own. It has a set of specific clinical and pathological characteristics that make it a distinct disease, such as its age of presentation – 5 to 10 years later than in women – and a predominantly retroareolar location. It is also more hormone-sensitive, and is frequently diagnosed at a more advanced stage than in women (1). The female/male ratio of BC in Western countries is 100/1. In Uruguay, in the period 2012-2016 the incidence of MBC was 102 cases, corresponding to 20 patients per year, which gives a crude rate of 1.29 and an adjusted rate based on the standard world population of 0.83 cases per 100,000 men (2). Like BC in women, the incidence of the disease increases with age; however, the median age at diagnosis is 65-67 years, somewhat higher than for women, where the median age at diagnosis is 61 years (3).

The aetiology of MBC is unclear. Most of those affected have no associated risk factors; however, genetic, environmental and hormonal factors have been implicated in its pathogenesis. The risk factor most associated with the development of MBC is Klinefelter syndrome, a very rare condition that arises from inheriting an extra X chromosome (XXY). Patients with this condition have elevated gonadotropin and low testosterone levels, which leads to testicular atrophy and gynecomastia. These patients have a higher oestrogen/testosterone ratio, and their risk of developing MBC is 20 to 50 times higher than in the general population (4). Approximately 15% to 20% of men diagnosed with BC have a family history of breast or ovarian cancer. The risk increases in proportion to the number of first-degree relatives who have been affected and the number of those who were diagnosed at an early age (5, 6). Genetic predisposition to MBC may result from autosomal dominant inheritance, particularly from mutations in the high-penetrance genes BRCA1 or BRCA2. There is little evidence linking an increased risk of developing MBC to mutations in the BRCA1 gene; however, a mutation in the BRCA2 gene is the most important genetic risk factor for the development of this disease. In men, BRCA2 mutations are more prevalent (4-40%) than BRCA1 mutations (0-4%). Men who inherit a BRCA2 mutation have a 6.8% cumulative risk of developing MBC by the age of 70, whereas for men with a BRCA1 mutation the risk is less than 1.2%. This risk is 80 to 100 times higher than in the general population (7-9).

Exposure to radiation is associated with an increased risk of developing MBC. Between January 1958 and December 1998, the Hiroshima and Nagasaki tumour registries recorded 9 cases of MBC (a rate of 1.8 per 100,000 population), while only 3 were recorded among unexposed persons (a rate of 0.5 per 100,000 population), which is a statistically significant difference (p = 0.01) (10).

The evidence regarding other risk factors is less conclusive. Gynecomastia associated with excess oestrogen may increase the risk of developing MBC; however, it is unclear whether gynecomastia is an independent risk factor for developing the disease or whether both conditions (MBC and gynecomastia) have similar risk factors (11).

Diagnosis is clinical, and can be confirmed by imaging and anatomopathological examination. Like in the case of BC in women, mammography is an essential diagnostic method for assessing a suspicious breast lesion, and it has a high degree of sensitivity and specificity (92% and 90% respectively) in the diagnosis of MBC. Mammography helps to differentiate common conditions, such as gynecomastia, and to identify suspicious lesions. Mammography examinations should be bilateral and should include the standard projections (craniocaudal and mediolateral oblique) (12-14).

Forty percent of MBC tumours are locoregionally advanced and more than half present nodal involvement at the time of diagnosis. The most frequent form of clinical presentation is a painless retroareolar lump, with permanent and progressive growth. Nipple involvement appears early and can manifest itself as umbilication, ulceration or discharge. Involvement of other areas of the skin and of the pectoral muscles is also common. This form of presentation could be explained by breast tissue in men being located at a retroareolar level, where this tissue is scarce. A second explanatory factor is late diagnosis, which is generally linked to a lower clinical suspicion of the disease. Bilateral BC is very rare in men (12, 13).

Infiltrating ductal carcinoma (IDC) is the most frequent subtype, representing more than 90% of invasive tumours. In men, lobular carcinomas represent around 1% of breast carcinomas, while in women they represent around 10% (15). The vast majority of MBC cases (68-78%) are low grade (grade 1-2) (12, 13). MBC is hormone receptor (HR) positive (either oestrogen receptor [ER] or progesterone receptor [PR] positive) more often than BC in women, with up to 90% of tumours being ER-positive and up to 80% being PR-positive. Data on the overexpression of human epidermal growth factor receptor-2 (HER2) in MBC are contradictory, with estimates ranging from 2% to 42% depending on the study (13, 16).

Recommendations regarding adjuvant therapy based on chemotherapy (CTx) ± trastuzumab ± hormone therapy (HT) are founded on the benefits demonstrated in prospective randomised studies involving women operated on for BC. Adjuvant CTx should be considered in patients operated on for BC where there is a high risk of recurrence, that is: when the patient is under 35 years old; when the tumour is classified as final histological grade (FHG) 2-3; when the tumour is HR-negative; when the tumour is HER2-positive and larger than 1 cm and/or has axillary node involvement; or when there is regional lymph node involvement. The updated Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meta-analysis, which assesses results of polychemotherapy (PCTx) in 100,000 patients with operable BC, including more than 100 clinical trials of adjuvant treatments, found that both anthracycline-based regimens and non-anthracycline-based regimens of chemotherapy reduced the risk of death due to BC by 20-25% when compared to no chemotherapy, with an absolute reduction of mortality of 6.2% to 6.5% at 10 years. For patients with a positive axillary node, PCTx with both anthracyclines and taxanes achieved better results, with sequential regimes being better tolerated (17). In patients with HER2-positive tumours, the use of adjuvant trastuzumab should be considered for a period of one year when there is a positive axillary node or when the tumour is larger than 1 cm, even if the axillary nodes are negative. Adjuvant HT is indicated in all cases of ER-positive and/or PR-positive BC, regardless of whether or not other complementary treatments such as chemotherapy, radiotherapy or immunotherapy have been administered (18). Therefore, we can say that for patients with MBC presenting any of the above-mentioned risk factors with triple negative tumours (HR-negative and HER2-negative), CTx is the only option for systemic treatment, while for patients with HER2-positive tumours larger than 1 cm or with positive axillary nodes, CTx with concurrent trastuzumab is a good option. Patients with HR-positive tumours should also receive additional adjuvant HT.

An understanding of this disease, and of the management of diagnostic criteria and prognostic and predictive factors for treatment, as well as a knowledge of different therapeutic options, will allow clinicians to provide the best possible care and treatment to patients. In this study, we analyse 22 clinical cases of MBC from three centres in Uruguay, and we discuss the results.

**Objective:**

To understand the characteristics of MBC, its standard management in clinical practice, and the process of disease progression in our area.

**Patients and Methods:**

We selected all patients diagnosed with MBC during the period between 1/06/2006 and 1/06/2020 in three Oncology Departments in Uruguay: Hospital de Clínicas, Servicio Médico Integral and CASMER. The data were collected through detailed study of medical histories. A registration number was used during the research to identify each patient, in order to protect their personal data. The variables considered in this study were: patient’s age at diagnosis; personal history (PH) of malignant breast disease; significant family history (FH) (counting the patient, 3 or more cases of BC or ovarian cancer, with at least one presenting before the age of 50); histological type; histological grade; pathologic tumour size; axillary lymph node status; stage according to the TNM classification system; HER2, ER, and PR status determined by immunohistochemical (IHC) analysis; treatments performed (surgery, radiation and/or systemic treatment); and tumour recurrence (local and/or systemic). Three subtypes were defined based on positive or negative tumour expression of HER2, ER and PR, determined by IHC analysis and fluorescence in situ hybridisation (FISH) where necessary:

1. HER2-, ER/PR+ = ER+ and/or PR+, HER2-.
2. HER2+ = ER+ and/or PR+, HER2+.
3. ER-, PR-, HER2- (triple negative).

**Ethical Considerations:**

The study was conducted in accordance with international ethical standards for biomedical research: MERCOSUR guidelines on the regulation of clinical trials, the Declaration of Helsinki, and the research regulations approved by the National Ethics Commission in 2019. Patient anonymity was maintained in the statistical analyses, and approval for this study was obtained from the Ethics Committee of Hospital de Clínicas.

**Results:**

The median age at diagnosis was 62.5 years (range: 32-78 years). Twenty-seven percent (6 patients) had a FH of BC, but only two patients had significant FH and none had a personal history of BC. All patients reported a palpable breast lump; 17 of the 22 patients presented with a breast tumour with no involvement of the skin or chest wall structures, and 5 patients were classified as pT4 (tumours with skin or chest wall involvement). Of the 22 patients, 68.1% (15 patients) had clinical nodal involvement at diagnosis. The time delay between the appearance of the breast lump and the patient’s first visit ranged from 1 to 8 months, and was longer in patients with pT4 tumours. All 22 patients underwent bilateral mammography, which in most cases revealed a dense mass at the retroareolar level, with infiltrating margins. In patients with skin involvement, this mass showed dense tracts that connected with the nipple, resulting in its ulceration. These findings were categorised as BI-RADS 5. It should be noted that microcalcifications were present in two of the patients. The distribution by stages (S) was as follows: 13.6% (3 patients) were S I, 54.5% (12 patients) were S II, 27.3% (6 patients) were S III, and one patient was S IV. All tumours were IDC and most (20 cases, 90.9%) were poorly differentiated (FHG 2-3). Two cases were FHG 1. The remaining clinical-pathological characteristics are shown in Table 1. With regard to biological profile: 73% (16 patients) had ER-positive and/or PR-positive and HER2-negative tumours; 23% (5 patients) had HER2-positive tumours; and 1 patient was triple negative (TN), as shown in Figure 1.

Initial treatment for patients without metastatic disease (21 patients) was surgical in most cases (19 patients), while the remaining 2 patients were initially treated with neoadjuvant CTx. Almost all patients underwent mastectomy, with 16 patients undergoing modified radical mastectomy (MRM) and 4 patients undergoing mastectomy plus sentinel node biopsy (SNB); one patient was treated with conservative surgery plus SNB. In total, 77.3% (17 patients) received systemic treatment with CTx; of these, 16 patients received CTx with curative intent and the remaining patient received it as palliative therapy. Out of the total number of patients treated with CTx with curative intent, 14 patients received it as adjuvant therapy and two patients received it as neoadjuvant therapy, with good clinical and imaging response, undergoing surgical treatment after the end of the CTx. The most frequently employed regimen was TC (docetaxel plus cyclophosphamide) (9 patients, 52.9%), followed by regimens involving anthracyclines (7 patients, 41.1%), mostly involving sequential use of anthracyclines and taxanes. The 5 patients with HER2-positive tumours received systemic treatment with HER2 blockade. Four of these patients received treatment with adjuvant trastuzumab; the remaining patient received palliative treatment, with taxanes plus trastuzumab as first-line therapy and with lapatinib plus capecitabine following disease progression. Twelve of the twenty-one patients (57.1%) who received treatment with curative intent were treated with adjuvant radiotherapy (RTx) in the breast area, using tangential fields, and receiving a dose of 5000 cGy with standard fractionation. These patients were at greater risk of relapse, since they had four or more involved lymph nodes, tumours that were larger than 5 cm, or involvement of locoregional structures and/or skin. All patients with non-metastatic disease and HR-positive tumours (20 patients) received treatment with adjuvant HT based on adjuvant tamoxifen for 5 years; two of these patients continued with aromatase inhibitors until completing 10 years of treatment. Most patients exhibited good adherence and tolerability to the treatment. Only one patient discontinued the treatment due to poor tolerability. Four of the twenty-one patients (19%) treated with curative intent relapsed, while the remaining patients are still undergoing monitoring or treatment with no evidence of relapse. Patients who only relapsed locally promptly received local and systemic treatment. In patients who presented systemic relapse, systemic treatment was initiated; all are undergoing treatment to date. The remaining patients remain disease-free to date. The patient who initially presented with metastatic disease died due to disease progression.

**Discussion:**

On a national and international level, the median age at diagnosis for MBC is higher than for female BC, which was also reflected in this study (3). As previously mentioned, the aetiology of MBC is unclear. Most of those affected have no associated risk factors; however, genetic, environmental and hormonal factors have been implicated in its pathogenesis. None of the patients included in this study had been exposed to radiation prior to disease development, and none had Klinefelter syndrome, the risk factor that is most strongly associated with the development of MBC (4, 19). Most of the patients included seemed to correspond to isolated cases with no familial links; 27% had a FH of BC, and two of these had significant FH, a figure that is somewhat higher than what is usually reported, as only 5-10% of all BC cases are attributable to a mutation in the BRCA1 and BRCA2 genes. Although the presence of MBC naturally leads one to suspect the presence of a mutation in the BRCA genes, it is not known if any of the patients included in this study were carriers of this mutation, since this test was not carried out, despite being requested.

Similar to what has been found on a national (20, 21) and international level (22), the predominant histological type was IDC. Lobular carcinomas are extremely unusual in men (23). On the other hand, most of the tumours in our series (20 cases, 90.9%) differed from what has previously been reported in that they were poorly differentiated (FHG 2-3), and only two cases were FHG 1. In the literature, approximately 80% of MBC cases are FHG 1 and 2, both internationally (12, 13) and nationally (21). Although determining Ki-67 is routine in the pathological anatomy departments of the centres where the patients were attended, the retrospective nature of this study limits any recording of this variable.

In accordance with previous studies, most of the tumours (20 tumours, 90.9%) were HR-positive. This percentage is slightly higher than that found in women (13, 16).

Twenty-three percent of our patients were HER2+, which is similar to the figure reported for women internationally (20%) (24) and somewhat lower than the figure reported nationally (27%) (25).

Although half of all MBC patients initially present with S III and IV, most of those included in this study (15 patients, 68.1%) were diagnosed while the tumour was still localised (S I and II). Similar to what has previously been described in the literature, all patients reported a palpable breast lump, and over half had clinical lymph node involvement at the time of diagnosis (12, 13). Although skin and pectoral muscle involvement is common, most of the patients in our series (17 patients, 77.2%) presented with a breast tumour with no involvement of these tissues. None of the patients had bilateral BC, which is extremely rare in men. Coinciding with previous studies, in most cases mammography revealed a dense mass located at a retroareolar level, and the presence of microcalcifications was less frequent than in women (12-14).

With regard to therapeutic guidelines, although there are no prospective and randomised studies that include male patients, like in the case of women, locoregional and systemic treatment will depend on the extent of the disease at the time of diagnosis and the general condition and comorbidities of the patient. Regarding surgical treatment, almost all the patients were subjected to mastectomy, which is in keeping with what has been seen in other centres, since, although the general principles of surgery do not vary in relation to sex, conservative surgery is less frequently used in male patients (3, 26).

Experts recommend managing the axilla in a similar way for both men and women, which is why sentinel node biopsy (SNB) is currently an alternative to axillary node clearance (ANC) for patients diagnosed with BC with no clinical evidence of node involvement, thereby reducing morbidity. Thus, axillary management is similar for both sexes, with a general consensus that it is best not to perform ANC in patients with a negative SNB (16, 27-30). Only five of the patients were treated with mastectomy and ANC, but the retrospective nature of this study prevents us from knowing the reasons behind this decision (clinical axillary involvement or ultrasound confirmed by fine needle aspiration [FNA] biopsy), or whether this recommendation was in force at the time of selecting the treatment.

Recommendations regarding adjuvant therapy based on CTx ± trastuzumab ± HT are based on the benefits demonstrated in prospective randomised studies involving women operated on for BC. The low incidence of MBC limits the implementation and timely completion of clinical studies that assess the role of adjuvant or palliative systemic treatment. In total, 77.2% of patients (17 patients) received systemic treatment with CTx; of these, 16 patients received CTx with curative intent and one patient received it as palliative therapy. Of the 16 patients treated with curative intent, 14 initially presented with operable disease and received adjuvant treatment; the remaining 2 received neoadjuvant treatment, since they presented with tumours that had skin involvement (pT4). The regimens used were similar to those used in the treatment of female BC, with most patients undergoing regimens that included docetaxel and cyclophosphamide (9 patients, 52.9%) or anthracyclines and taxanes (7 patients, 41.1%). The 5 patients with HER2-positive tumours received systemic treatment with HER2 blockade. Four of these patients received adjuvant trastuzumab; the remaining patient received palliative treatment, with trastuzumab plus taxanes as first-line therapy and with lapatinib plus capecitabine as second-line therapy.

Twelve of the twenty-one patients (57.1%) treated with curative intent received treatment with adjuvant RTx in the chest wall and lymph node areas. The indication criteria were similar to those in women: pT4 tumours and/or positive margins and/or axillary involvement (16).

All patients with non-metastatic disease with HR-positive tumours (19 patients) received treatment with adjuvant HT based on tamoxifen for 5 years. Two of these patients continued with aromatase inhibitors until completing 10 years of treatment. In accordance with what has been reported in previous studies, adherence to HT was lower than in women due to the occurrence of adverse side effects (1, 3).

As a limitation of this research, it is worth reiterating that this work was conducted in three centres in the country. This may generate a bias in the results if interpreted as representative of the national population. Thus, an assessment of the characteristics of the disease in other centres in Uruguay remains pending for future studies.

**Conclusion:**

We present a series of 22 patients with MBC, a rare condition that, while sharing some similarities with BC in women, has a unique disease profile of its own. In accordance with what has previously been reported, most cases were ER/PR+ and HER2-. However, in this series, the median age at diagnosis was similar to that of BC in women, and a higher proportion of the patients initially presented with localised stages and high-grade tumours when compared to what has previously been described in the literature.

**Table 1:** Clinical-pathological characteristics, stage, and HR and HER2 status of the patients included in the study (n = 22).

|  |  |
| --- | --- |
| **Variables** | **N**  |
| **Histological type** |  |
| **IDC** | **22** |
| **Final histological grade** |  |
| **FHG 1** | **2** |
| **FHG 2** | **8** |
| **FHG 3** | **12** |
| **Size of tumour** |  |
| **pT1** | 9 |
| **pT2** | **8** |
| **pT4** | **5** |
| **Axillary lymph node status** |  |
| **pN0** | 7 |
| **pN1** | 12 |
| **pN2** | 2 |
| **pN3** | 1 |
| **Stage** |  |
| **I** | 3 |
| **II** | 12 |
| **III** | 6 |
| **IV** | 1 |
| **HR status** |  |
| **ER+ and/or PR+** | 20 |
| **ER- and PR-** | 2 |
| **HER2 status** |  |
| **HER2+ (3+/2+ FISH+)**  | 5 |
| **HER2- (1+/2+ FISH-)** | 17 |

 HER2- ER/PR+ HER2+ Triple negative

Figure 1: Biological subtypes.

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