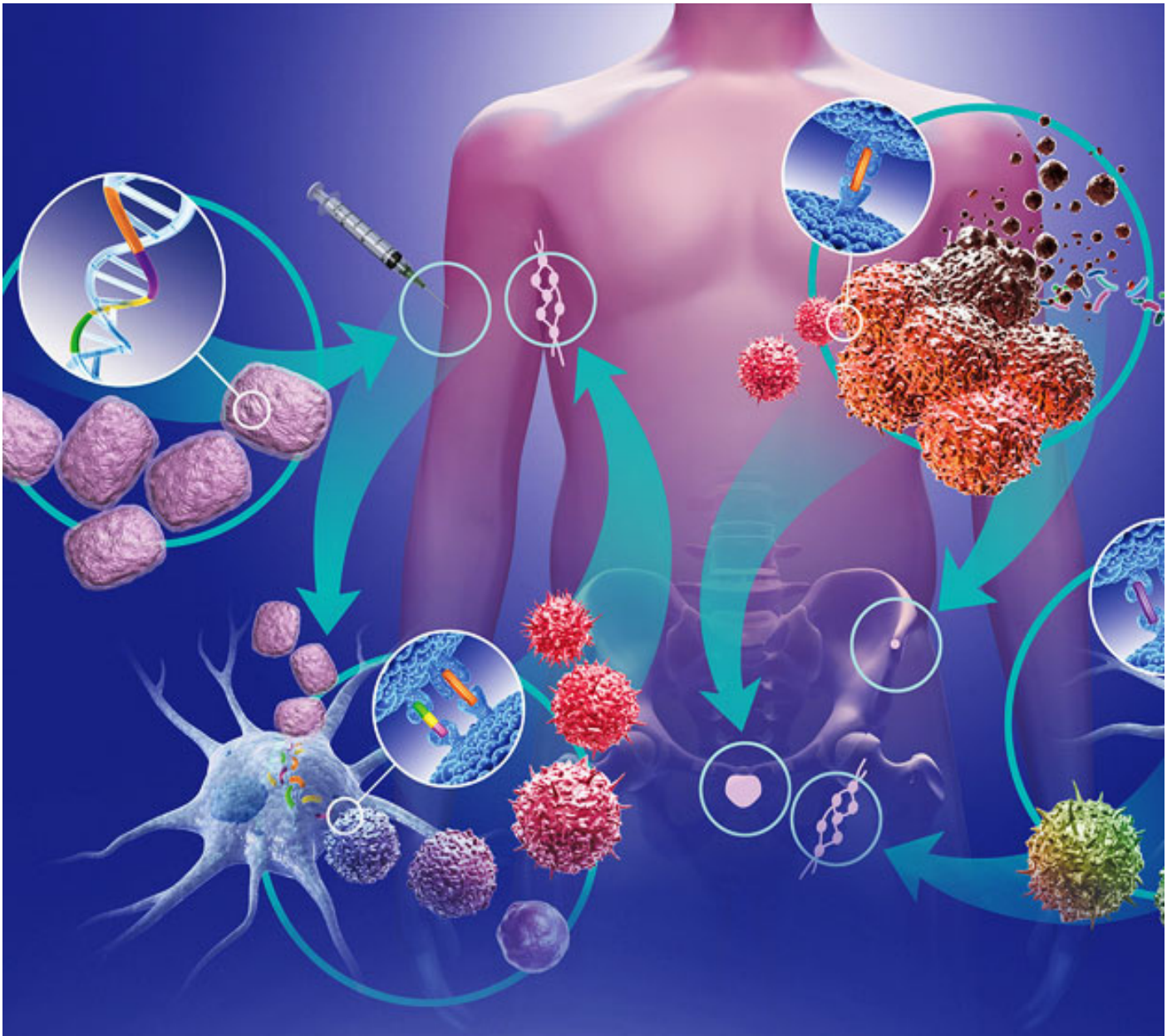

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Male breast cancer: Clinical, histopathological, genetic aspects and metastatic pattern

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Introduction

The oldest known reference to male breast cancer (MBC)-although the word cancer was not used-has been found in an Egyptian manuscript on trauma surgery, the Edwin Smith Papyrus, around 3000-2500 BC [1]. The Greek physician Hippocrates (460-370 BC) used the term carcinoma to describe the "crab-like" spreading pattern of certain tumors, which roman physician Celsus (28-50 BC) translated into cancer. A second important historical registry, with an extensive clinical description of MBC is attributed to John of Arderne, an English surgeon, in 1307 [2]. Not until the late nineteenth century can one find sufficient reference to cases in the literature.

MBC is a rare clinical entity and it is estimated that it represents less than 1% of all cases [3]. In some specific areas of Africa and Egypt, however, the incidence of MBC is almost 5%. This high incidence in those areas seems to be due to infectious liver diseases caused by schistosomiasis (bilharziasis), which like in a chain reaction, leads to high levels of estrogen (hyperestrogenism), strongly related to an increased risk of MBC [4]. Unlike female breast cancers, MBCs appear at a more advanced age, contributing to a higher mortality and comorbidity rate, and are frequently associated with metastasis and multiple primary cancers at other locations. Additionally, hormonal receptors for Estrogen (ER) and Progesterone (PR) are expressed in 90% and 96%, respectively, of MBCs, a higher proportion than in women [5,6].

The majority of the current information on MBC has been collected from retrospective studies of isolated cases with a very low number of patients [7-9]. Its low incidence highlights the difficulty of performance of randomized clinical trials, and only a scarce number of prospective studies with a significant number of cases have been published. As a consequence of this lack of data, very often the therapeutic decisions to treat MBCs are extrapolated from what has been learned from the study of female breast cancers.

The objective of this study is to describe the various types of clinical presentations and evolution of 78 MBCs found in 75 patients diagnosed in several hospitals in Vigo (Galicia, Spain) between the years 1977 and 2019. Our hope is that the information provided here will contribute to bridge the gap and increase awareness among patients and physicians, to eventually optimize the current management of this disease in males.

Materials and methods

A protocol was designed to record retrospective and prospective data from male patients diagnosed with Breast Cancer (MBC) from October 1977 to March 2019 at four different hospitals in the area of Vigo (Hospital Xeral Universitario de Vigo, Hospital Meixoeiro, Hospital Universitario Álvaro Cunqueiro and Hospital Povisa). Our study initially consisted in a total of 81 histological cases of MBC, but 7 cases of primary breast carcinomas (PBC) had to be excluded due to absence of validated clinical data and incomplete follow-ups. The remaining 78 histological cases included in this protocol were presented in 75 patients and constituted our valid study.

The study variables included: Age at initial diagnosis, type of breast cancer, primary tumor location, histological type/grade, clinical stage, ER/PR and HER2 status, Ki67 index, family history of breast cancer, genetic profile, secondary tumor location, relapse and 5-10 year survival rates. The immunohistochemical study allowed us to present the data as a function of the new classification for their genetic profile. The individual clinical follow-up of each of the 75 patients made possible the collection of information about local relapses, metastasis and dates of fatal termination of disease (exitus letalis).

The data collected in this study was introduced in a database built in Microsoft Excel and statistically analyzed with SPSS-PC software. The Kolmogorov-Smirnov test was initially used to detect normal distribution. The χ-square test was used to compare qualitative variables and the student's t-test and ANOVA were used to compare quantitative variables with two or more categories, respectively. For those variables not following a normal distribution, the Mann-Whitney U test was used for two independent samples and the Kruskal-Wallis H test for more than two independent variables of equal/different sample sizes.

The Kaplan-Meier estimator was used for the analysis of survival from lifetime data. Survival graphs were constructed and compared using the Log-Rank test. The follow-up time (a quantitative variable measured in months) was calculated by measuring the time between the first cytological or histological confirmation of cancer and the end of the follow-up for each individual. The patient's stage at the end of the follow-up period was considered a dichotomic categorical variable: A "2" value was assigned to those patients with an evaluated event ("death" in the global survival curves or "relapse" in the free of disease survival curves) whereas a "1" value was assigned to censured cases, due to loss of data during the follow-up or because they didn't show the evaluated event (death/relapse) at the end of the study and continued alive.

Results

The initial demographic data indicated that the mean age at diagnosis for the 75 patients was 68.8 ± 9.8 years. The youngest and the oldest patients were 41 and 90 years old, respectively (**Table 1**). The study of the histological types of breast cancers revealed that 94.9% (74 out of the total 78 breast cancers presented in these men) were PBCs. Considering that 3 men presented bilateral breast carcinomas, the total number of males included in our study with PBC was 71. The other four men included: Two cases of primary breast sarcomas (one malignant fibrous histiocytoma and one Kaposi's sarcoma), one case of metastatic breast cancer (of gastric origin) and one case of cutaneous microcystic adnexal carcinoma (or sclerosing carcinoma of sweat duct) located in the breast.

The detailed breakdown of the different histological subtypes for the 74 PBCs showed that 86.5% of these cases were Invasive Ductal Carcinomas Not Otherwise Specified (IDC-NOS), diagnosed in patients with an average age of 69.9 ± 9.0years, with the youngest and the oldest patients 47 and 90 years old, respectively (**Table 2**). The remaining 13.5% cases of PBC were very variable, including subtypes such as infiltrating carcinomas, secretory, mixed and ductal, and they seemed to affect men in a younger range age (41-70 years).

Table 1: Histological types of breast cancer and mean age of the 75 male patients included in this study. (*indicate total number of cancers, not patients)

Histological Types (HiT)	Cases*		Age (Mean± SD)(years)	AgeRange
Primary Breast Carcinoma (PBC)	74	Infiltrating=73	69.0 ± 9.6	41-90
		In situ = 1		
Primary breast sarcomas	2		65.5 ± 12.0	57-74
Metastasis in the breast	1		78	
Microcystic adnexal carcinoma	1		46	
Total Serie (HiT)	n = 78		68.8 ± 9.8	41-90

Table 2: Histological subtypes of the 74 PBCs and mean age of the male patients with these subtypes (71 patients, *indicate total number of PBCs)

Histological Subtypes (PBC)	Cases*	Age (Mean± SD) (years)	Age Range (years)
Invasive Ductal Carcinoma (IDC) NOS	64	69.9 ± 9.0	47-90
Infiltratingpapillary carcinomas	2	69 ± 16.9	56-74

Micropapillary carcinomas	2	65 ± 12.7	57-81
Cribriform carcinoma	1	66	
Secretory carcinoma	1	63	
Mixed Carcinoma	1	70	
Paget's disease (clinical)	1	41	
Infiltrating lobular carcinoma	1	63	
Ductal carcinoma *in situ*	1	69	
Total Serie (PBC)	n = 74	69.0 ± 9.6	41-90

PBCs: Clinical presentations

The clinical presentations of the PBCs varied among the male patients. In our study we were able to trace back the history (patients' reasons for first medical visit) of 68 of the 74 primary breast carcinomas (**Table 3**). All breast cancers were symptomatic, and the appearance of a lump was the main reason for a medical visit in 75% of the cases. The presence of a lump was associated in some of the other cases with a retraction of the nipple/areola, erythema or cutaneous ulceration. Clinical Paget's disease of the breast was found in 3 cases and a posterior finding after diagnosis of metastasis (stage IV) in 2 cases. Only 3% of these carcinomas were discovered accidentally while evaluating other non-oncologic processes.

The initial evaluation by the physician (clinical exploration) is shown in **Table 4**. In agreement with what the patients have reported during their medical visit, the presence of a mass was the most common clinical sign (58.1%), followed by a mass with retraction of nipple and/or areola (20.3%), mass with cutaneous ulceration (8.1%) and eczema/crusty skin (4.1%).

Table 3: Reasons for medical visits by 68 of the male patients with PBCs included in this study

Reasons for Medical Visit (MV)	Cases (Incidence %)
Lump	42 (61.8)
Lump with retraction of nipple and/or areola	8 (11.8)
Nipple retraction	1 (1.5)
Lump with erythema and retraction of nipple and/or areola	1 (1.5)
Cutaneous ulceration with/out palpable lump	9 (13.2)
Eczema or crusty skin (clinical Paget's disease of the breast)	3 (4.4)
Incidental finding due to other benign causes	2 (2.9)
Posterior finding after diagnosis of metastasis	2 (2.9)
Total Serie (MV)	n = 68 (100 %)

Table 4: Initial evaluation by physician of the 74 PBCs included in this study.

Clinical presentations (detected by physician)	Cases (Incidence %)
Mass	43 (58.1 %)
Mass with retraction of nipple and/or areola	15 (20.3 %)
Mass and cutaneous ulceration	6 (8.1 %)
Eczema or crusty skin (clinical Paget's disease of the breast)	3 (4.1 %)
Metastasis and / or Cachexia from disseminated disease	3 (4.1 %)
Mass with erythema and retraction of nipple and/or areola	1(1.4 %)
Mass with retraction of nipple and/or areola and cutaneous ulceration	1 (1.4 %)
Retraction of nipple and/or areola and cutaneous ulceration	1 (1.4 %)
Cutaneous ulceration	1 (1.4 %)
Total Serie (PBC)	n = 74 (100 %)

PBCs: Location

In the 71 male patients with PBCs, 54.1% of these PBCs (40 of 74) were located in the right breast and the rest (45.9%, 34 of 74) were located in the left breast. As previously mentioned, only 3 men (4.2% of the 71) presented bilateral breast carcinoma. Neither multi centricity nor multi focality was observed in any case. **Figure 1** shows the general location of the 74 PBCs with a clear dominance, 83.8% of the cases, in the central or subareolar region.

<table>
<tr><td>Upper inner quadrant
2 (2.7 %)</td><td>Junction upper quadrants 1 (1.4 %)</td><td>Upper outer quadrant
4 (5.4 %)</td></tr>
<tr><td>Junction inner quadrants 2 (2.7 %)</td><td rowspan="2">Central region or subareolar
62 (83.8 %)</td><td>Junction outer quadrants
1 (1.4 %)</td></tr>
<tr><td>Lower inner quadrant
0 %</td><td>Junction lower quadrants 0 %</td><td>Lower outer quadrant
2 (2.7 %)</td></tr>
</table>

Figure 1: Location of the 74 PBCs in the males included in this study

PBCs: Histopathology

The characterization of the histological grade of 61 of the PBCs resulted in 14.8% classified as Grade I, 49.2% as Grade II and 36.1% as Grade III (**Table 5**). None of the tumors presented multifocality (originated from a unique cellular clone) or multicentricity (presented in another breast quadrant other than the one with the dominant mass). Additionally, we didn't observe an extensive intraductal component (when the carcinoma constitutes more than 25% of the primary tumor with intraductal foci).

The presence of intramural vascular invasion was detected in 45.6% of 57 cases, and in 11.4% of 70 cases the intradermal presence of Paget's cells was confirmed. The patient distribution by the pTNM system (Pathological Tumor Node Metastasis) indicated that 23.8% of 67 cases were T2/T3 tumors and 17.9% were T4, with extension to the chest wall/skin/inflammatory. When the axillary invasion was evaluated, 60% of 60 cases were positive, with 50% of these (18 of 36 cases) classified as N1a (involving 1-3 lymph nodes) and 27.7% (10 of 36) as N2a (involving 4-9 lymph nodes).

Based on the results from the histological studies and the pTNM classification system, we found that 29.7% of 64 breast carcinomas were stage I, 34.4% were stage II, 26. 6% were stage III and 7.8% were stage IV. Only 1 of the 64 breast carcinomas was at stage 0.

PBCs: Immunochemistry

The immunochemical profile of the PBCs involved hormonal Receptors for Estrogen (ER) and Progesterone (PR), Human Epidermal Growth Factor Receptor 2 (HER2) and Ki67 proliferative index (**Table 6**). Expression of ER or PR was observed in 61 of 66 (92.4%) and 53 of 62 (85.5%) of the PBCs. The HER2 test performed with immunohistochemistry (IHQ) in 66 of the carcinomas revealed that 77.3% were HER2 negative, 7.6% were HER2 positive and 15.2% were border line. To clarify these results, an amplification study using Fluorescent in Situ Hybridization (FISH) was used to reclassify the borderline HER++/+++ carcinomas found with IHQ. This additional test allowed us to regroup the cases as 12.3% (8 of 65) HER2 positive and 87.7% (57 of 65) as HER2 negative, leaving only 1 case out of 66 as unclear (but only because information about the FISH test was unknown).

Another diagnostic indicator measured in our studyof PBCs was the Ki67-marker of proliferating cells (**Table 6**). The information collected for 53 of the primary breast carcinomas, indicated that 66% of them presented a high proliferation index≥ 20%, with 11.3% and 22.6% of the carcinomas presenting intermediate and low indexes, respectively.

Table 5: Histopathology of the PBCs found in the male patients included in this study

Breast cancer description and staging			Cases	Incidence (%)
Histological Grade	Grade I (well differentiated)		9 of 61	14.8
	Grade II (moderately differentiated)		30 of 61	49.2
	Grade III (poorly differentiated)		22 of 61	36.1
Presence of intratumoral vascular invasion			26 of 57	45.6
Paget's disease, histologically confirmed			8 of 70	11.4
Tumor Size (pTNM)	pTis (carcinoma in situ)		1 of 67	1.5
	pT1 (tumor≤ 20 mm in greatest dimension)		38 of 67	56.7
	pT2 (tumor >20 mm but ≤ 50 mm in greatest dimension)		15 of 67	22.4
	pT3 (tumor > 50 mm in greatest dimension)		1 of 67	1.5
	pT4 (any size, with direct extension to the chest wall/skin/inflammatory)		12 of 67	17.9
Axillary invasion (pTNM)	Negative 40 %	pN0 (no regional lymph node metastasis)	24 of 60	40
	Positive 60 %	pN1mi (micrometastases, 0.2 - 2 mm) pN1a (1-3 lymph nodes, at least one > 2 mm) pN2a (4-9 lymph nodes, at least one > 2 mm) pN3a (> 10 lymph nodes, at least one > 2 mm) pN3c (metastases in ipsilateral supraclavicular lymph nodes)	5 of 60 18 of 60 10 of 60 2 of 60 1 of 60	8.3 30 16.7 3.3 1.7
Staging (pTNM system)		Stage 0	1 of 64	1.6
		Stage I	19 of 64	29.7
		Stage II	22 of 64	34.4
		Stage III	17 of 64	26.6
		Stage IV	5 of 64	7.8

Table 6: Immunochemical profile of the PBCs found in the male patients included in this study

Immunohistochemistry profile		Cases (Incidence %)
Hormonal Receptors	Estrogenic Receptor (ER) positive	61 of 66 (92.4)
	Progesterone Receptor (PR) positive	53 of 62 (85.5)
HER2	HER2 +++ (>80% positive) – IHQ With additional FISH amplification	5 of 66 (7.6) 8 of 65 (12.3
	HER2 ++ (>80% nuclear) – IHQ With additional FISH amplification	10 de 66 (15.2) Unknown
	HER2 -/+ (<80% negative) - IHQ With additional FISH amplification	51 of 66 (77.3) 57 of 65 (87.7)
Ki67 Proliferative index	Low Ki67 (≤ 10%)	12 of 53 (22.6)
	Intermediate Ki67 (< 11% and ≤19%)	6 of 53 (11.3)
	High Ki67 (≥ 20%)	35 of 53 (66.0)

Genetic risk factors for PBCs

This study also involved the collection of the family history of breast cancer in the 71 patients with PBC (**Table 7**). In 28.1% of the patients, the carcinomas could be traced to a family cluster of genetic origin (7% BRCA1/2 positive and 21.1% with at least one family member with cancer) and 25.3% of suspected genetic origin (**Table 5**). The genetic testing results for BRCA1/2, MUTYH and a complete genetic panel of some of the carcinomas are shown in **Table 8**. Despite the fact that no genetic testing has been performed in 80.3% of the 71 patients investigated, and results were pending for 2 patients, the data obtained from the remaining tested 12patients indicated that 33.3% were BRCA2 positive, 25% were BRCA1/2 negative and 8.3% were BRCA1 unclear or MUTYH + BRCA1/2 negative. The amplified genetic study of 3 patients was also negative.

Table 7: Family history of breast cancer in the 71 male patients with PBCs

Clusters of breast cancer within the family	Cases (Incidence %)
Hereditary cancer syndrome (BRCA1/2 positive)	5 (7.0)
Clinical phenotype with suspected genetic origin*	18 (25.3)
At least one family member with cancer (first degree relative)	15 (21.1)
Not family history of cancer (first degree relative)	19 (26.7)
Not data available	14 (19.7)
Total Serie (patients)	n = 71 (100 %)

*Clinical phenotype with suspected genetic origin: The male patients presenting carcinomas had also familial breast cancer, but not necessarily affecting three generations.

Table 8: Genetic studies of BRCA1 and BRCA2 in the 71 male patients with PBCs

Performed genetic testing	Cases (Incidence %)
No genetic testing	57 (80.3)
Pending results	2 (2.8)
Complete genetic panel with negative results*	3 (4.2)
BRCA1 and BRCA2 negative	3 (4.2)
BRCA 1 variant of uncertain results	1 (1.4)
MUTYH positive and BRCA1/BRCA2 negative	1 (1.4)
BRCA 2 positive	4 (5.6)
Total Serie (Patients)	n = 71 (100 %)

* In these 3 cases, a first testing for BRCA1/2 gave negative results. A second amplified genetic study was performed to include testing for PTEN, TP53, CDH1, RAD51C, RAD51D, MLH1, MSH2, MSH6, PALB2, CHEK2, BRIP1, STK11 and ATM. This test also gave a negative result.

Associated primary cancers to PBCs

The analysis of the comorbidity (presence of one or more additional conditions co-occurring) in our male patients with PBC revealed that 11.3% (8 of the 71 patients included in our study) presented chronic hepatopathy. In seven of these cases, due to chronic alcoholism and in one case caused by the hepatitis C virus (data not shown). The evaluation of our patients also revealed that a third of them (33.8%, 24 of the 71) presented multiple primary cancers, besides the primary breast carcinoma, with 14% of them (10 patients) showing three or more cancers (**Table 9**). The most common locations for these associated cancers were: Prostate (8 adenocarcinomas), skin (4 basal and 3 squamous cell carcinomas), colon (4 adenocarcinomas) and bladder (4 carcinomas). Other less frequent malignant tumors affected the kidneys, pancreas and larynx.

We were able to confirm the presence of systemic relapse/recurrence in 19 (26.8%) of the 71 males with breast cancer. **Tables 10 and 11** show the initial and final clinical presentations of the different types of metastases found in 16 of these 19 patients. More than 50% of the initial metastasis involved the bone, lung and/or pleura and skin/soft tissue, and only a 6.3% of the metastases affected more than three areas (multiple locations). The final spread patterns for the metastases found in these patients revealed that all 16 patients were affectedovertime atmultiple areas, with 43.75% of the patients with metastasis affecting two areas and 31.25% of the patients affected in more than three areas, a 5-fold increase when compared with the initial clinical presentation.

Recurrence and survival rate

In our study we observed that only 5 (7%) of the 71 male patients with PBCs presented locoregional recurrence (LRR). The intervals between diagnostic and LRR in these 5 maleswere 12, 15, 59, 96 and 99 months (data not shown).

The Kaplan-Meier survival curve for our study of 74 PBCs indicated that the overall 5-year survival rate wasnear 80% and continued to decrease at a similar decline until year 7-8, showing a steeper decrease at the 8-10year interval.This indicated that from the time of initial diagnosis, the survival rate at 10 years decreased more than 40%.

Table 9: Types of primary cancers and other malignant tumors found in 24 of the 71 males with PBCs

Patient	Breast	Prostate	Cutaneous*	Colon *	Bladder	Lung	Other malignant tumors *
1	*Bilateral*	------	------	------	------	------	------
2	*Bilateral*	------	------	------	------	------	------
3	*Bilateral*	*Prostate*	------	------	------	------	------
4	*Unilateral*	*Prostate*	------	------	------	------	------
5	*Unilateral*	*Prostate*	*BCC*	------	------	------	------
6	*Unilateral*	*Prostate*	*BCC*	------	------	------	*Kidney*
7	*Unilateral*	*Prostate*	*BCC*	*CRC*	------	------	------
8	*Unilateral*	*Prostate*	------	*CRC*	------	------	------
9	*Unilateral*	------	*BCC*	------	------	------	------
10	*Unilateral*	*Prostate*	*SCC*	------	------	------	------
11	*Unilateral*	*Prostate*	*SCC*	------	------	------	*Angiosarcoma*
12	*Unilateral*	------	*SCC*	------	------	------	------
13	*Unilateral*	------	*Melanoma*	------	------	------	------
14	*Unilateral*	------	------	*CRC*	------	------	*PDAC*
15	*Unilateral*	------	------	*CRC*	*Bladder*	------	------
16	*Unilateral*	------	------	------	*Bladder*	------	------
17	*Unilateral*	------	------	------	*Bladder*	------	------
18	*Unilateral*	------	------	------	*Bladder*	------	*CLL*
19	*Unilateral*	------	------	------	------	*Lung*	------
20	*Unilateral*	------	------	------	------	*Lung*	------
21	*Unilateral*	------	------	------	------	------	*Larynx*
22	*Unilateral*	------	------	------	------	------	*Kidney*
23	*Unilateral*	------	------	------	------	------	*Gastric*
24	*Unilateral*	------	------	------	------	------	*Glioma*

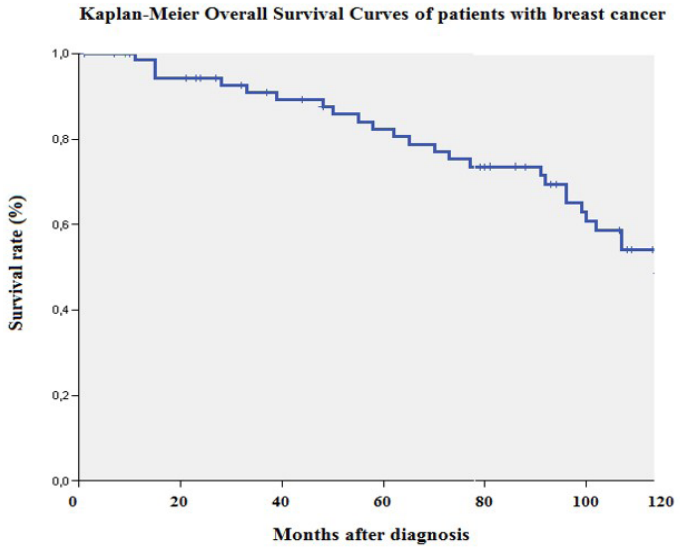
*BCC: Basal Cell Carcinoma; CLL: Chronic Lymphocytic Leukemia; CRC: Colorectal Carcinoma; PDAC: Adenocarcinoma of the Pancreatic Biliary Duct; SSC: Squamous Cell Carcinoma

Table 10: Types of metastases initially found in 16 of the patients with PBC

Distant metastases: Initial clinical presentations	Cases (Incidence %)
Bone Metastases	5 (31.1)
Lung and/or pleural metastases	4 (25)
Skin and soft tissue metastases	2 (12.6)
Bone and lung metastases	1 (6.3)
Bone and liver metastases	1 (6.3)
Liver and lung metastases	1 (6.3)
Liver metastases and mesenteric adenopathies	1 (6.3)
Multiple locations (more than three)	1 (6.3)
Patients	n = 16 (100 %)

Table 11: Types of final patterns for metastasis found in 16 patients with PBC. A "visceral" pattern indicates the affectation of the pleura, lung and/or liver

Distant metastases: Final spread patterns	Cases (Incidence %)
Multiple metastases: Visceral and bone	4 (25)
Multiple metastases: Visceral	3 (18.9)
Multiple metastases: Visceral, bone, brain and ganglia	2 (12.6)
Multiple metastases: Visceral, bone and ganglia	1 (6.3)
Multiple metastases: Visceral, bone and cutaneous	1 (6.3)
Multiple metastases: Visceral and ganglia	1 (6.3)
Multiple metastases: Visceral, cutaneous and ganglia	1 (6.3)
Multiple metastases: Visceral and cutaneous	1 (6.3)
Bone Metastases	1 (6.3)
Multiple metastases: Cutaneous and ganglia	1 (6.3)
Patients	n = 16 (100 %)



Diagnosis	Nº cases	Nº events	Censored	
			Nº	Percentage
Breast cancer male	74	44	30	40,5 %

Figure 2: Kaplan-Meier survival curve of patients with PBCs.

Discussion

Breast cancer is an important health problem that affects women in 99% of the cases, being an uncommon entity in men with an incident ratio of 1:1000. Because this disease is rare among men, our knowledge of its biological characteristics, risk factors, clinical presentations and prognosis is very limited, and although it shares many similarities with breast cancer in women, there are also important differences.

In 1979, Yap et al. reported an incidence rate of 0.9% in a study of MBC in 90 men [10]. A similar percentage was found in a 1988 study of 1075 breast cancers in Vigo (Spain), with 10 male cases (3), and in another study of 8355 breast cancers diagnosed between 1990-1999 in 24 hospitals in Cataluña (Spain), where 77 cases were MBC [11].

Similarly, to what happens in women, exposure to ionizing radiation is an important risk factor for breast cancer in males, with a period of induction of 20-25 years [12]. Specifically, the radiation related with the treatment for Hodgkin's disease is considered of high risk (RR = 7.2) [13]. Other environmental and work factors that are often mentioned in the literature and may play a role in male breast cancer are exposure to mammary carcinogens (petroleum products, organic petroleum-based solvents, polycyclic aromatic hydrocarbons) and endocrine disruptors (alkyl phenolic compounds). Additionally, high temperature environments (ovens, steel factories) have been reported to induce testicular abnormalities and failure, and therefore increase 2-4 times the risk for breast cancer in males working in these conditions. Igci et al. mentioned in a study [14] that obesity and chronic liver disease might also be contributing factors.

Clinical presentations

The average age at diagnosis of PBCs for our 71 male patients was 69 ± 9.6 years. Considering that three of these men presented bilateral carcinomas, the total count of detected PBCs was considered to be 74. The mean age found in our study coincide with the mean age found in a study of 24 PBCs (22 men, 2 with bilateral carcinomas) described by McKinley et al. [15]. Other studies have reported average ages oscillating between 63 and 68 years, with a percentage of MBC representing 0.5-0.8% of all cases of PBC [16-24]. Unlike breast cancer in women, where a bimodal age distribution for incidence is found, with peaks at 55 and 65 years [3], the incidence of breast cancer in men increases at a constant rate with age. In fact, MBC is considered a disease of advanced age (over 65 years) with distinctive features from female breast cancer [25].

The most common histological type of PBC found in our study of males was the IDC-NOS, representing 86.5% (64 of 74) of the cases. This frequency was similar (84.7%) to what Burga et al [26] observed in their study of 778 cases in 2006. The breast tissue in boys and girls is similar until puberty. During male puberty, unlike in females, the levels of testosterone increase, causing the involution and atrophy of the ducts. Therefore, the breast of an adult male consists of subcutaneous adipose tissue with some remnants of ductal tissue in the subareolar region, and the development of lobules is not observed unless exposure to high hormonal concentrations (estrogens and progesterone) has happened. In adult females, the breast tissue contains ducts and lobules at the end of those ducts, and infiltrating lobular carcinoma represent almost 10% of all the PBCs. In men, however, the absence of acinose glands and lobules in their breasts makes this type of tumors less frequent [27,28]. In our study we found that only 1 of the 74 PBCsevaluated (1.35%) was diagnosed as an infiltrating lobular carcinoma.

Considering that the majority of the mammary tissue in adult males is located in the subareolar central region of the breast, it is logical to think that the most common clinical presentationis a mass in that area. In fact, 75% of our patients mentioned during their initial medical visit the presence of a lump, with a few cases mentioning additional retraction of nipple and/or areola or cutaneous ulceration. The evaluation by the physician confirmed patients' descriptions, with only a 4.1% of cases with clinical breast affectation with Paget's disease, and 4 cases of accidental findings while exploring other pathologies.

Histology and immunochemistry

MBC is, unfortunately, often diagnosed at a more advanced stage than in females, probably due to a lack of knowledge and understanding of men's risk for this disease and the absence of preventive exams. Due to the low amount of breast tissue (fibroglandular parenchyma) in males, cutaneous and pectoral muscle affectations and lymph node involvement are frequently found (40-50% of the cases), however, only 3.8% present de novo metastases [29]. **Tables 5-6** in this study show the clinical characteristics, histology and immunochemistry of the PBCs found in our male patients, as well as the patterns of metastasis observed. Our data indicates that in more than 50% of the cases, when these carcinomas are detected, they are already moderately differentiated, with axillary and intratumoral vascular invasion, an increasing tumor size and a stage II/III (pTNM system).

MBC is characterized by a higher frequency of tumors with positive hormonal receptors. In our study we found that 92.4% of 66 cases of PBCs were ER positive, and these patients could benefit from a treatment with tamoxifen, and unlike from the use of aromatase inhibitors [30]. Despite the known benefits in survival rates of treatments with tamoxifen, some studies indicate that a great percentage of males interrupt the treatment before the 5-year mark due to their lower tolerance to the

treatment, contributing to a lower success in males from this when compared with females [31].

MBCs are very sensitive to hormonal changes. The hormonal imbalance between an excess of estrogen and a deficiency of androgens (testosterone) increases the risk. This imbalance can happen endogenously, due to abnormalities in the testicles, such as undescended testicles (12 times higher risk), orchitis or testicular lesions [32], which decrease the production of androgens. They can also be due to hepatic dysfunctions and chronic liver diseases such as cirrhosis, because of a decrease in the hepatic inhibition of estrogens and an increase in their peripheric expression [33]. In our study, we paid special attention to patients' previous history of hepatopathy. We observed that 11.3% (8 of 71) of the MBCs had a chronic hepatopathy: Seven cases of chronic alcoholism and one case of chronic hepatitis caused by hepatitis C virus.

Klinefelter syndrome (genotype XXY) is also considered a strong risk factor for MBC (50-fold higher compared to a male with normal genotype) and can represent 3-7.5% of the cases [34]. This syndrome is characterized by gynecomastia, testicular dysgenesis and a disequilibrium in the hormonal levels of estrogen (elevated) and androgens (decreased). Exogenous causes, such as treatments for prostate cancer, or androgenic and estrogenic therapies for transgender treatments can also increase the risk of breast cancer.

Genetics

Family history of first-degree cancer is associated with a higher risk for breast cancer. Studies show that approximately, 15-20% of MBCs have family history of breast or ovarian cancer, and only 10% can be traced to a known genetic origin (18).In our study, more than 50% of the patients had a hereditary cancer syndrome, a family cluster of genetic origin, or at least one family member with cancer (first degree relative).

BRCA2 mutations can be present in up to 14% of the males with breast cancer, with BRCA1 mutations occurring very rarely (0-4%), except in individuals of Ashkenazi's Jewish origin, where they can represent 4.5% [35]. Other genes found to be associated to MBC include CHECK2, PALB2, PTEN (Cowden's Syndrome), TP53 (Li-Fraumeni's Syndrome), and genes involved in repair (Lynch's Syndrome) [36-39]. The CYP17 gene, that codes for an enzyme responsible for producing sexual steroids, has also been proposed as a candidate gene. Despite the discovery of these several genes, the presence of a BRCA2 mutation continues to be considered of higher risk for breast cancer. In our study 4 of the 12 tested patients with PBC (33.3%) presented this type of mutation.

An association between specific genetic mutations and some other types of cancers, besides breast cancer, is well documented. The breast cancer linkage consortium reported in 1999 that BRCA2 mutations increase the risk of prostate cancer (RR = 4.65), bile vesicular (RR = 4.97), pancreas (RR = 3.51) and malign melanoma (RR = 2.58) [40]. Additionally, BRCA1 mutations are associated with a higher risk (two times higher) of colorectal cancer, pancreatic (three times higher) and gastric (four times higher) when compared with the general population [41]. Therefore, it is important for all men diagnosed with breast cancer to receive genetic counseling and testing. In our study, what caught our attention was the fact that, in spite of recording more than 50% of the patients with a family history of known cancers, only 20% of these patients have had a genetic study done. This absence of genetic testing could be due to a lack of resources or lack of awareness by the physicians or the patients. Regardless of the motive for this gap, it is crucial to recognize the importance of these types of tests and the existence of ongoing projects where these individuals could be perfect candidates (for example NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Genetic/Familial High-Risk Assessment: Breast and OvarianVersion 3.2019 - January 18, 2019).

Metastases and survival rate

Patients with previous history of breast cancer have a high probability of having a second contralateral breast cancer and/or associated non-mammary primary cancers, but published data is inconsistent [42-44]. The possible causes for the development of multiple cancers seem to be closely related to a late appearance of the breast cancer in the male and probably linked to genetic factors that predispose them to the development of malignant neoplasia's. In our study, we observed that up to one third of the patients (33.8%, 24 of 71 males) presented multiple primary cancers and 14% (10 of 71) showed at least three different types. The non-mammary cancers associated more frequently were: 8 prostate adenocarcinomas, 4 basaliomas, 4 colorectal adenocarcinomas and 4 bladder carcinomas. The follow-up of 16 of these patients revealed distant metastases affecting more than three areas overtime.

Some studies have shown that MBC has a lower survival rate than breast cancer in females, with a morbidity risk 41% higher in the male population and a survival rate lower at 5 and 10 years (85% and 73% respectively) than those in the female population (90 and 85% respectively) [45]. These differences in the prognosis could be explained as a consequence of the specific biological characteristics of breast cancer in males: A higher histological grade and a higher Ki67 (marker of proliferating cells). The patients included in our study presented a decreased survival rate to 80% at 5-year and less than 60% at a 10-year period, mostly due to the increased presence of multiple metastases affecting vital organs, and the difficulty to treat these metastases successfully in patients of advanced age.

Closing remarks

The preferred current treatment for MBC is the mastectomy followed by a selective biopsy of the sentinel lymph node and/or axillary dissection in case of a confirmed affectation of the lymphatic nodes. The systemic adjuvant treatment with chemotherapy and/or hormone therapy is decided, as in the case with females, based on the age of the patient, the stage of the disease and the stage of the hormonal receptors. In this regard, the advanced age of most of the patients at the time of the diagnosis, makes difficult the application of more aggressive treatments.

MBC continues to be a rare disease at this time, but due to its higher mortality and comorbidity, it should be considered a topic of interest to improve its prevention, treatment and survival rate. It is necessary to increase the appropriate education at health care centers and create awareness in the society about the importance of its early diagnosis.Additionally, since we also know that a high number of these patients and their family members are carriers of genes that predispose them to cancer, we should provide appropriate genetic counseling and testing, and the correct clinical follow-up to these patients and their relatives.

References

1. Breasted JH. The Edwin smith papyrus Chicago. The University of Chicago press. 1930: 403-406.
2. Ravandi-Kashani F, Hayes TG. Male breast cancer. A review of the literature. Eur J Cancer. 1998; 9: 1341-1347.
3. Cameselle-Teijeiro JF. Epidemiología y factores de riesgo del cáncer de mama en el sur de Galicia (Tesis doctoral). Universidad de Santiago de Compostela. 1988.
4. Mohamed M, El-Gazayerli and Abdel-Aziz AS. On bilharziasis and male breast cancer in Egypt: A preliminary report and review of the literature. Br J Cancer. 1963; 17: 566-571.
5. Meijer-van Gelder MEI, Look MP, Bolt-de Vries J, Peters HA, Klijn JG, et al. Clinical relevance of biological factors in male breast cancer. Breast Cancer Res Treat. 2001; 68: 249-260.
6. Rayson D, Erlichman C, Suman VJ, Roche PC, Wold LE, et al. Molecular markers in male breast carcinoma. Cancer. 1998; 83: 1947-1955.
7. White J, Kearins O, Dodwell D, Horgan K, Hanby AM, et al. Male breast carcinoma: Increased awareness needed. Breast Cancer Res. 2011; 13: 219.
8. Spiegel RL, Miller KD, Jemal A. Cancer statistics. Cancer J Clin. 2017; 67: 7-30.
9. SascoAJ, LowenfelsAB, Pasker-DejongP. Review article: Epidemiology of male breast cancer. A meta-analysis of published case control studies and discussion of selected aetiological factors. Int J Cancer. 1993; 53: 538-548.
10. Yap HY, Tashima CK, Blumenschein GR, Eckles NE. Male breast cancer: A natural history study. Cancer. 1979; 44: 748-754.
11. Thomas DB, Rosenblatt K, Jimenez LM, McTiernan A, Stalsberg H, et al. Ionizing radiation and breast cancer in men (United States). Cancer Causes Control. 1994; 5: 9-14.
12. Ottini L, Palli D, Rizzo S, Federico M, Bazan V, et al. Male breast cancer. Crit Rev Oncol Hematol. 2010; 73: 141-155.
13. Culell P, Solernou L, Tarazona J, Roma J, Martí E, et al. Male Breast Cancer: A multicentric study. Breast J. 2007; 13: 213-215.
14. Igci A, Tukenmez M, Ozkurt E. Male breast cancer. Breast disease: Management and Therapies. 2016; 23: 389-403.
15. McKinley N, McCain S, Kirk S. Long term follow up of male breast cancer. Ulster Med J. 2017; 86: 177-180.
16. Goss PE, Reid C, Pintilie M, Lim R, Miller N. Male breast carcinoma: A review of 229 patients who presented to the princess margaret hospital during 40 years: 1955-1996. Cancer. 1999; 85: 629-639.
17. Anderson WF, Althuis MD, Brinton LA, Devesa SS. Is male breast cancer similar or different than female breast cancer? Breast Cancer Res Treat. 2004; 83: 77-86.
18. Giordano SH, Cohen DS, Buzdar AU, Perkins G, Hortobagyi GN. Breast carcinoma in men: A population-based study. Cancer. 2004; 101: 51-57.
19. Hodgson NC, Button JH, Franceschi D, Moffat FL, Livingstone AS. Male breast cancer: Is the incidence increasing? Ann Surg Oncol. 2004; 11: 751-755.
20. Anderson WF, Jatoi I, Tse J, Rosenberg PS. Male breast cancer: A population-based comparison with female breast cancer. J Clin Oncol. 2010; 28: 232-239.
21. Masci G, Caruso M, Caruso F, Salvini P, Carnaghi C, et al. Clinicopathological and immunohistochemical characteristics in male breast cancer: A Retrospective Case Series. Oncologist. 2015; 20: 586-592.
22. Cronin PA, Romanoff A, Zabor EC, Stempel M, Eaton A, et al. Influence of age on the clinical outcome of breast cancer for men and the development of second primary cancers. Ann Surg Oncol. 2018; 25: 3858-3866.
23. Yadav S, Karam D, Bin Riaz I, Xie H, Durani U, et al. Male breast cancer in the United States: Treatment patterns and prognostic factors in the 21st century. Cancer. 2020; 126: 26-36.
24. Lomma C, Chan A, Chih H, Reid C, Peter W. Male Breast Cancer in Australia. Asia Pac J Clin Oncol. 2020: 1-6.
25. Gucalp A, Traina TA, Eisner JR, Parker JS, Selitsky SR, et al. Male breast cancer: A disease distinct from female breast cancer. Breast cancer research and treatment. 2019; 173: 37-48.
26. Burga AM, Fadare O, Lininger RA, Tavassoli FA. Invasive carcinomas of the male breast: A morphologic study of the distribution of histologic subtypes and metastatic patterns in 778 cases. Virchows Archiv. 2006; 449: 507-512.
27. Willsher PC, Leach IH, Ellis IO, Bell JA, Elston CW, et al. Male breast cancer: Pathological and immunohistochemical features. Anticancer Res. 1997; 17: 2335-2338.
28. Hecht JR, Winchester DJ. Male breast cancer. Am J Clin Pathol. 1994; 102: S25-30.
29. Cardoso F, Bartlett JMS, Slaets L, van Deurzen CHM, van Leeuwen-Stok E, et al. Characterization of male breast cancer: Results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. Ann Oncol. 2018; 29: 405-417.
30. Harlan LC, Zujewski JA, Goodman MT, Stevens JL. Breast cancer in men in the United States: A population-based study of diagnosis, treatment, and survival. Cancer. 2010; 116: 3558-3568.
31. Xu S, Yang Y, Tao W, Song Y, Chen Y, et al. Tamoxifen adherence and its relationship to mortality in 116 men with breast cancer. Breast Cancer Res Treat. 2012; 136: 495-502.
32. Thomas DB, Jimenez LM, McTiernan A, Rosenblatt K, Stalsberg H, et al. Breast cancer in men: Risk factors with hormonal implications. Am J Epidemiol. 1992; 135: 734-748.
33. Sørensen HT, Friis S, Olsen JH, Thulstrup AM, Mellemkjaer L, et al. Risk of breast cancer in men with liver cirrhosis. Am J Gastroenterol. 1998; 93: 231-233.
34. Gucalp A, Traina TA, Eisner JR, Parker JS, Selitsky SR, et al.

Male breast cancer: A disease distinct from female breast cancer. Breast Cancer Res Treat. 2019; 173: 37-48.

35. Struewing JP, Coriaty ZM, Ron E, Livoff A, Konichezky M, et al. Founder BRCA1/2 mutations among male patients with breast cancer in Israel. Am J Hum Genet. 1999; 65: 1800-1802.

36. Rizzolo P, Silvestri V, Tommasi S, Pinto R, Danza K, et al. Male breast cancer: Genetics, epigenetics, and ethical aspects. Ann Oncol. 2013; 24: viii75-viii82.

37. Ding YC, Steele L, Kuan CJ, Greilac S, Neuhausen SL. Mutations in BRCA2 and PALB2 in male breast cancer cases from the United States. Breast Cancer Res Treat. 2011; 126: 771-778.

38. Pritzlaff M, Summerour P, McFarland R, Li S, Reineke P, et al. Male breast cancer in a multi-gene panel testing cohort: Insights and unexpected results. Breast Cancer Res Treat. 2017; 161: 575-586.

39. Boyd J, Rhei E, Federici MG, Borgen PI, Watson P, et al. Male breast cancer in the hereditary nonpolyposis colorectal cancer syndrome. Breast Cancer Res Treat. 1999; 53: 87-89.

40. Breast cancer linkage consortium. Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst. 1999; 91: 1310-1316.

41. Brose MS, Rebbeck TR, Calzone KA, Stopfer JE, Nathanson KL, et al. Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. J Natl Cancer Inst. 2002; 94: 1365-1372.

42. Hemminki K, Scélo G, Boffetta P, Mellemkjaer L, Tracey E, et al. Second primary malignancies in patients with male breast cancer. Br J Cancer. 2005; 92: 1288-1292.

43. Auvinen A, Curtis RE, Ron E. Risk of subsequent cancer following breast cancer in men. J Natl Cancer Inst. 2002; 94: 1330-1332.

44. Satram-Hoang S, Ziogas A, Anton-Culver H. Risk of second primary cancer in men with breast cancer. Breast Cancer Res. 2007; 9: R10.

45. Liu N, Johnson KJ, Ma CX. Male Breast Cancer: An updated surveillance, epidemiology, and end results data analysis. Clin Breast Cancer. 2018; 18: e997-1002.