Original Article

Male Breast Cancer: A Study on Clinical and Biological Characteristics from a Portuguese Certified Breast Center

Cancro de Mama Masculino: Estudo das Características Clínicas e Biológicas de um Centro de Mama Certificado Português

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ABSTRACT

Introduction: To describe the clinical and biological characteristics of breast carcinoma in men, to compare with the characteristics observed in women and to evaluate the results of the treatment.

Methods: A retrospective analysis was conducted involving all male patients with breast carcinoma treated between 2000 and 2022 at the Breast Center of the Unidade Local de Saúde de São João, Porto, Portugal. A 3:1 random selection of women, treated over the same period, was made for comparison. Patients were followed up until 2023 and survival analyses were performed.

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Results: Thirty-two men and ninety-six women were analyzed**.** The median age of male patients at diagnosis was 62 years**.** Compared to women, there was a significantly higher percentage of male patients over the age of 50 years. *BRCA2* mutations were identified in a significantly higher percentage of men. We observed larger tumor sizes in male patients (pT2 25.0%), a higher percentage of lymph node metastasis (pN1 40.6%) and a higher percentage of distant metastasis (21.9%) compared with female patients. Significant differences were found in the type of surgery (90.6% of men underwent mastectomy), the use of chemotherapy and axillary lymph node dissection (46.9% and 34.4% of men, respectively). Male patients diagnosed with breast cancer presented a lower cumulative survival than female patients. Age over 50 years and stage IV tumors increased the risk of death.
Conclusion: Male patients were diagnosed at an older age with more advanced tumors, which may explain the worse survival rates compared to female patients. Male breast cancer is a significant condition that needs increased awareness, to promote early detection.

Keywords: Breast Neoplasms, Male/drug therapy; Breast Neoplasms, Male/radiotherapy; Breast Neoplasms, Male/surgery; Mastectomy

RESUMO

Introdução: Descrever as características clínicas e biológicas do carcinoma da mama em homens, comparar com as características observadas em mulheres e avaliar os resultados do tratamento.
Métodos: Foi realizada uma análise retrospetiva envolvendo todos os doentes do sexo masculino com carcinoma da mama tratados entre 2000 e 2022 no Breast Center da Unidade Local de Saúde de São João, Porto, Portugal. Para comparação, foi feita uma seleção aleatória de mulheres na proporção de 3:1, tratadas no mesmo período. Os doentes foram acompanhados até 2023 e foram realizadas análises de sobrevivência.
Resultados: Foram analisados 32 homens e 96 mulheres. A mediana de idade ao diagnóstico nos homens foi de 62 anos. Comparativamente às mulheres, verificou-se uma percentagem significativamente maior de doentes masculinos com mais de 50 anos. As mutações *BRCA2* foram identificadas com uma frequência significativamente superior nos homens. Observou-se um maior tamanho tumoral nos doentes masculinos (pT2 25,0%), uma maior percentagem de metástases nos gânglios linfáticos (pN1 40,6%) e uma maior percentagem de metástases à distância (21,9%) em comparação com as doentes femininas. Foram encontradas diferenças significativas no tipo de cirurgia (90,6% dos homens foram submetidos a mastectomia), na utilização de quimioterapia e na dissecção dos gânglios linfáticos axilares (46,9% e 34,4% dos homens, respetivamente). Os doentes masculinos diagnosticados com cancro da mama apresentaram uma menor sobrevivência cumulativa em comparação com as doentes femininas. Idade superior a 50 anos e tumores em estádio IV aumentaram o risco de morte.
Conclusão: Os doentes do sexo masculino foram diagnosticados em idades mais avançadas e com tumores mais agressivos, o que pode justificar as taxas de sobrevivência inferiores em comparação com as mulheres. O cancro da mama masculino é uma condição significativa que necessita de maior sensibilização para promover o diagnóstico precoce.

Palavras-chave: Mastectomia; Neoplasias da Mama Masculino/cirurgia; Neoplasias da Mama Masculino/radioterapia; Neoplasias da Mama Masculino/tratamento farmacológico

INTRODUCTION

Currently, breast cancer (BC) is the most frequently diagnosed cancer worldwide, accounting for 1 in 8 cancer diagnoses.[1] In Europe, in 2022, the incidence and mortality rates of BC in women were estimated up to 190 new cases and 45 deaths per 100 000 women. For men, BC incidence rates were estimated below 3 new cases and mortality rates below 1 death per 100 000 men.[1] In Portugal, in 2020, the incidence of BC in women was 136.2 per 100 000 and the gross mortality was 32.7 per 100 000 cases. The incidence and mortality rates of male BC were, respectively, 1.6 and 0.5 per 100 000 cases. [3,4] Just as this data supports, male BC is a rare disease that comprises about 1% of all diagnosed breast cancers.[5,6]

Despite its rarity, several studies investigated risk factors for male BC including age, genetics, family history, obesity, radiation exposure, liver diseases, alcohol consumption, Klinefelter syndrome, estrogen exposure, testicular diseases, and mutations in *CHECK2*, *BRCA1*, *BRCA2*, *PALB2*, *ATM*, and *PTEN* genes.[7-14]

Male and female BC share genetic, hormonal, and environmental factors, but differ in epidemiology with lower incidence and later onset in men. From a clinical and biological point of view, it has been described that BC in men and women differ in the frequency of histological types and in the expression of hormone receptors and epidermal growth factor receptor 2 (HER2).[6,15,16] A "no special type" carcinoma (NST) with high expression of estrogen receptors and progesterone receptors has been found in the vast majority of cases.[17,18] In contrast to women, mutations in the *BRCA2* gene seem predominant.[11,16]

Several studies suggest that male patients with BC are diagnosed at a more advanced stage of the disease, with tumors of higher malignancy grade, which compromises prognosis and leads to higher mortality.[19] Men also have a higher prevalence of positive hormone receptors, a lower sensitivity to adjuvant therapy, and a lower likelihood of conservative surgery.[20-22]

Since it is a rare pathology, therapeutic strategies (surgery, radiotherapy, chemotherapy and hormone therapy) are defined according to the results of clinical trials in women.[18,23]

Assuming the differences presented, several investigators argue that BC in men is a distinct disease with peculiar biological and clinical characteristics, which justifies that the generalization and adoption of clinical applications extrapolated from studies performed in women with BC may be considered inappropriate.[17,18,20,23]

The rising trend and insufficient studies warrant regional data aggregation, as conducted here, for broader national or international analysis. Further studies are crucial for understanding and improving outcomes in male BC.

The main objective of this study was to describe the clinical and biological characteristics of BC in men treated and followed-up at the Breast Center of Unidade Local de Saúde de São João (ULSSJ), Porto, Portugal. Secondarily, we intended to compare with the characteristics observed in women with BC in this Center and to evaluate the results of the treatment.

METHODS

1. TYPE OF STUDY

A retrospective study was conducted involving all male patients with BC treated and followed at the Breast Center of the ULSSJ, Porto, Portugal, from 01.01.2000 to 31.12.2022. To compare with the characteristics observed in men, we used the data of all female patients registered in the European Society of Breast Cancer Specialists (EUSOMA) database from the same Breast Center. Therefore, the study was based on the Breast Center database, on the hospital-based Cancer Registry and on the patients' digital records.

2. INCLUSION AND EXCLUSION CRITERIA

For this study, we defined as inclusion criteria male gender, age over 18 years, confirmation of the diagnosis of male BC and complete follow-up at the ULSSJ Breast Center. Female gender, age under 18 years, secondary breast tumors from another primary cancer site and lack of information were exclusion criteria.

3. DEFINITION OF THE SAMPLE OF PATIENTS TO BE STUDIED

Fig. 1 presents the flowchart of the participants. From a total of 55 male BC patients, 23 were excluded, of which 6 had a pathology misclassification by assigning the wrong code (3 diagnosed with other cancers and 3 diagnosed with other pathologies), 3 presented only benign lesions and 2 had a gender misclassification. When retrieving data from the digital records, we found 12 male patients without clinical/follow-up information. To obtain a comparable sample of female patients, from a total of 3029 patients registered in the EUSOMA database, we started by excluding 13 male patients enrolled in this database. We also excluded 1046 patients diagnosed before 01.01.2018 and after 31.12.2022, since before 2018 there was no reliable record for most of the variables analyzed for male patients. We further excluded 44 patients who had a previous diagnosis of breast carcinoma and 3 who had bilateral malignant disease. Of the remaining 1923 female patients, a 3:1 random selection was carried out, obtaining a final number of 96 women included in this study.

4. VARIABLES

All clinical and biological data was collected through a detailed review of the patient's medical records. Information on age at diagnosis, family history, smoking history, body mass index, *BRCA1/2* status, tumor histological type and histological grade, hormone receptor status, HER2 status, Ki-67 index, and lymph node status was retrieved. Tumor stage, including pathological tumor size (pT), pathological axillary nodal status (pN) and distant metastasis (M) was recorded according to the TNM classification system (8th edition).[24] The histological type was evaluated according to World Health Organization classification.[25] Molecular subtype was obtained by integrating the following data: estrogen receptors, progesterone receptors, histological grade and HER2 status. Information on the breast surgical treatment, the need for axillary lymph

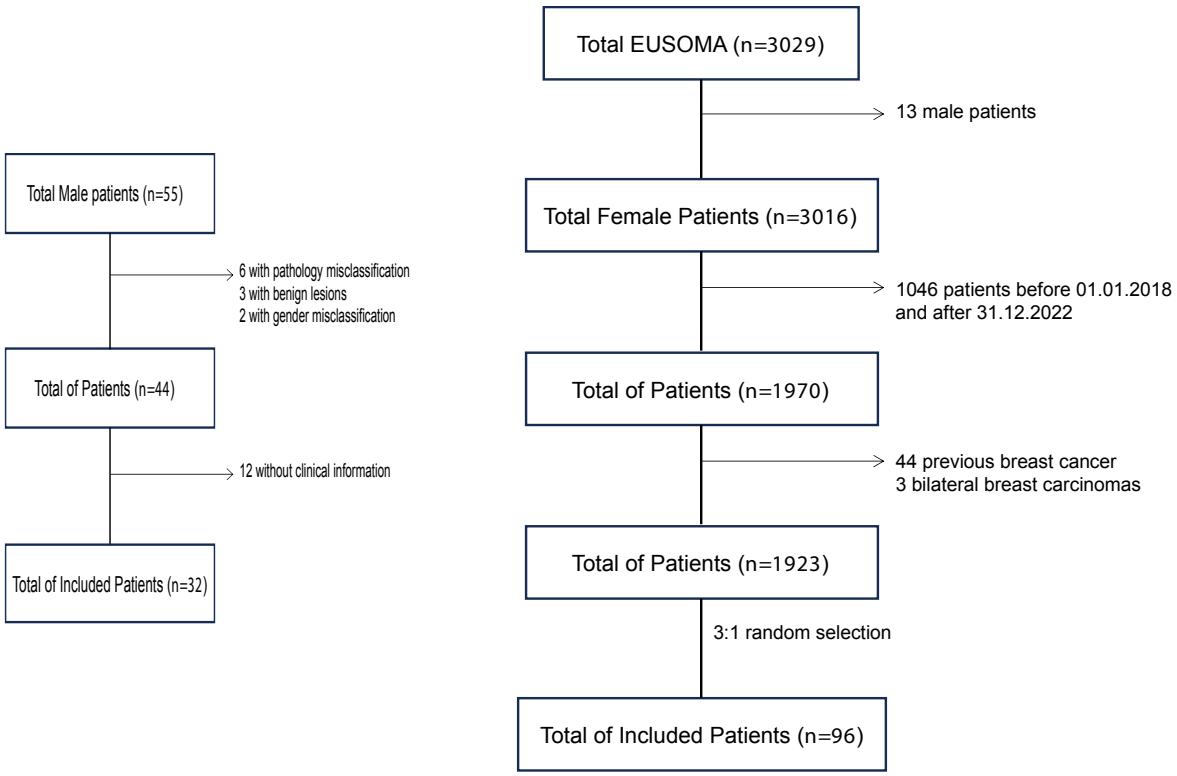

Figure 1. Flowchart of patients' selection.

node dissection, neoadjuvant/adjuvant treatments and the vital status at the last appointment were also registered.

5. CLINICAL EVALUATION

Every patient was assessed by a surgical oncologist on the first visit to the Breast Centre; every patient underwent mammography and breast and axillary ultrasound; diagnosis was established in the multidisciplinary team meeting as well as the treatment plan. Patients were informed of the diagnosis by the surgical oncologist and the treatment plan was discussed with the patient.

6. SURGICAL TREATMENTS

Patients could be proposed for total mastectomy (excision of the entire breast gland, of the nipple-areolar complex (NAC) and of the skin that covers the breast) or breast conservation (partial mastectomy and preservation of NAC). The nodal staging was obtained with the sentinel node biopsy; according to the nodal stage, the patient could be proposed to axillary lymph node dissection, *i.e.*, excision of the Berg level I+II axillary lymph nodes.

7. NEOADJUVANT AND ADJUVANT TREATMENTS

Depending on the tumor stage, molecular features, patient health status and preferences, the adjuvant therapy available may have included radiotherapy, chemotherapy, targeted therapy and/or hormonal therapy.

Adjuvant radiotherapy could be performed, not only after breast conservative surgery but also after total mastectomy, when indicated.

A neoadjuvant approach could be proposed in more advanced tumors (>2 cm) with lymph node involvement, especially in subtypes highly sensitive to chemotherapy, such as "triple-negative" and "HER2-positive". Male patients with metastatic cancer could be proposed to hormonal therapy, chemotherapy and/or HER2-targeted therapy. The personalized decision was taken at the multidisciplinary team meeting.

Tamoxifen was the standard adjuvant hormonal treatment for male breast cancer patients, or a combination of aromatase inhibitors plus a luteinizing hormone-releasing hormone agonist if a strong contraindication exists.

8. FOLLOW-UP

Patients were regularly followed up at the out-patients office twice in the first year and yearly thereafter; they were submitted to physical examination of the breast area, axilla and peri-clavicular area, to mammography and to breast and axilla ultrasound.

9. DATA ANALYSIS

All data was analyzed using IBM® SPSS® Statistics version 26 (Chicago, Illinois). Descriptive statistics for continuous variables were expressed as the median and range. Descriptive statistics for categorical variables were presented as frequencies and percentages. The Chi-square or Fisher's exact test, as appropriate, was used for comparison of proportions, while the Mann-Whitney test was used for comparison of medians. Survival analyses were performed using Cox proportional hazards models and the Kaplan–Meier method and log-rank tests for comparisons across groups. A p value<0.05 was considered statistically significant.

10. CONFIDENTIALITY, DATA SECURITY AND ETHICS

All data was obtained from a confidential database on the Breast Centre used for EUSOMA certification, from the Cancer Registry and from the patients' digital records of ULSSJ. This research ensured the privacy of patient data, since any sort of personal information that allows identification was not used or shown in the database that was built. The retrospective nature of the analysis supported the informed consent waiver, for the sake of feasibility. This study was approved by ULSSJ/Faculdade de Medicina da Universidade do Porto Ethics Committee (n. 235/2023; October 2023).

RESULTS

A total of 32 male patients and 96 female patients, diagnosed with BC, were studied (Fig. 1). The clinical and biological characteristics of both genders are described in Table 1.

1. SOCIODEMOGRAPHIC AND LIFESTYLE CHARACTERISTICS

The median age of male patients at diagnosis was higher (62 years, range 42-95) compared to female patients (58.5 years, range 26-97); however, this difference was not significant (p=0.085). We found a significantly higher proportion of male patients aged over 50 compared to female patients (93.8% *vs* 65.6%, p=0.002).

The majority of patients had no family history of BC (65.6% of male *vs* 62.5% of female patients, p=0.681). *BRCA2* mutations were identified in a higher percentage of male patients compared to female patients (12.5% *vs* 2.1%, p<0.001).

A higher proportion of male patients reported a smoking history in comparison with female patients (31.3% *vs* 15.6%, p<0.001). Nevertheless, smoking history was not evaluated in 28.1% of male and 6% of female patients. No information on weight and/or height was available to compute body mass index in 28.1% of male and 8.3% of female patients. Still, overweight and obesity were more frequent in women compared to men (24.0% *vs* 12.5% and 24.0% *vs* 15.6%, respectively, p=0.025).

2. TUMOR CHARACTERISTICS

While most tumors were NST carcinomas (81.3% in males and 69.8% in females), male patients presented a higher proportion of other tumor types (9.4% *vs* 1.0%) and female patients presented a higher proportion of lobular carcinomas (12.5% *vs* 3.1%).

Most tumors in men were grade 2 or 3 (56.3% and 40.6%, respectively), and this finding represents a borderline trend towards higher nuclear grades in men (p=0.069).

Most tumors were estrogen receptors (ER)-positive in both men and women (87.5% and 78.1%, p=0.196), and progesterone receptors (PR)-positive (59.4% and 54.2%, p=0.706). Also, no statistically significant differences were found in HER2 status for either male or female patients (9.4% *vs* 9.4% positive, p=0.930). High Ki-67 was assigned to 21.9% of men and 14.6% of women, with no statistically significant difference between genders (p=0.626).

Concerning molecular subtypes, a total of 21 male patients (65.6%) were labeled as luminal B without HER2 expression (HER2-), 3 (9.4%) as luminal B with HER2 expression (HER2+), 1 (3.1%) as luminal A, 1 (3.1%) as triple negative and 1 (3.1%) as HER2-positive. The distribution of these subtypes in women is similar (p=0.414), with a predominance of luminal B without HER2 expression (HER2-).

Regarding tumor clinical stage, significant differences were found for axillary nodal status (cN), with men displaying a higher axillary staging (cN1 56.3% *vs* 22.9%, p<0.001), but not for tumor size (cT) (p=0.062).

Considering pathological staging, we observed larger tumor sizes in males (pT2 25.0% *vs* 12.5%, p<0.001) as well as a higher percentage of lymph node metastasis (pN1 40.6% *vs* 18.8%, p=0.005).

Male patients presented a higher percentage of distant metastasis (M1) compared with female patients (21.9% *vs* 7.3%, p<0.001), with bone metastasis being the most frequent in men (71.4%).

Table 1. Clinical and Biological Characteristics of Male and Female Patients with Breast Carcinoma

Characteristics	Total Male Patients (n=32) N (%)	Total Female Patients (n=96) N (%)	*p* value
Age at Diagnosis, years [median (range)]	62 (42-95)	58.5 (26-97)	0.085
Age at Diagnosis, years			0.002
≤50	2 (6.3)	33 (34.4)	
>50	30 (93.8)	63 (65.6)	
Family History[1]			0.681
No History	21 (65.6)	60 (62.5)	
Mother	2 (6.3)	6 (6.3)	
Uncles/Aunts Mother	0 (0)	9 (9.4)	
Uncles/Aunts Father	0 (0)	8 (8.3)	
Brother/Sister	4 (12.5)	1 (1.0)	
Other	2 (6.3)	7 (7.3)	
Unknown	3 (9.4)	5 (5.2)	
BRCA1/2 Status			<0.001
Negative	19 (59.4)	22 (22.9)	
Positive	4 (12.5)	2 (2.1)	
Unknown	9 (28.1)	72 (75.0)	
Smoking History			<0.001
No	13 (40.6)	75 (78.1)	
Yes	10 (31.3)	15 (15.6)	
Unknown	9 (28.1)	6 (6.3)	
Body Mass Index			0.025
Normal Weight (18.5-24.9 kg/m^2)	14 (43.8)	42 (43.8)	
Overweight (25-29.9 kg/m^2)	4 (12.5)	23 (24.0)	
Obesity (≥30 kg/m^2)	5 (15.6)	23 (24.0)	
Unknown	9 (28.1)	8 (8.3)	
Histological Type[1]			0.021
NST (No Special Type)	26 (81.3)	67 (69.8)	
Lobular	1 (3.1)	12 (12.5)	
CDIS (Ductal Carcinoma in Situ)	2 (6.3)	16 (16.7)	
Other	3 (9.4)	1 (1.0)	
Histological Grade[1]			0.069
G1 (Low)	0 (0)	18 (18.8)	
G2 (Intermediate)	18 (56.3)	42 (43.8)	
G3 (High)	13 (40.6)	34 (35.4)	
Unknown	1 (3.1)	2 (2.1)	
Estrogen Receptors[1]			0.196
Negative	2 (6.3)	18 (18.8)	
Positive	28 (87.5)	75 (78.1)	
Unknown	2 (6.3)	3 (3.1)	
Progesterone Receptors[1]			0.706
Negative	6 (18.8)	25 (26.0)	
Positive	19 (59.4)	52 (54.2)	
Unknown	7 (21.9)	19 (19.8)	
HER2 Status[1]			0.930
Negative	23 (71.9)	66 (68.8)	
Positive	3 (9.4)	9 (9.4)	
Unknown	6 (18.8)	21 (21.9)	
Ki-67			0.626
Low (<15)	2 (6.2)	7 (7.3)	
High (≥15)	7 (21.9)	14 (14.6)	
Unknown	23 (71.9)	75 (78.1)	
Molecular Subtype[1]			0.414
Luminal A	1 (3.1)	10 (10.4)	
Luminal B (HER2-)	21 (65.6)	48 (50.0)	

Characteristics	Total Male Patients (n=32) N (%)	Total Female Patients (n=96) N (%)	*p* value
Luminal B (HER2+)	3 (9.4)	5 (5.2)	
HER2-Positive	1 (3.1)	4 (4.2)	
Triple Negative	1 (3.1)	10 (10.4)	
Unknown	5 (15.6)	19 (19.8)	
Tumor Size - Clinical Staging (cT)[1]			0.062
cTis	0 (0)	9 (9.4)	
cT1	12 (37.5)	38 (39.6)	
cT2	14 (43.8)	33 (34.4)	
cT3	1 (3.1)	6 (6.3)	
cT4	0 (0)	6 (6.3)	
Unknown	5 (15.6)	4 (4.2)	
Axillary Nodal Status- Clinical Staging (cN)[1]			<0.001
cN0	11 (34.4)	71 (74.0)	
cN1	18 (56.3)	22 (22.9)	
cN3	0 (0)	2 (2.1)	
Unknown	3 (9.4)	1 (1.0)	
Tumor Size- Pathological Staging (pT)[1]			<0.001
pTis	2 (6.3)	15 (15.6)	
pT0	0 (0)	5 (5.2)	
pT1	12 (37.5)	45 (46.9)	
pT2	8 (25.0)	12 (12.5)	
pT3	2 (6.3)	0 (0)	
pT4	7 (21.9)	1 (1.0)	
Unknown	1 (3.1)	18 (18.8)	
Axillary Nodal Status- Pathological Staging (pN)[1]			0.005
pN0	12 (37.5)	55 (57.3)	
pN1	13 (40.6)	18 (18.8)	
pN2	4 (12.5)	4 (4.2)	
pN3	1 (3.1)	0 (0)	
Unknown	2 (6.3)	19 (19.8)	
Distant Metastasis (M)			<0.001
M0	21 (65.6)	89 (92.7)	
M1[1]	7 (21.9)	7 (7.3)	0.053
Liver	1 (14.3)	0 (0)	
Bone	5 (71.4)	1 (14.3)	
Multiple	1 (14.3)	3 (42.9)	
Unknown	0 (0)	3 (42.9)	
Unknown	4 (12.5)	0 (0)	
TNM Stage			0.156
0	2 (6.3)	12 (12.5)	
I	6 (18.8)	28 (29.2)	
II	14 (43.8)	42 (43.8)	
III	3 (9.4)	7 (7.3)	
IV	7 (21.9)	7 (7.3)	
Surgery			<0.001
Not Performed	1 (3.1)	16 (16.7)	
Mastectomy	29 (90.6)	13 (13.5)	
Conservative Surgery	2 (6.3)	67 (69.8)	
Sentinel Lymph Node Biopsy[1]			0.356
Not Performed	6 (18.8)	27 (28.1)	
Performed	26 (81.3)	69 (71.9)	
Axillary Lymph Node Dissection			0.003
Not Performed	19 (59.4)	80 (83.3)	
Performed	11 (34.4)	16 (16.7)	
Unknown	2 (6.3)	0 (0)	

Characteristics	Total Male Patients (n=32) N (%)	Total Female Patients (n=96) N (%)	*p* value
Radiotherapy			0.585
No	13 (40.6)	39 (40.6)	
Yes[1]	19 (59.4)	57 (59.4)	<0.001
Chest Wall/Breast	1 (5.3)	34 (59.6)	
Nodal Drainage Area	3 (15.8)	0 (0)	
Chest Wall/Breast plus Nodal Drainage Area	11 (57.9)	16 (28.1)	
Unknown	4 (21.1)	7 (12.3)	
Adjuvant Chemotherapy			0.002
No	16 (50.0)	77 (80.2)	
Yes	15 (46.9)	19 (19.8)	<0.001
AC+T	5 (33.3)	0 (0)	
TC	3 (20.0)	1 (5.3)	
AC	1 (6.7)	0 (0)	
EC+T	1 (6.7)	0 (0)	
Other	5 (33.3)	18 (94.7)	
Unknown	1 (3.1)	0 (0)	
Adjuvant Hormonotherapy			0.606
No	7 (21.9)	21 (21.9)	
Yes	25 (78.1)	75 (78.1)	0.003
Tamoxifen	19 (76.0)	25 (33.3)	
Aromatase Inhibitor	6 (24.0)	47 (62.7)	
Other	0 (0)	1 (1.3)	
Unknown	0 (0)	2 (2.7)	
Biological Treatment			0.075
No	30 (93.8)	84 (87.5)	
Yes	1 (3.1)	12 (12.5)	
Unknown	1 (3.1)	0 (0)	
Neoadjuvant Chemotherapy			0.083
No	29 (90.6)	73 (76.0)	
Yes	3 (9.4)	23 (24.0)	
Neoadjuvant Hormonotherapy[1]			0.154
No	30 (93.8)	95 (99.0)	
Yes	2 (6.3)	1 (1.0)	
Vital Status[1]			<0.001
Live Without Evidence of Cancer	15 (46.9)	88 (91.7)	
Live With Evidence of Cancer	2 (6.3)	3 (3.1)	
Death	15 (46.9)	5 (5.2)	

[1] The sum of the percentages may not add up to 100% due to rounding.

3. TREATMENT CHARACTERISTICS

In total, 90.6% of men underwent mastectomy and only 6.3% (2 cases) had breast-conserving surgery. On the contrary, most women (69.8%) performed breast-conserving surgery (p<0.001).

Sentinel lymph node biopsy was performed in 81.3% of male patients and 71.9% of female patients, with no statistically significant differences (p=0.356). Axillary lymph node dissection was carried out in 34.4% of male patients and 16.7% of female patients (p=0.003).

Radiotherapy was performed in a similar proportion in men and women (59.4% *vs* 59.4%, p=0.585), however, the majority of male patients (57.9%) underwent radiotherapy on chest wall plus nodal drainage area, compared to the majority of female patients (59.6%) that underwent radiotherapy only on chest wall/breast (p<0.001).

Adjuvant chemotherapy was offered to a higher percentage of male patients compared to female patients (46.9% *vs* 19.8%, p=0.002). Adjuvant hormonotherapy was also carried out on the same percentage of men and women (78.1%, p=0.606). Most men (76%) were prescribed tamoxifen and most women (62.7%) with aromatase inhibitors (p=0.003). Only 3.1% of male patients underwent biological treatment, 9.4% neoadjuvant chemotherapy and 6.3% neoadjuvant hormonotherapy. There were no differences in these

therapeutic strategies between men and women (p=0.075, p=0.083, and p=0.154, respectively).

4. SURVIVAL ANALYSIS

According to Table 1, there was a higher percentage of deaths among male patients compared to female patients (46.9% *vs* 5.2%, p<0.001). The proportion of men alive without evidence of cancer at the last appointment was lower compared to women (46.9% *vs* 91.7%, p<0.001).

A statistically significant difference in cumulative survival was found between the two groups (p=0.015, Fig. 2A). However, no statistically significant differences between sexes were observed according to TNM stage (p=0.116, p=0.090, and p=0,144 for TNM stages II, III and IV, respectively, Figs. 2B-D). No deaths were registered in both male and female patients in TNM stages 0 and I, except for one death in TNM stage 0, precluding the formal statistical comparison across sexes within these TNM stages.

Cox proportional hazards models showed that the crude hazard ratio (HR) for sex was 3.60 (95%CI: 1.21-10.77) and Adjusted HR was 1.13 (95%CI: 0.33-3.91), assuming "female" patients as the reference. For age, assuming the reference as "≤50 years", crude HR and adjusted HR were 6.24 (95%CI: 0.83-47.02) and 11.78 (95%CI: 1.36-102.01), respectively. Regarding TNM stage and assuming "0" as the reference, crude HR and adjusted HR were respectively 2.08 (95%CI: 0.26-16.73) and 2.10 (95%CI: 0.25-17.39) for stage II, 5.17 (95%CI: 0.45-58.86) and 7.05 (95%CI: 0.60-82.76) for stage III, 8.82 (95%CI: 1.08-71.87) and 13.45 (95%CI: 1.49-121.75) for stage IV (Table 2).

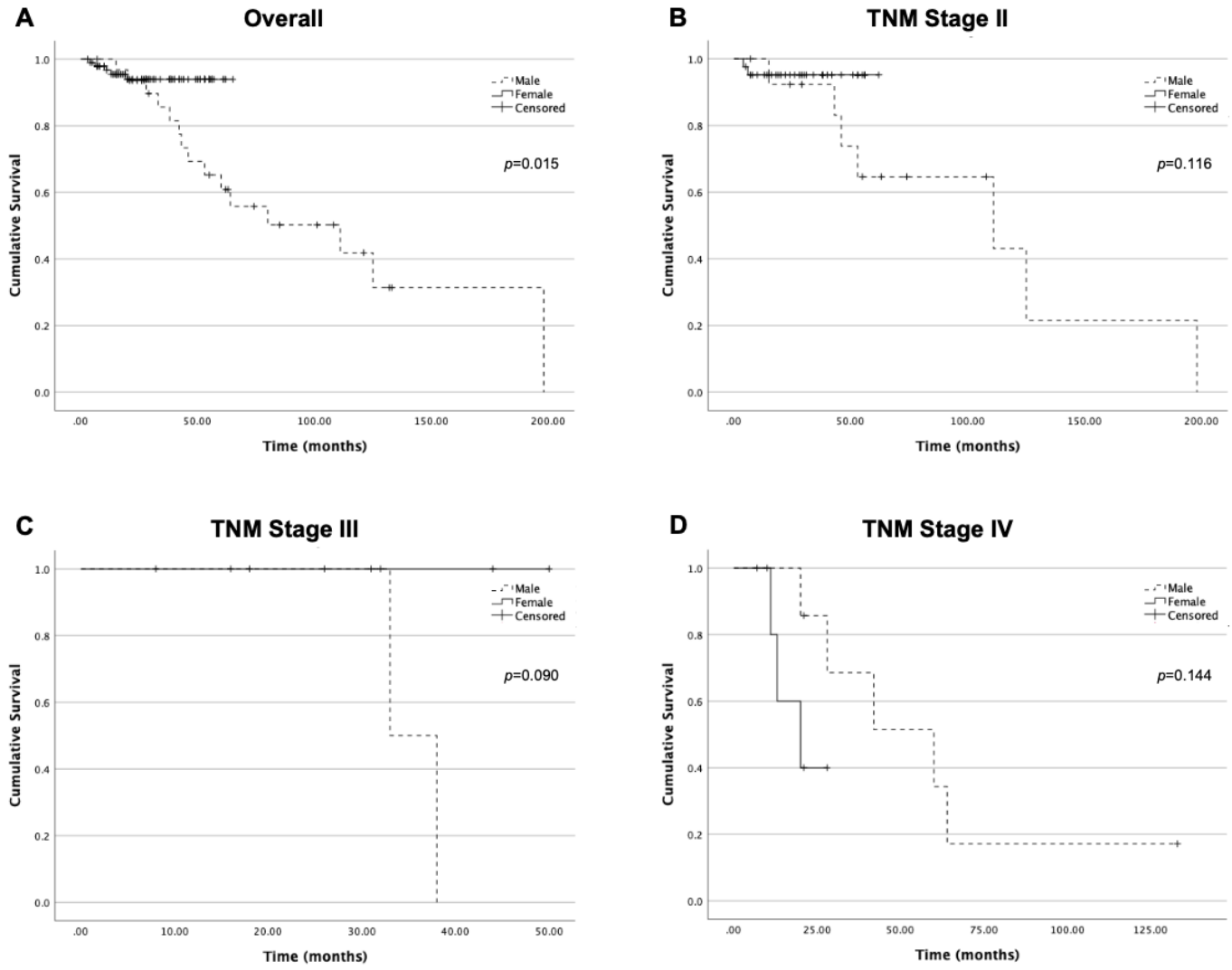

Figure 2. Kaplan-Meier cumulative survival curve of male and female patients, overall (A) according to TNM stage (B-D).

Table 2. Crude hazard ratio and adjusted hazard ratio for sex, age and TNM stage

	Crude Hazard Ratio (95%CI)	Adjusted Hazard Ratio (95%CI)
Sex		
Female	[Ref]	[Ref]
Male	3.60 (1.21-10.77)	1.13 (0.33-3.91)
Age		
≤50 years	[Ref]	[Ref]
>50 years	6.24 (0.83-47.02)	11.78 (1.36-102.01)
TNM Stage		
0	[Ref]	[Ref]
I	—[1]	—[1]
II	2.08 (0.26-16.73)	2.10 (0.25-17.39)
III	5.17 (0.45-58.86)	7.05 (0.60-82.76)
IV	8.82 (1.08-71.87)	13.45 (1.49-121.75)

[1] No deaths were observed among subjects in stage I.

DISCUSSION

Breast cancer is a complex condition impacting both genders, with the main distinction being the incidence rate. Comparisons between BC in females and males uncover both commonalities and divergences. This study, which also compared male and female patients, tested the hypothesis that BC in men has its own biological and clinical features.

Although the difference was not significant, we found that the median age at diagnosis in male was 3.8 years later than in females. As mentioned previously, the fact that men are treated according to studies carried out on women may imply inadequate treatment for men, and this may contribute to worse survival.[6,7,20,21,23,26]

Among the factors identified as possible contributors to the development of BC, genetic factors appear to relevantly contribute,[7] especially in men. Although the majority of men had no family history of breast cancer, we found a higher percentage of men with the *BRCA2* mutation, which is in line with other studies.[10,23,27,28] History of smoking is considered a risk factor for breast cancer in women but is not defined as a risk factor for male breast cancer, however, it may play a role in the development of the disease.[29] Obesity is considered a significant risk factor for developing breast cancer in men and postmenopausal women.[5-10,16,21,23,29,30] We found a higher percentage of women with obesity and a higher percentage of men with a history of smoking. Although the percentage of obesity is similar to that identified by other studies,[10,23] the percentage of men with a history of smoking is higher, which can contribute to a worse prognosis.

Regarding tumor characteristics, the current study shows a predominance of NST carcinomas in male and female patients. Since men do not develop terminal lobes, invasive lobular carcinoma, the second most common in women, is extremely rare in men (only one case in this study).[23,31] Confirming data from other studies, grade 2 tumors were predominant in both male and female patients.[14,26,32] Our findings revealed that most men have positive estrogen and progesterone receptors, which explains the high percentage of men who underwent adjuvant hormonotherapy. HER2 positivity is generally connected with aggressive phenotypes,[23] and we found it in the same proportion in men and women. However, only a small proportion of HER2-positive men underwent biological treatment, since this recommendation for men is very recent and is not routinely performed on patients over the age of 80.

The Ki-67 value plays an important prognostic role and can help define the best therapeutic strategy.[33] In fact, there is some disagreement as to the cut-off points and to which Ki-67 value is more frequently observed in male patients. Our study indicates a slight predominance of high Ki-67 in men without significant differences between sexes. It is important to note that a high number of unknown cases were observed since this quantification is not systematically carried out on grade 1 or grade 3 tumors in our Breast Center.

Like other studies,[14,23,34,35] men have a predominance of luminal B without HER2 expression (HER2-).

Summarizing all the biological characteristics presented, and despite the trend towards higher grade, men's tumors were similar to women's since no differences were found in

estrogen receptors, progesterone receptors, HER2 status, ki67 or molecular subtype.

One of the main findings of our study was the difference found between genders in terms of TNM staging.[24] Our results showed that male patients tend to have larger tumors, more regional lymph node involvement and metastasis in distant organs, compared to female patients. The proximity between the primary tumor and the subareolar lymphatic plexus may explain the greater progression of tumor cells to the axilla in men.[19]

In terms of therapeutic characteristics, our results were identical to those obtained by others.[10,23,29] The majority of males underwent a mastectomy, unlike the majority of females who underwent breast-conservative surgery. Mastectomy is the preferred surgical procedure in men due to the lack of breast tissue, allowing a small tumor to quickly infiltrate skin, and the frequent subareolar location of carcinomas, increasing the likelihood of metastasis.[10,14,23,31] Sentinel lymph node (SLN) biopsy was performed on most men and women. Axillary lymph node dissection was performed in a higher percentage of male patients, which comes from a higher SLN involvement.

Due to the absence of controlled trials, the criteria of post-surgical radiotherapy are typically extrapolated from data collected in women. In this study, radiotherapy was performed in more than half of male patients, the same as female patients, although the reasons for this treatment may have been different between genders. We registered a higher number of male patients with irradiation of the chest wall and nodal drainage area, probably due to the pN+ stage.

Since male patients presented with advanced stages, chemotherapy was given in a higher percentage to men compared to women.

Adjuvant hormonotherapy was carried out in most of male patients, although there was a slightly higher percentage of ER-positive carcinomas. This discrepancy was also found in other studies and is justified by the fact that tamoxifen use in men has only recently been recommended.[14,23,36] We found a predominance of tamoxifen, with aromatase inhibitors (AI) being used only in a small percentage of patients. Tamoxifen improves disease-free and overall survival, which is why it is considered the standard of care. Monotherapy with AI does not completely restrain estrogen production because they do not inhibit the testicular production of estrogen, which represents 20% of circulating estrogen.[10] Since the administration of AI causes an increase in the levels of luteinizing hormone and follicle-stimulating hormone, they can be used in combination with an analogue of the luteinizing hormone-releasing hormone. They are mainly used in metastatic patients resistant to tamoxifen or with contraindications to tamoxifen therapy.

Survival has always been a controversial topic. Most research has shown that male patients have a worse prognosis than females, although some studies that paired individuals based on specific groupings found no difference in the prognosis between the sexes.[20,23,26,27] In our investigation, in general, male patients demonstrated a worse cumulative survival compared to female counterparts. However, survival analysis by TNM stage showed no differences between genders.

We realized that men had a lower survival but our analyses were carried out to understand the effect of some variables on survival and to control confounding. Our results showed that the risk of death was 13.45 times higher in stage IV tumors than in stage 0 tumors, regardless of age and sex. Additionally, the risk of death among older patients was 11.78 times higher than in younger patients, regardless of sex and TNM stage. This analysis reinforced the idea that the main determinant of survival is not the difference in the biological characteristics of carcinomas between genders, but rather the timing of diagnosis.

In men, the diagnosis is made later and this difference in time could be explained by the unexistence of a screening program. Their tumors tend to be larger and with a higher risk of SLN metastasis. Improved outcomes for female patients can be attributed in part to screening initiatives, heightened awareness, early-age diagnosis, advancements in treatment, and the establishment of standardized protocols in international guidelines. More effective medical investigation of gynecomastia cases, the dissemination of public information about male BC, and a concomitant improvement in access to healthcare, are paramount.

To ensure the correct selection of women for subsequent comparison with men, we excluded bilateral tumors, to not be at risk of selecting one of the two tumors registered in the database for which no treatment was carried out, representing the treatment of the contralateral tumor with different clinicopathological characteristics.

This study has the limitations of a retrospective study from a single institution. However, the results are similar to those obtained by other studies previously carried out in other

centers. Due to its rarity, the number of patients involved in this study was low, therefore even when selecting patients for comparison we always tried to obtain the most accurate clinicopathological information. Some variables had a high number of unknown results, but there were only 5 variables with more than 20% of unknown results, which is justified by the large time span encompassing this study.

CONCLUSION

Male patients with BC were diagnosed at an older age, with larger tumors, more regional lymph node involvement and more metastasis in distant organs, which may explain the worse survival rates compared to female patients. *BRCA2* mutations and a history of smoking were found to be significantly higher in men. Axillary lymph node dissection and chemotherapy were carried out in a significantly higher percentage of male patients. Regarding hormonotherapy and radiotherapy, significant differences between genders can only be found in the type of drug and the area of irradiation, respectively.

Male BC is a significant condition that needs increased awareness, to promote early detection.

ETHICAL DISCLOSURES

Conflicts of Interest: The authors have no conflicts of interest to declare.
Financing Support: This work has not received any contribution, grant or scholarship
Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.
Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2024).
Provenance and Peer Review: Not commissioned; externally peer-reviewed.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
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Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2024 e da Associação Médica Mundial.
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CONTRIBUTORSHIP STATEMENT

JAP: Data collection and interpretation, statistical analysis, manuscript preparation and editing.
BP: Data collection and interpretation, statistical analysis and manuscript review.
JLF: Data collection and interpretation, conceptualization, study.
All authors approved the final version to be published.

DECLARAÇÃO DE CONTRIBUIÇÃO

JAP: Recolha e interpretação de dados, análise estatística, preparação e edição do manuscrito.
BP: Recolha e interpretação de dados, análise estatística e revisão do manuscrito.
JLF: Recolha e interpretação de dados, concetualização, estudo.
Todos os autores aprovaram a versão final a ser publicada.

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