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Assessment of Prognostic and Therapeutic Factors in Male Breast Cancer: An Observational Study of a Southwest Spanish Single Center

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ABSTRACT

Background: Male breast cancer (MBC) accounts for less than 1% of breast cancer, requiring extrapolation of results from studies in women. The aim of the study is to evaluate prognostic and therapeutic factors with special focus in endocrine treatment (ET) on the disease outcome.

Methods: Observational, retrospective, single-center study of 53 MBC treated between January 1997 and December 2018 participated in the study. Among the participants, 48 patients had a performance status (PS) 0-1 (91%), 48 were hormone-receptor-positive (91%) and 4 were human epidermal growth factor 2 receptor (HER2) positive (8%). A total of 45 patients (85%) were treated with ET, with 36 patients (68%) receiving treatment in an adjuvant setting. The association analysis was performed using Chi-square test and survival was estimated using Kaplan-Meier with SPSS v25.

Results: The cohort had a median age of 68 years old (range: 40-88). We found that 84% had a non-metastatic breast cancer. A breast cancer gene (BRCA) analysis was carried out in 43% of the patients, showing BRCA2 mutated in 26.1% of those analyzed, without obtaining a benefit in overall survival (P=0.698). The analysis showed higher 5-year overall survival (OS) for PS 0 (P=0.010), absence of vascular invasion (P=0.033), Ki67 ≤14% (P=0.041) and absence of metastasis at diagnosis (p<0.0001). Patients receiving adjuvant ET above 5 years had a longer median OS (89 vs 69.6 months, P=0.024), disease-free survival (DFS), and distant relapse (84 vs 48 months; P=0.005, and P=0.002, respectively).

Conclusions: Several prognostic factors for male breast cancer have been described. Noteworthy, patients receiving adjuvant ET above 5 years had a higher OS and DFS. BRCA did not show prognostic value in OS in this cohort. Further studies with larger sample size are necessary.

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Introduction

Male breast cancer (MBC) accounts for less than 1% of all breast cancer (BC) diagnosed annually in western countries.[1, 2] The incidence in the United States (US) has been increasing in recent decades from 0.85 cases per 100,000 men in the mid-70s to

1.44 cases per 100,000 men in 2011 according to Surveillance, Epidemiology and End Result (SEER)[3] while in Northern European countries it has remained stable in a similar period around 0.4 cases per 100,000 men.[4] In Southern Europe, Portugal showed an incidence of 1.77 cases per 100,000 men in 2011.[5] Mortality in the western world has decreased in the last decades. For instance, Spain reports a decrease from 0.74 deaths per 100,000 men in 2012 to 0.64 deaths per 100,000 men in 2017.[6]

One of the main risk factors is the age, with the average age at diagnosis being slightly older in men than in women.[4] Other risk factors reported are family history,[7] breast cancer gene (BRCA) germline mutations, especially BRCA2, having a cumulative risk for developing BC above 6%[8], and the existence of hyperestrogenism favored by alterations such as Klinefelter syndrome, testicular disorders, obesity, liver dysfunction, etc.

Compared with female BC, the MBC immunohistochemical expression is similar although it seems that there is a higher proportion of hormone-sensitive tumors and a higher expression of the androgen receptor suggesting higher endocrine treatment (ET) options.[9]

The treatment applied to MBC has been limited by the small sample size represented in clinical trials, with no men appearing in the vast majority. Therefore, treatment decisions are based on studies conducted in women.[10]

The aim of this study is to analyze the prognostic value of clinical and therapeutic characteristics, focusing on ET due to lack of evidence in some indications, and their differences from female BC. This study is one of the largest in Spain with the largest sample size recorded in the Andalusian region. Additionally, the impact of BRCA mutations on survival has been assessed. This research is presented in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist.

Methods

Patients and design

An observational retrospective cohort study of 53 MBC patients between January 1997 and December 2018 in an Andalusian single center participated in the study. The sample size is the largest possible since it is a low incidence disease.

Inclusion criteria consisted of male patients of any age histologically diagnosed with BC with an intent to receive treatment. Exclusion criteria included cases with only partial clinical data available. Finally, 13 out of 66 patients were excluded for this reason. In addition, 6 patients receiving adjuvant ET were excluded because ET was not completed. Stage was assessed according to the 8th American Joint Committee on Cancer (AJCC) Staging Classification.[11]

The functional status of the patients was evaluated using the Eastern Cooperative Oncology Group (ECOG) performance status (PS) scale.[12]

Patients with localized disease who underwent surgery initially, were followed every 3-6 months during the first 2-3 years and then every 6 months until the first 5 years. A physical and analytical examination was performed with the study of tumor biomarkers, as well as annual mammography, and bone densitometry every 2 years for those patients undergoing ET. Additionally, patients with advanced disease also underwent chest and abdomen computerized tomography every 2-4 months.

The patients were considered to be estrogen receptor (ER) positive and the progesterone receptor (PR) positive when there was ≥1% of immunohistochemical expression. The status of the human epidermal growth factor 2 receptor (HER-2) was initially determined by immunohistochemistry (IHC), considering the values of 3+ as positive, 2+ equivocal, and 1+ as negative. In equivocal cases, fluorescent in situ hybridization (FISH) was performed. Values of ≥2.3 for FISH were classified as positive, <1.8 as negative and values between 1.8-2.3 were classified as equivocal. If the values were not reported, especially before 2010, it was defined as an unknown value. The BRCA 1/2 mutational study was performed using direct sequencing and detection methods with amplification of the DNA by Polymerase chain reaction (PCR).

The information collected in this research has been obtained exclusively from human participants with the approval of a Spanish ethics board (ID EMS/dgc) in accordance with the 1964 Declaration of Helsinki and its later amendments.

Ethical Statement

All persons listed as authors have given their approval for the submission of the paper.

The information collected in this research has been obtained exclusively from human participants with the approval of a Spanish ethics board (ID EMS/dgc) in accordance with the 1964 Declaration of Helsinki and its later amendments. The results of this study will not affect the standard management of men with breast cancer. Due to the retrospective nature of the study, formal consent was not required but all authors declared that patients' personal data have been secured. No animals were involved in this study.

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Statistical analysis

Overall survival (OS) was defined as time from diagnosis to death due to any cause. Cancer specific survival (CSS) was defined as time from diagnosis to death due to BC. Disease-free survival (DFS) was defined as those patients rendered disease free and alive until a new event. Events in the analysis of DFS

included any locoregional or distant failure, or death from any cause. Locoregional relapse was defined as local failure at the primary site or any nodal failure after treatment. Finally, distant relapse was defined as the recurrence of neoplastic disease at a location other than the primary tumor, and distant disease-free survival (DDFS) as the time from diagnosis until distant event or death. Categorical variables were expressed as frequencies and percentages and continuous variables as the median and range. The associations between the patient factors (age, familiar history of breast or ovarian cancer, ECOG, smoking status, cardiovascular disease, history of alcoholism, BRCA status), disease factors (histological and immunohistochemical characteristics, stage), and treatment factors (surgery, radiotherapy [RT], chemotherapy [CT], ET) and the survival outcome at 5 years were assessed using the Chi-squared statistical test. Multivariate analysis was not used due to the limited sample size. Survival was estimated by the Kaplan-Meier (KM) method using log-rank test to compare different variables. A p value of 0.05 or less was considered statistically significant. Data was analyzed using SPSS v.25 software (SPSS Inc, Chicago, IL, USA).

Results

Characteristics of the 53 patients are shown in Table 1. The cohort consisted of 53 men with a median age of 68 years (range, 40-88 years). They had some comorbidities such as history of cardiac disease (47%) or thromboembolic events (9%). Among the participants, 77% were current or former smokers and 17% had history of alcoholism. Most patients (90%) had a PS 0-1 and 12 patients (23%) had a family history of breast or ovarian cancer and BRCA 1/2 mutations were examined in 43% (n=23) patients of the sample. BRCA positive mutations were observed in 26% (n=6) of BRCA patients assessed, increasing this percentage to 42% (n=5) in those patients who had a family history of breast or ovarian cancer. The mutations observed were of BRCA2 type in these patients. The median follow-up time for all patients was 73 months, being less than 1 year in only 3 patients due to premature death caused by the BC disease.

Tumor characteristics

Histological characteristics were as follows: 89% had infiltrating carcinoma (n = 47) while the rest had non-infiltrating histology (ductal carcinoma in situ, micropapillary and apocrine carcinoma), 60% grade 1-2 of modified Bloom Richardson classification (n = 32), 42% vascular invasion (n = 22), 26% in situ component associated (n = 14), 47% primary tumor size less than 2 cm (n = 25), and 64% had Ki67 proliferation index > 14 (n = 34). Also, 91% had a luminal tumor phenotype with 91% positive ER expression and 87% positive PR expression. In addition, 3 patients (6%) had HER2 positive status with only 1 patient being non luminal HER2 positive. Stage II was the most common stage (41%) followed by stage 0-I (19%) and stage III (19%). Additionally, 57% had nodal infiltration and up to 23% of all patients had ≥4 affected nodes. Only 14% (n = 8) presented with distant metastases at diagnosis, with 50% of the patients showing this at bone level and the rest at visceral level.

Oncological treatment

A total of 47 patients (89%) underwent surgery, which was mastectomy in 87% of the patients. Also, 25 patients (47%) received adjuvant RT with a dose ≥50 Gy in 76% of the irradiated cases while 85% received ET at some point during the follow up. Of the participants, 36 patients received adjuvant ET containing tamoxifen in 89% of cases, while only 11% received aromatase inhibitors (AIs) exclusively. After distant relapse, 13 patients received ET with tamoxifen as one of the treatments in 54% of the patients. LHRH agonists were administered in 10 patients (19%), which was guided in many patients (n=9) by presenting prostate cancer simultaneously. In addition, 3 men received cyclin inhibitors (2 with Ribociclib and 1 with Palbociclib) and 13 bisphosphonates (68% of stage IV patients).

On the other hand, 26 patients (49% of all cases) received CT, administered with neoadjuvant intention in 3 patients based on anthracyclines (epirubicin / doxorubicin every 3 weeks) and taxanes (docetaxel every three weeks/ paclitaxel weekly), with one of the patients receiving trastuzumab due to his amplified HER2 status. In relation to adjuvant CT, 16 patients received treatment, 12 of them based on anthracyclines and taxanes, with one patient receiving CMF (cyclophosphamide, methotrexate and fluorouracil) probably related to a history of arrhythmia, one patient receiving FEC (fluorouracil, epirubicin and cyclophosphamide) x6 cycles, one patient receiving 4 cycles of capecitabine, and lastly one patient receiving Carboplatin AUC2 + paclitaxel 80 mg / m2 x 6 cycles. After distant relapse, 14 patients received some CT-based treatment.

Statistical analysis

Irrespective of the treatment modality, the OS and CSS rates for all patients at 5 years were 58.5% and 63.3% respectively. Table 2 and 3 shows all parameters that were evaluated in the univariate analysis. PS 0 (OR: 0.20; P= 0.010; CI95%, 0.06–0.67), absence of vascular invasion (OR: 0.26; P= 0.033; CI95%, 0.07–0.92), Ki67≤14% (OR: 0.16; P= 0.041; CI95%, 0.03-0.83), and absence of distant metastasis at diagnosis (OR: 0.31; P <0.001; CI95%, 0.20–0.48) were associated with better OS at 5 years. In contrast, patients who did not undergo surgery (OR: 2.94; P= 0.003; CI95%, 1.97-4.37) were associated with worse prognosis. Absence of vascular invasion, Ki67≤14%, absence of distant metastasis, and no treatment with CT also showed

Table 1. Patient characteristics

Variables			N (%)
Age, years		<70	32 (60)
		≥70	21 (40)
History of cardiac disease[a]		No	28 (53)
		Yes	25 (47)
Smoking status		Current	6 (12)
		Former	32 (65)
		Never	11 (22)
Performance status			
		0	33 (62)
		1	15 (28)
		2	5 (9)
Infiltrating carcinoma		No	6 (11)
		Yes	47 (89)
ER status		Negative	4 (7)
		Positive[b]	48 (91)
		Unknown	1 (2)
PR status		Negative	6 (11)
		Positive[c]	46 (87)
		Unknown	1 (2)
HER2 status		Negative	46 (87)
		Positive[d]	3 (6)
		Unknown	4 (7)
Ki 67 proliferation index (%)		≤14	12 (23)
		>14	34 (64)
		Unknown	7 (13)
Primary tumor size (cm)		≤2	25 (47)
		>2	24 (45)
		Unknown	4 (8)
Number positives nodes		0	20 (38)
		1-3	18 (34)
		≥4	12 (23)
		Unknown	3 (6)
Metastasis at diagnosis		None	45 (85)
		Bone	4 (7)
		Visceral	4 (7)
Stage at diagnosis		0 and I	10 (19)
		II	22 (41)
		III	10 (19)
		IV	8 (15)
		Unknown	3 (5)
BRCA mutation		Negative	17 (32)
		Positive	6 (11)
		Unknown	30 (57)
Surgery		No	6 (11)
		Yes	47 (89)
Pathological margins[e]		Margins free of tumor	41 (77)
		Tumor at margins	5 (9)
		Unknown	7 (13)
Type of endocrine therapy	Adjuvant (N=36)	Tamoxifen	32 (89)
		AIs	4 (11)
	Metastatic (N=13)	Tamoxifen	7 (54)
		Ais	6 (46)
LHRH agonist		No	42 (79)
		Yes	10 (19)
		Unknown	1 (2)

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; AIs, aromatase inhibitors.
a. History of cardiac disease includes pathologies such as ischemic heart disease, arrhythmias, valvulopathies, heart failure or hypertensive heart disease
b. It is considered ER positive if ≥1% of tumor cells demonstrate positive nuclear staining by immunohistochemistry.
c. It is considered PR positive if ≥1% of tumor cells demonstrate positive nuclear staining by immunohistochemistry.
d. HER2 is positive when there is overexpression by immunochemistry or FISH in equivocal cases.
e. All patients with tumor at margins were treated by mastectomy.

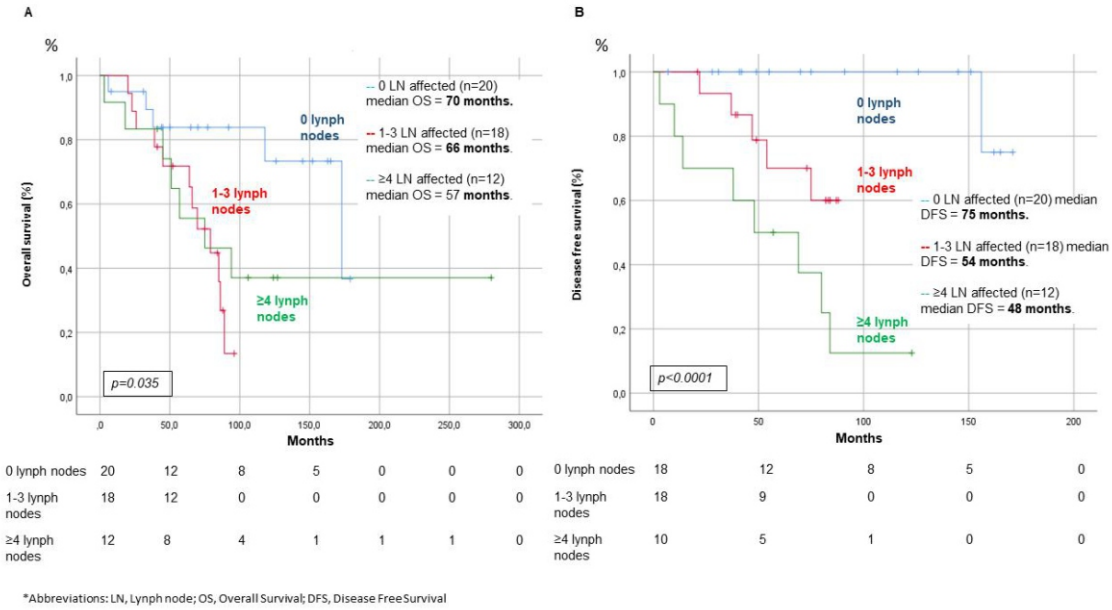

Figure 1. Kaplan-Meier curve for overall survival (A) and disease-free survival (B) in male breast cancer depending on the lymph node involvement, showing better survival in patients with less lymph node metastasis.

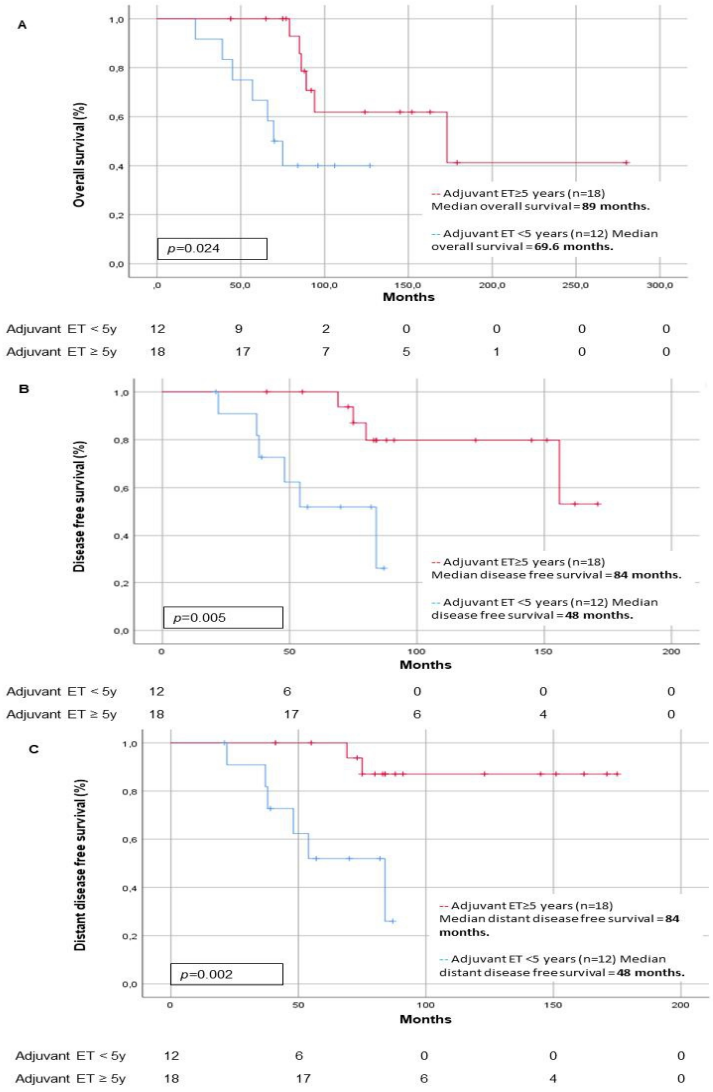

Figure 2. Kaplan-Meier curves showing the effect of the duration of ET intake and its prognostic impact on overall survival (A), disease free-survival (B) and distant disease free-survival (C) in male breast cancer. There is a statistically significant increase in survival with ET for at least 5 years.

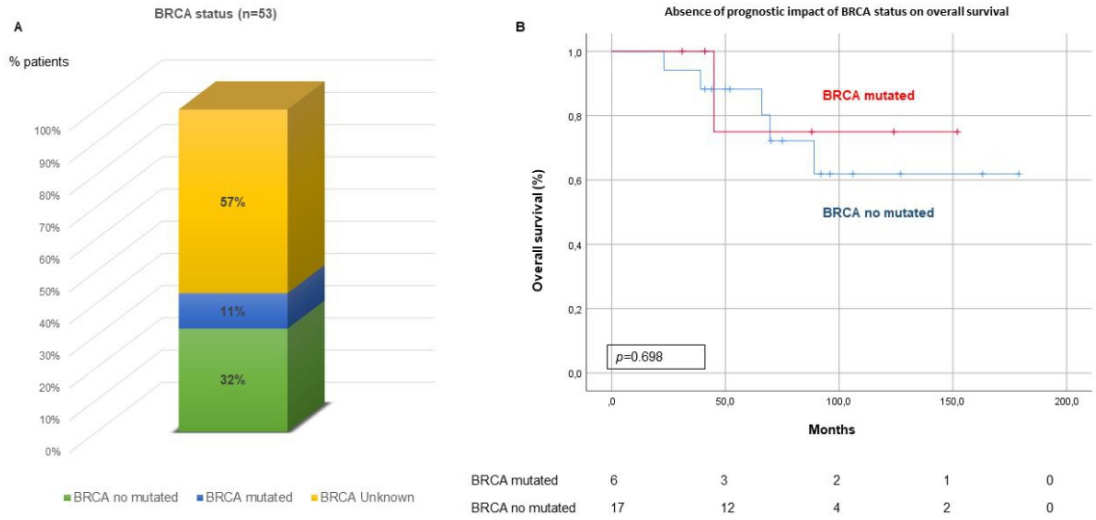

Figure 3. Description of the BRCA status in the cohort studied (A) and Kaplan-Meier curve for overall survival (B) without being able to demonstrate positive or negative impact for the mutated state

better CSS at 5 years (P <0.05), while negative PR expression and not receiving surgery were associated with worse CSS (OR: 11.1; P= 0.022; CI95% 1.18-105.24; and OR: 3.38; P= 0.004; CI 95% 2.14-5.34, respectively). KM estimated better OS in patients with better PS at diagnosis (median OS for PS 0 = 88 months; PS 1 = 45 months; PS 2 = 39 months; P<0.001), early stages (median OS for stages 0-IA = 92 months; stages IB-III = 75 months; stage IV= 20 months; P<0.001), low lymph node involvement, (median OS for no lymph node involvement = 70 months; 1-3 lymph nodes = 66 months; ≥4 lymph nodes = 57 months; P=0.035; Figure 1), absence of metastasis at diagnosis (median OS 79 months vs 20 months, P< 0.001) compared with those with metastasis. Those who received adjuvant ET for at least 5 years (median OS 89 months vs 69.6 months, P=0.024; Figure 2) showed better results. The size of primary tumor at diagnosis did not show better OS by KM test (median OS for <2cm = 70 months vs ≥2cm = 64 months, P= 0.219).

Figure 3 shows the absence of impact in OS for those patients analyzed according to BRCA mutational status with the KM estimation.

Having PS 0 (OR: 0.18; p = 0.014; CI95%, 0.05-0.66) or Ki67≤14% (OR: 0.05; P= 0.001; CI95%, 0.01-0.45) were associated with better DFS at 5 years while those treated with adjuvant ET < 5 years (OR: 34.00; P= 0.001; CI95%, 3.25-355.41) had lower DFS. KM analysis estimated a better median DFS when having Ki67≤14% vs >14% (84 months vs 48 months, P= 0.004), early stages (median DFS for stages 0-IA = 91 months; stages IB-III = 57 months; stage IV= 10 months; P<0.001), lower lymph node involvement, (median DFS for no lymph node involvement = 75 months; 1-3 lymph nodes = 54 months; ≥4 lymph nodes = 48 months; P<0.001; Figure 1) or receiving adjuvant ET for at least 5 years (84 months vs 48 months, P= 0.005; figure 2).

Sixteen patients (33%) experienced relapse after treatment for curative intention (3 [19%] were local, and 13 [81%] were distant). Patients with histological grade 1-2 (OR: 0.04; P = 0.001; CI95% 0.01-0.27), absence of vascular invasion (OR: 0.14; P= 0.026; CI95% 0.03-0.82), Ki67≤14% (OR: <0.1; P= 0.017), absence of lymph node involvement (OR: <0.1; P= 0.001) and early disease stages 0-II (OR: 0.07; P= 0.001; CI95% 0.01-0.36), absence of in situ component associated (OR: 0.19; P = 0.047; CI95% 0.04-0.94) showed better DDFS. In contrast, patients having adjuvant ET < 5 years (OR: 8.00; P = 0.034; CI95% 1.25-51.13) had an increased risk of distant relapse and shorter DDFS (84 months vs 48 months, P = 0.002; Figure 2).

Discussion

There are many publications about the clinical characteristics of MBC. However, the scientific information related to the treatment outcome is scarce, probably due to the small samples assessed.

In agreement with the literature, our study has found similarities in relation to conventional prognostic factors such as the early pathological stage, the low histological grade, having positive hormonal receptors, the absence of lymph node involvement or having low levels of proliferation index Ki67 associated with better outcome.[13] However, one of the main prognostic factors that has been described in MBC, the size of primary tumor, was not found to be significantly associated with survival in our cohort. In addition and unlike previous published studies [14-16], cardiovascular risk factors such as smoking habit or having a history of cardiovascular or thromboembolic disease did not

associate with poorer prognosis. These results are probably due to the limited sample size.

Our study included patients that were diagnosed and treated between 1997 and 2018 and many of them did not have a genomic platform test, nor met the criteria for this assessment. Currently, these platforms are a very useful tool in the prognostic assessment of the risk of recurrence in early hormone-sensitive BC [17] and perhaps its application could have modified the type of adjuvant treatment administered and therefore the reported survival results.

As in other studies on men, there was a higher percentage of hormone-sensitive tumors (91%) and negative HER2 (87%) in our sample compared to what has been described in several studies in women [18, 19] with worse results in 5-year OS in our cohort compared to MBC and BC in women reported in the American National Cancer Database (58% vs. 74% and 83% respectively).[20] Similar to the study of Anderson et al. [21] based on data collected from the SEER database, there was a BC peak incidence between 62 and 73 years with a median age of 68 years, differing from women who usually had 2 incidence peaks at 52 and 71 years.

The analysis of mutations in the BRCA genes was carried out in 43% of the patients, finding mutations in 11% of this subset, which was BRCA2 in all of them. These results are similar to those described in previous studies where 10-14% of men with BC had BRCA2 mutations.[18, 22] Nevertheless, the hypothesis that mutations in BRCA 2 could associate with worse prognosis in MBC, could not be validated in our cohort although there is controversy on this subject currently. [23] The vast majority of the patients with BRCA2 mutations (83.3%) had a family history of breast or ovarian cancer, which is a higher rate than in previous published cohorts.[24]

Most of the patients underwent mastectomy versus breast conservative surgery (BCS) (87% vs. 13%) in agreement with Cloyd et al. who reported a series of 5425 MBC patients where 87% underwent mastectomy between 1983 and 2009.[25] These data clearly differ from the management performed in women, where in the early stages, the percentage of conservative surgeries is around 53%.[26] BCS does not appear to decrease MBC CSS at 5 years compared to mastectomy.[27]

In the absence of randomized studies, the addition of adjuvant ET in MBC is supported by several retrospective studies, where improvement in OS is shown.[28] The administration of adjuvant tamoxifen (89% of the patients) did not show a significant association with OS, CSS or DFS at 5 years compared with AIs exclusively. These results differ from other studies such as Eggemann et al., where tamoxifen seemed to decrease mortality and increase survival compared to AIs.[29] Additionally, the subgroup treated with AIs exclusively did not receive GnRH agonists, which could improve the efficacy of AIs by blocking the estrogenic effect of testicular origin.[30]

Interestingly, the duration of ET for at least 5 years showed an improvement in the 5-year DFS,a decrease in the risk of distance relapse and a better 5-year OS. One of the potential explanations for these findings is the fact that 58% of MBC patients who received adjuvant ET for less than 5 years died before completing the adjuvant treatment, while the remaining 42% did not complete the 5-year prescription due to low adherence. This finding is in agreement with some previous studies.[31]

The main limitation of the present study is the small sample that can influence the statistical analysis. Our future intention is to contact nearby hospital centers to obtain a larger sample and to have results that are as close as possible to reality. Secondly, it was not possible to perform a multivariate analysis that could allow us to eliminate possible confounding factors that may have an impact on the outcome. Finally, the effect of cyclin inhibitors was not evaluated because all patients receiving this treatment had started it recently.

In conclusion, we found a greater hormonal sensitivity in MBC. Additionally, there was a lower percentage of BCS in MBC compared to women despite having a similar survival in early stages. BRCA mutational state did not show a prognostic impact on the outcome. ET played a significant role, and the duration, at least 5 years, was important for the prognosis. No differences were found with the intake of tamoxifen or AIs exclusively in the adjuvant setting although the sample size was limited for this analysis.

The absence of consensus regarding the best therapeutic option, together with the advent of new treatments in clinical practice, means the lack of knowledge about the best therapeutic option to apply both in adjuvant setting and in advanced stages of the disease, and therefore conducting studies on this population is needed.

Conflicts of Interest

All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.

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