18 Years Experience of an Italian Breast Unit Among Male Breast Cancer: A Retrospective Observational Study

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AIM: Male breast cancer has increased by approximately 26% over the past 25 years, there is a need to research specific treatment options. Currently, there is no established standard treatment which is therefore based on female disease. The purpose of this study is to analyze the clinical characteristics, survival outcomes, and the need for tailored treatment strategies in male breast cancer patients.
METHODS: This is an observational, retrospective, single-center clinical study. The research involved 21 male patients who underwent surgery for breast cancer from 2003 to 2020 in our hospital. In order to strengthen the statistical value of the results obtained, the survival curves of three selected studies in the literature were compared with that obtained in the present study.
RESULTS: All our patients underwent total mastectomy and axillary lymph node dissection. Twenty patients were diagnosed with invasive ductal carcinoma, while only one patient with invasive lobular carcinoma. The 5-year survival was 71.4% with a median survival for metastatic patients of 5.7 years. A statistically significant difference was found when comparing 5-year survival with one of the other three studies ($p = 0.048$).
CONCLUSIONS: Our findings highlight the delayed clinical presentation of male breast cancer and a 5-year overall survival of 71.4%, underscoring the need for targeted screening strategies to improve early diagnosis and outcomes.The lack of knowledge of this disease at sociocultural and health level is the main reason for delay in diagnosis, a factor that strongly affects the prognosis.

Keywords: male breast cancer; risk factors; screening programme

Introduction

Male breast cancer (MBC) is an uncommon neoplasm, representing less than 1% of cancers that arise in men and approximately 1% of all breast cancers worldwide [1–19]. It is estimated that 1/100,000 men per year in Italy and Europe will be diagnosed with breast cancer (BC). Although the treatment of MBC patients is based on the female counterpart, studies have demonstrated that there are some molecular and pathological differences between male and female breast cancer [2–18,20]. Risk factors were defined as age, exposure to electromagnetic fields, testicular disease, conditions associated with an abnormal estrogen-to-androgen ratio such as obesity, liver disease, Klinefelter's syndrome and medication taken [4,5]. Genetics plays a major role in male breast cancer, approximately 10% of men with breast cancer carry the BReast CAncer Gene 2 (*BRCA2*) mutation, while mutations in *BRCA1* are rare [6,7]. Treatment consists in surgery with total mastectomy followed by either sentinel node biopsy or axillary lymphadenectomy. As the condition is predominantly hormone-receptor-positive, hormonal therapy is an essential component of treatment as well as radiotherapy according to the local extension of the tumor [6–17]. Due to the very low occurrence of this disease, the treatment is based on the female BC and there is no standard of care for MBC [21,22]. Indeed, there are very few researches and clinical trials published and the awareness of this pathological entity is very low in the population. The aim of this study is to report our experience and identify a risk category of male breast cancer patients.

Materials and Methods

This is an observational, retrospective, single-center clinical study. The investigation included male patients who underwent breast surgery for breast cancer between 2003 and 2020 at the Department of General Surgery, Breast Unit, S. Andrea University Hospital, Rome, Italy. Inclusion criteria were: patients with breast cancer at all stages (early stage, locally advanced and metastatic), regardless

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of treatment received. We recorded the following patient characteristics into a computerized database: age at diagnosis, family history, risk factors (gynecomastia, smoking and alcohol), time elapsed between symptoms and diagnosis, tumor location and size, date and type of surgical procedure, lymph node status, histological type with receptor characteristics and if they underwent either hormonal or chemotherapy treatment and results of the follow-up conducted. Familiarity for neoplastic pathology up to the second degree was investigated as well as the presence of mutations in *BRCA1* and *BRCA2* genes and, by Next Generation Sequencing (NGS), the expression of 25 genes (*APC, ATM, BARD1, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, MLH1, MRE11, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, RECQL1, SMAD4, STK11, TP53*) involved in the DNA repair pathway [8]. The extent of disease was described with traditional classification criteria according to the TNM system in use since January 2018 revised by the American Joint Committee on Cancer (AJCC)-eighth edition [9]. Each selected patient followed a standardized diagnostic and therapeutic procedure, based on the protocols used for female breast cancer. The follow-up period started at the time of surgery and continued until the last recorded visit or death, with a minimum duration of 5 years for inclusion in survival analysis. Follow-up evaluations were conducted every 6–12 months and included clinical examination, imaging (mammography, ultrasound, or Magnetic Resonance Imaging as appropriate and as decided by oncologists), and assessment of recurrence or progression of disease.

Given the small number of patients involved in the study, we decided to select three retrospective studies from the international literature to compare our results with, in order to strengthen their statistical value [7,10,11]. McKinley *et al.* (2017) [7] analyzed treatment strategies and outcomes of male breast cancer patients in a UK cohort. van der Pol *et al.* (2016) [11] assessed the performance of prognostic tools in male breast cancer across European centers. Serarslan *et al.* (2015) [10] reviewed 20 years of clinical data on male breast cancer from a Turkish tertiary hospital, focusing on treatment modalities and survival outcomes [7,10,11].

Collected data were inserted in a database on Microsoft Excel (version 16.0, Microsoft Corp., Redmond, WA, USA) and then analyzed using R statistical software (version 4.4.3, The R Foundation for Statistical Computing, Vienna, Austria) via the RStudio interface (version 1.4.1103, RStudio, PBC, Boston, MA, USA). Survival curves were compared using the Log-rank test, and a p value of less than 0.05 was considered statistically significant. The Kaplan-Meier overall survival curve was generated considering only patients with follow-up greater than or equal to 5 years, with 95% confidence interval. Discrete quantitative variables (age, ki-67 antigen (ki67), survival) and qualitative variables (risk factors, comorbidities, histological type, genetics, familiarity, TNM, receptor status, surgery, adjuvant therapy) were collected. Of the latter, mean, median, and symmetry were evaluated, whereas quantitative variables were expressed in binary mode and the distribution and representation within the population indicated as absolute number and percentage was calculated for each of them.

This retrospective study received departmental approval, and written informed consent was obtained from all patients for the collection and use of their data.

The research was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Results

Of a total of 44 male patients who underwent breast surgery in our department, we found 21 eligible patients, 23 patients were excluded because they didn't meet inclusion criteria. Median age was 75 years. 18 patients present risk factors as shown in Table 1 and 38% of them had more than one. The 19.0% of our population had a first-degree relative affected by breast cancer. All patients underwent genetic counseling and tests to find any mutations in *BRCA1/2* genes; in patients who did not show *BRCA1/2* mutations the expression of 25 genes of the reflex panel was tested. Only seven patients agreed to undergo the genetic test, 5 patients were negative, two patients resulted to be carriers of *BRCA1/2* mutations (one with *BRCA1* and one with *BRCA2*). Most of our patients presented with ductal invasive carcinoma, just one with lobular invasive carcinoma. The characteristics of the dimension (T), lymph nodes involvement (N), the presence/absence of metastasis (M), grade of tumor, hormonal receptors, the expression of ki-67 antigen and Human Epidermal Growth Factor Receptor 2/neu are represented in Table 2. The treatment performed such as radiotherapy (RT), chemotherapy (CHT), hormone therapy with Tamoxifen or aromatase inhibitors (Als) are represented in Table 3. None of the patients who presented with bone metastases survived. The estrogen receptor (ER) was expressed in the total of 21 patients and the progesterone receptor in 95% of cases, just one patient presents expression for Human Epidermal Growth Factor Receptor 2 (HER2/neu). All patients underwent total mastectomy with axillary lymphadenectomy. The overall survival (71.4%) was calculated excluding patients with a follow up shorter than 5 years, as shown in Fig. 1. Of a total of 14 patients, 5 didn't survive.

Table 1. Risk factors summary table.

Risk factor	Yes n (%)	No n (%)
Family history	4 (19.0%)	17 (81.0%)
Gynecomastia	13 (61.9%)	8 (38.1%)
Smoke	8 (38.1%)	13 (61.9%)
Obesity	2 (9.5%)	19 (90.5%)
Antidepressants	3 (14.3%)	18 (85.7%)
Statins	3 (14.3%)	18 (85.7%)

Table 2. Patients' characteristics.

Variables		n (%)
Age	≤65	9 (42.9)
	>65	12 (57.1)
T	1	6 (28.6)
	2	9 (42.9)
	>3	6 (28.6)
N	0	6 (28.6)
	1	8 (38.1)
	2	5 (23.8)
	3	2 (9.5)
M	0	15 (71.4)
	1	6 (28.6)
ER	+	21 (100)
PGR	+	20 (95.2)
	-	1 (4.8)
G	1	3 (14.3)
	2	8 (38.1)
	3	10 (47.6)
HER2/neu	+	1 (4.8)
ki67	Low (<10)	4 (19)
	High (>10)	17 (81)

T, tumor size; N, nodal involvement; M, metastasis; ER, estrogen receptor; PGR, progesterone receptor; G, tumor grade; HER2/neu, Human Epidermal Growth Factor Receptor 2; ki67, ki-67 antigen.

Table 3. Treatment performed.

Treatment	n
RT	8
AHT	1
TAM	16
CHT	11

RT, radiotherapy; AHT, androgen hormone therapy; TAM, tamoxifen therapy; CHT, chemotherapy.

We compared our findings with those of three similar studies presented in literature [7,10,11], in particular examining the overall survivals (OS) using Log rank test.

Considering the study conducted by van der Pol *et al.* [11] the OS at 5 years was 55%, showing a significant statistical difference with our OS ($p = 0.048$) Fig. 2. Taking into account the studies conducted by Serarslan *et al.* [10] and McKinley *et al.* [7] the OS respectively are 40% and 67%, with both not a significant statistical difference with our overall survival Fig. 3 (Ref. [7,10]) ($p = 0.06$ and $p = 0.6$ rexpectively).

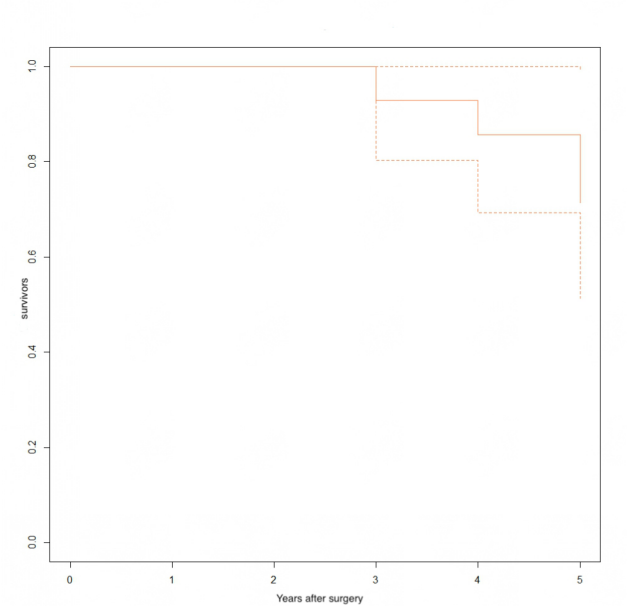

Fig. 1. Kaplan-Meier overall survival curve. The Kaplan-Meier curve shows the overall survival of patients. One patient died 3 years after surgery, another at 4 years, two patients at 5 years, and one at 8 years post-surgery.

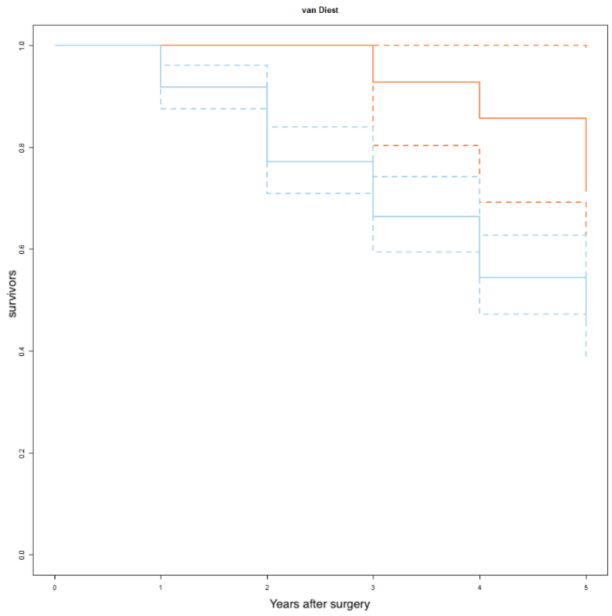

Fig. 2. Survival curve comparison with van Diest's Study. This figure compares our overall survival (OS) curve with the OS curve from van Diest's study. The survival rate at 5 years in van Diest's study was 55%, significantly lower than our study's OS ($p < 0.05$). Legend: -Blue line: OS curve from van Diest's study. -Orange line: OS curve from our study. Statistical results: *Chi*-squared = 3.7 (1 degree of freedom), $p = 0.048$.

Discussion

The reported risk factors for male breast cancer are family history, Breast Cancer 2 Gene mutation, androgen re-

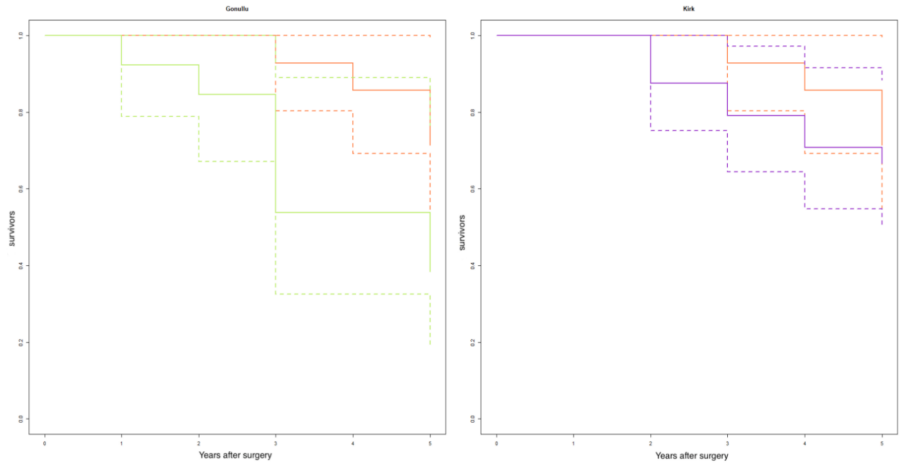

Fig. 3. Survival curve comparison with Gonullu and Kirk's Studies. This figure presents a comparison of our overall survival (OS) curve with the OS curves from the studies of Serarslan *et al*. [10] and McKinley *et al*. [7]. The OS values were 40% and 67% respectively, showing no statistically significant difference compared to our study. Legend: -Green line: OS curve from Gonullu's study. -Purple line: OS curve from Kirk's study. -Orange line: OS curve from our study.

ceptor gene mutation, Checkpoint Kinase 2 mutation (Li-Fraumeni Syndrome), Phosphatase and Tensin Homolog mutation (Cowden Syndrome), hereditary non-polyposis colorectal cancer (Lynch syndrome), Kleinfelter's syndrome, low frequency magnetic field exposure, alcohol, obesity, chest wall irradiation, estrogen intake, antiandrogen therapy [12]. According to our results, smoke and obesity represented an important risk factor. The size of the study population did not permit a detailed evaluation of prevalence of *BRCA1* and *BRCA2* mutations.

It might be interesting that the majority of our population present a locally advanced stage at diagnosis, 72% of them presented a >2 cm tumor size and lymph node involvement. These data differ from those reported in female breast cancer (FBC) (10–15% of lymph node involvement at diagnosis) [13]. Surgery should be the primary treatment for MBC patients [14]. The surgical procedure performed was total mastectomy with axillary lymphadenectomy, breast-conserving surgery is controversial due to the advanced stage at diagnosis and the anatomical characteristics of the male mammary gland [6]. Despite the evidence that the surgical evaluation of axillary lymphnodes should be performed by sentinel lymph node biopsy, a most radical approach was conducted in our population [14].

The total of 21 patients presented the expression of the ER and 16 patients underwent hormonal therapy with Tamoxifen and one with Aromatase Inhibitor, according to the recent guidelines of the American Society of Clinical Oncology (ASCO) [15].

Comparing the survival curve of our study with van der Pol *et al*. [11] study, a statistically significant difference (5-year survival 71.4% vs 55%) was found. However, this result may be influenced by the discrepancy between the two populations examined. Nevertheless, the most important data to highlight is that all these curves differ significantly from data regarding female patients in which the survival rate is certainly influenced by the screening programme. Moreover, the overall survival rate at 5 years after surgery is comparable to the survival rate found in the statistics regarding female breast cancer before 1989 (i.e., the year in which mammographic screening was introduced). According to the Italian Association of Medical Oncology (AIOM), the 5-year survival rate of women with breast cancer in Italy is 87% and does not present high heterogeneity among age groups [16].

The main limitations of this study include the small sample size, inherent to the rarity of the disease, and its monocentric design, which may limit the generalizability of the results; the variability in genetic testing due to the long data collection period; the absence of a long-term follow-up to assess late recurrences or survival outcomes; the lack of a matched control group to further analyze risk factors and outcomes; and the standardization of treatments performed, which does not allow for the evaluation of the effectiveness of multiple therapeutic approaches.

Conclusions

The lack of knowledge of male breast cancer in the population is the main reason for a delayed diagnosis, affecting the prognosis. Raising awareness about this disease is therefore one of the objectives of the study. The diagnostic and therapeutic protocols are based on female breast cancer studies, despite the prevalence of ductal histotype and the rarity of other histological variants, the constant expression of estrogen receptors and peculiar genetic characteristics allow us to consider male breast cancer as a nosological entity distinct from the female one.

Considering the lack of knowledge in the population and the high aggressiveness of the disease when diagnosed in locally advanced or metastatic stages, the results of our study

allow us to suggest the introduction of a targeted screening programme in all patients with first-degree relatives with breast cancer or known genetic mutations in *BRCA1* and *BRCA2* genes from 60 years of age onwards. Ultrasound examination is recommended as the screening method. Furthermore, the economic impact of implementing such a targeted screening programme should be thoroughly investigated to evaluate its feasibility and cost-effectiveness.

Our findings confirm that the majority of cases involve invasive ductal carcinoma, consistent with the known prevalence of this histological subtype in male breast cancer. The limited diversity in histological subtypes, with only one patient presenting invasive lobular carcinoma, highlights the distinct biological behavior of male breast cancer compared to its female counterpart.

This study does not allow to acquire data regarding the totality of the possible expressions and characteristics of male breast cancer, but it is proposed as a portrait of 18 years of mono-institutional experience. Indeed, although the existing literature onthe subject has already addressed the issue, we still not have all the pieces of the puzzle that allow the scientific community to fully understand this disease.

Availability of Data and Materials

Data and materials are available from the corresponding author upon reasonable request.

Author Contributions

FT and SM designed the study. FT, AL EMN and AC collected and analyzed the data. FT and AC drafted the manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The Sant'Andrea Hospital, Sapienza University of Rome Ethics Committee exempted the study from ethical approval. This study was conducted in accordance with the principles of the Declaration of Helsinki. All participants provided informed consent prior to inclusion in the study.

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Conflict of Interest

The authors declare no conflict of interest.

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