Breast Cancer Research and Treatment
https://doi.org/10.1007/s10549-024-07380-0

RESEARCH

Male breast cancer: a multicenter study to provide a guide for proper management

Germana Lissidini[1] · Luca Nicosia[2] · Manuela Sargenti[1] · Maria Cristina Cucchi[3] · Alessandra Fabi[4] · Giuseppe Falco[5] · Marco Gardani[6] · Greta Grilz[7] · Ilaria Maugeri[8] · Roberto Murgo[9] · Alessandro Neri[10] · Francesca Pellini[11] · Cristiana Sensi[12] · Serena Scomersi[13] · Mario Taffurelli[14] · Vincenzo Bagnardi[15] · Chiara Oriecuia[16,17] · Eleonora Pagan[15] · Claudia Sangalli[18] · Massimo Dessena[19] · Paolo Veronesi[1,20] · Viviana Galimberti[1]

Received: 29 February 2024 / Accepted: 14 May 2024

Abstract

Introduction To offer an extensive retrospective experience on the management of male breast cancer.

Methods A multicenter retrospective observational cohort study was conducted, including male patients diagnosed with breast cancer (invasive or in situ) in 12 Italian breast units from January 1975 to December 2019. Patients aged 18 years or older were assessed for eligibility. Exclusion criteria were metastatic cancer at diagnosis, previous cancer(s), received neoadjuvant treatment, incomplete data on (neo) adjuvant treatment(s), and/or follow-up data. Data on radiological examinations, demographic characteristics, risk factors, histological features, receptor status, treatments, and follow-up were collected.

Results In a series of 671 male patients with breast cancer assessed for eligibility, 403 (28 in situ and 375 invasive neoplasms) were included in the study. All included patients underwent surgery. The median age at surgery was 63.8 years (IQR 56.1–72.1). In 68% of cases, patients underwent echography, and in 55.1%, a mammography. Most patients were ER and PR positive (63.8%), HER2 negative (80.4%), with high (≥ 20%) Ki67 values (61.3%), and luminal B subtype (51.1%). The 10-year overall survival was 73.6% (95% CI 67.0–79.1) for invasive breast cancer and 90% (95% CI 65.6–97.4) for in situ breast cancer. In patients with invasive breast cancer, at univariable analysis, having a G3 tumor (vs. G1), pT2/3/4 (vs. pT1), pN2/3 (vs. pN0), luminal B subtype with Ki67 ≥ 20% (vs. Luminal A), were significantly associated with a higher risk of death. In multivariable analyses, pT2/3/4 (vs. pT1) remained significantly associated with a higher risk of death (HR 3.14, 95% CI 1.83–5.39), and having a HER2 positive or a triple-negative subtype (vs. Luminal A) was also significantly associated with a higher risk of mortality (HR 4.76, 95% CI 1.26–18.1).

Conclusion Male breast cancer is a rare disease, the better understanding of which is necessary for a more effective diagnostic and therapeutic approach.

Keywords Male breast cancer · Surgical treatment · Follow-up · Breast

Introduction

Breast cancer in men, though exceptionally rare, presents a multifaceted medical challenge, and a complete understanding of its intricacies and associated risk factors continues to elude the medical community. The incidence rate of male breast cancer (MBC) is a mere 1 in 100,000 in Europe, contributing just 1% to the total breast cancer cases globally, and representing a mere 0.3% of all cancers diagnosed in men [1]. What sets MBC apart is its heightened mortality rate when compared to its female counterpart, underscoring the urgent need for increased awareness and exploration of this relatively neglected condition [2].

The challenges intertwined with MBC, including delayed diagnosis due to its later onset and limited awareness leading to fewer screenings, pose significant threats to the survival outcomes of affected individuals. Despite these formidable obstacles, an array of studies suggests that male breast neoplasia is intricately linked to distinct risk factors and biological foundations. Recognizing and disseminating knowledge about this disease is paramount, as it plays a pivotal

Germana Lissidini and Luca Nicosia have contributed equally and share the first authorship.

Extended author information available on the last page of the article

Published online: 19 June 2024

role in improving prognosis through timely and appropriate management.

Against this backdrop, the principal objective of the present study is to conduct a thorough retrospective analysis, delving into various facets of MBC. This comprehensive exploration encompasses modes of presentation and diagnosis, identifiable risk factors, essential biological characteristics, major treatment modalities, and survival rates among male breast cancer patients. The overarching goal is to offer valuable insights that can illuminate medical professionals, researchers, and the general public about the nuanced dimensions of MBC, thereby contributing to a deeper understanding, early detection, and improved outcomes for those grappling with this exceedingly rare form of cancer. As we embark on this investigative journey, our commitment is to provide a wealth of information that transcends the statistical rarity of MBC, fostering a collective awareness that can drive advancements in research, medical practice, and public consciousness, ultimately leading to more effective strategies for the prevention, diagnosis, and treatment of male breast cancer.

Methods

This is a multicenter retrospective observational cohort study conducted by The Italian Society of Surgical Oncology (SICO) Breast Oncoteam, encompassing patients treated in 12 Italian breast units (the list of participating centers is provided in the Appendix). The study received notification to the Ethics Committee and obtained approval from the Institutional Review Board. The database included male patients, 18 years of age or older, diagnosed with breast cancer (invasive or in situ) from January 1975 to December 2019. However, due to limitations in available data or follow-up, only patients who underwent surgery between 1992 and 2019 were included in this analysis.

Data were collected regarding clinical information and radiological examinations conducted for diagnosis by the surgeons at each involved center. Patient characteristics encompassed age at surgery, family history of cancer(s), and prostate-specific antigen (PSA). Clinical characteristics comprised tumor size, nodal status, TNM stage according to the American Joint Committee on Cancer (AJCC), WHO histologic type, Nottingham combined histologic grade, estrogen receptor (ER) status, progesterone receptor (PR) status, proliferative index Ki67, human epidermal growth factor receptor 2 (HER2) status, and type of surgery performed. Postoperative adjuvant treatments (including chemotherapy, hormone therapy, and radiotherapy) were also documented. ER, PR, and HER2 expressions were determined through immunohistochemistry testing. In equivocal HER2 cases, data from fluorescent in-situ hybridization assay records were utilized for molecular stratification. Invasive breast cancer subtypes were categorized into the following groups according to St. Gallen 2013 [3]: luminal A cases (ER+/PR+/HER2−, Ki67 < 20%), luminal B cases (luminal B HER2−: HER+/HER2− and at least one of Ki67 ≥ 20% or PR−, luminal B HER2+: ER+/HER2+/any Ki67/any PR), HER2 + (ER−/PR−/HER2 +), and triple-negative breast cancers (ER−/PR−/HER2−). Data of molecular subtypes were collected in alignment with the TNM classification of the eighth edition of the American Joint Commission [4].

Follow-up data were also collected. Statistical analysis presented continuous variables as medians with interquartile ranges (IQR) and dichotomous variables as counts and percentages. Endpoints evaluated were disease-free survival (DFS) and overall survival (OS). DFS was defined as the time (years) from surgery until local recurrence, metastasis, other primary carcinoma, or death, whichever occurred first. OS was defined as the time (years) from surgery until death (from any cause). Kaplan–Meier method was used to estimate the OS and DFS functions. Clinically relevant variables, such as grade, tumor size, nodal status, and subtype were analyzed with univariable and multivariable Cox regression models to quantify their impact on OS and DFS for patients with invasive breast cancer. Variables of adjuvant treatments (chemotherapy, hormone therapy, and radiotherapy) were not considered in the univariable and multivariable analysis due to their high correlation with tumor characteristics and subtype. All reported p-values are two-sided. Statistical analyses were conducted using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

On a series of 671 male patients with breast cancer assessed for eligibility, 268 were excluded from our analyses for one or more of the following reasons: metastatic cancer at diagnosis, previous cancer(s), neoadjuvant treatment received, incomplete data on (neo) adjuvant treatment(s), and/or follow-up data. Four hundred-three patients (28 with ductal carcinoma in situ, DCIS, and 375 with invasive neoplasm) were included in the analyses (Fig. 1). All included patients underwent surgery during the period spanning from 1992 to 2019. Overall, the median age at surgery was 63.8 years (IQR 56.1–72.1) [64.3 years (IQR 56.3–72.6) in patients

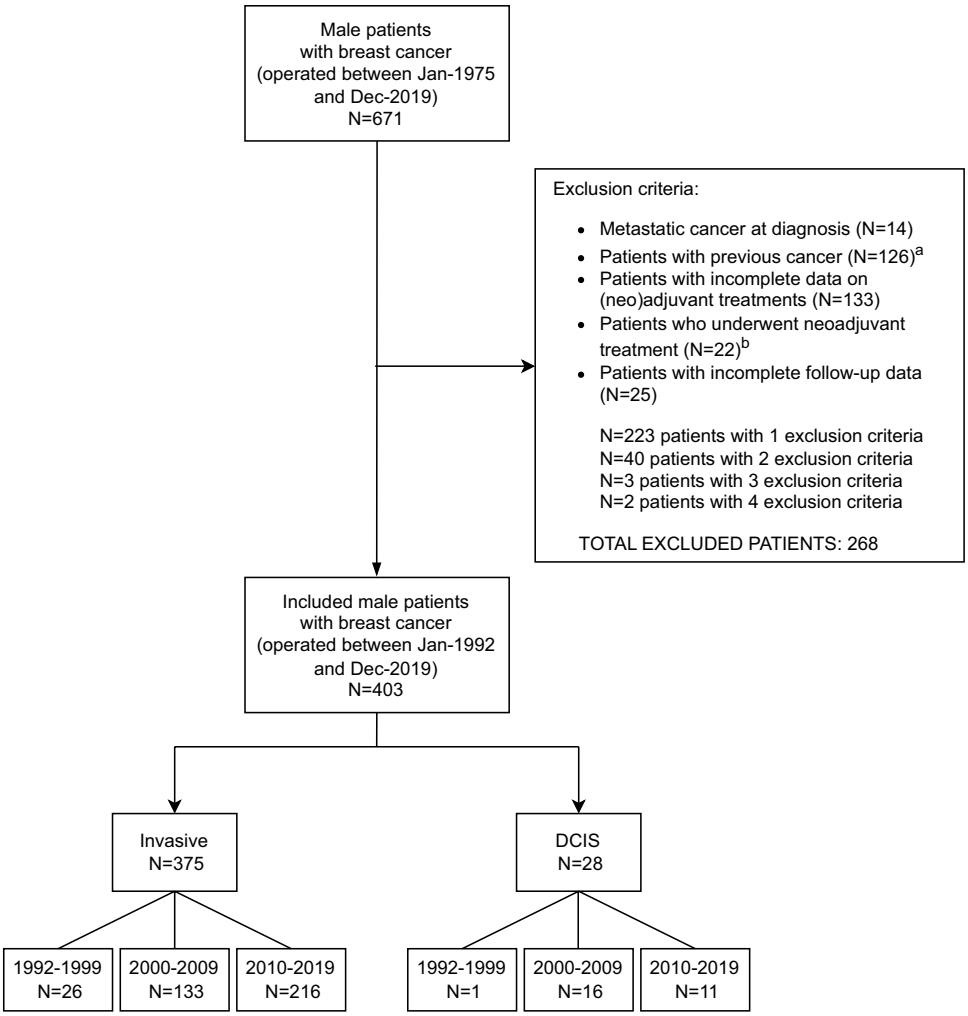

Fig. 1 Flowchart for patient's selection. *DCIS* ductal carcinoma in situ [a]Urinary and genital (N = 38), digestive system (N = 22), multiple sites (N = 20), skin (N = 15), hematopoietic and lymphoid tissues (N = 10), breast (N = 4), soft tissue and bone (N = 4), endocrine organs (N = 3), head and neck (N = 3), thoracic (N = 3), not specified (N = 4). [b]Only chemotherapy (N = 8), only hormone therapy (N = 11), both chemotherapy and hormone therapy (N = 3).

with invasive tumors, 60.5 years (IQR 47.4–66.1) in those with DCIS].

Table 1 shows the distribution of patient characteristics and preoperative diagnostic examinations. The vast majority of our patients were of Caucasian ethnicity (99.5%). In 31.3% of cases, familiarity with cancer was reported. Only 16.9% of patients had genetic testing, with a mutation found in 27.9% of cases. Most of the patients had a preoperative radiological diagnostic examination: 68% had at least an echography, and 55.1% had at least a mammography. In 10.7% of cases, patients had breast magnetic resonance imaging (MRI) with contrast. In 36.2% of cases, patients had preoperative needle biopsy or fine needle aspiration cytology (FNAC), respectively, while only 4.2% had both (Table 1).

The distribution of tumor stage and lymph node surgical procedures is summarized in Table 2. Most of the tumors presented with G2 grading (51.4%) and pT1 (58.6%). In 51.4% of cases, patients underwent axillary dissection (Table 2).

Table 3 shows the distribution of tumor characteristics and treatments. Most of the patients were ER and PR positive (63.8%) and HER2 negative (80.4%). Most of the neoplasms had high (≥ 20%) Ki67 values (61.3%) and luminal B subtype (51.1%). The main histological subtype was ductal carcinoma (87.8%). Most of the patients underwent hormone therapy (HT) with (31.8%) or without (52.4%) chemotherapy (CT) and did not undergo radiotherapy (RT, 56.8%; Table 3).

After a median follow-up of 7.5 years (IQR 3.9–12.3), 85 MBC patients died (21.1%), 3 with DCIS and 82 with invasive BC. The 10-year OS was 74.9% (95% CI 68.7–80.1) overall, 73.6% (95% CI 67.0–79.1) for invasive BC, and 90% (95% CI 65.6–97.4) for DCIS (Table 4 and Fig. 2A). One hundred twenty-nine patients experienced disease recurrence or death (DFS events). The most common event was distant

Table 1 Distribution of patient characteristics and preoperative diagnostic examinations

	Invasive N = 375		DCIS N = 28		All N = 403	
	N	%	N	%	N	%
Caucasian ethnicity						
No	2	0.5	0	–	2	0.5
Yes	373	99.5	28	100	401	99.5
Familiarity						
No	254	67.7	23	82.1	277	68.7
Yes	121	32.3	5	17.9	126	31.3
Genetic test						
No	310	82.7	25	89.3	335	83.1
Yes	65	17.3	3	10.7	68	16.9
Mutations						
No	37	56.9	3	100	40	58.8
Yes	19	29.2	0	–	19	27.9
Unknown	9	13.9	0	–	9	13.2
High PSA						
No	105	28.0	6	21.4	111	27.5
Yes	11	2.9	1	3.6	12	3.0
Unknown	259	69.1	21	75.0	280	69.5
Side						
Right	167	44.5	16	57.1	183	45.4
Left	195	52.0	12	42.9	207	51.4
Bilateral	3	0.8	0	–	3	0.7
Unknown	10	2.7	0	–	10	2.5
Mammography						
No	79	21.1	5	17.9	84	20.8
Yes	203	54.1	19	67.9	222	55.1
Unknown	93	24.8	4	14.3	97	24.1
Ecography						
No	20	5.3	3	10.7	23	5.7
Yes	253	67.5	21	75.0	274	68.0
Unknown	102	27.2	4	14.3	106	26.3
MRI						
No	268	71.5	25	89.3	293	72.7
Yes	42	11.2	1	3.6	43	10.7
Unknown	65	17.3	2	7.1	67	16.6
Biopsy						
None/missing	91	24.3	3	10.7	94	23.3
Only agobiopsy	135	36.0	11	39.3	146	36.2
Only FNAC	134	35.7	12	42.9	146	36.2
Both	15	4.0	2	7.1	17	4.2

DCIS ductal carcinoma in situ, *FNAC* fine needle aspiration cytology, *MRI* magnetic resonance imaging, *PSA* prostate-specific antigen

recurrence (35.7%). The 10-year DFS was 61.1% (95% CI 54.5–67.0) overall, 59.9% (95% CI 53.0–66.0) for invasive BC, and 75.6% (95% CI 44.8–90.7) for DCIS (Table 4 and Fig. 2B).

Tables 5 and 6 show the univariable and multivariable Cox regression models for OS and DFS, respectively, in the subgroup of patients with invasive BC (N = 375). In univariable analysis, having a G3 tumor (vs. G1), pT2/3/4 (vs. pT1), pN2/3 (vs. pN0), luminal B subtype with Ki67 ≥ 20% (vs.

Table 2 Distribution of tumor stage and lymph nodes surgical procedures

	Invasive N = 375		DCIS N = 28		All N = 403	
	N	%	N	%	N	%
Grade						
G1	26	6.9	8	28.6	34	8.4
G2	196	52.3	11	39.3	207	51.4
G3	139	37.1	0	–	139	34.5
Unknown	14	3.7	9	32.1	23	5.7
pT						
pT1	224	59.7	12	42.9	236	58.6
pT2	123	32.8	7	25.0	130	32.3
pT3	3	0.8	1	3.6	4	1.0
pT4	14	3.7	0	–	14	3.5
Unknown	11	2.9	8	28.6	19	4.7
pN						
pN0	174	46.4	21	75.0	195	48.4
pN1	111	29.6	0	–	111	27.5
pN2	30	8.0	0	–	30	7.4
pN3	42	11.2	0	–	42	10.4
pNx	18	4.8	7	25.0	25	6.2
SLNB						
Missing	2	0.5	1	3.6	3	0.7
No	168	44.8	11	39.3	179	44.4
Yes	205	54.7	16	57.1	221	54.8
Number of sentinel lymph nodes removed						
Unknown	3	1.5	0	–	3	1.4
1	113	55.1	8	50.0	121	54.8
> 1	89	43.4	8	50.0	97	43.9
Number of sentinel lymph nodes positive						
Unknown	3	1.4	0	–	3	1.4
0	130	63.4	16	100	146	66.1
1	66	32.2	0	–	66	29.9
> 1	6	2.9	0	–	6	2.7
Axillary dissection						
No	153	40.8	26	92.9	179	44.4
Yes	206	54.9	1	3.6	207	51.4
Unknown	16	4.3	1	3.6	17	4.2

DCIS ductal carcinoma in situ, *SLNB* sentinel lymph node biopsy

Luminal A) were significantly associated with a higher risk of death (Table 5).

In the multivariable analysis, having a HER2 positive or a triple-negative subtype (vs. Luminal A) was also significantly associated with a higher risk of mortality (HR 4.76, 95% CI 1.26–18.1; Table 5).

Similar results were found for DFS. In univariable analysis, having a G3 tumor (vs. G1), pT2/3/4 (vs. pT1), pN2/3 (vs. pN0), luminal B subtype with Ki67 ≥ 20% or HER2 positive or triple-negative disease (vs. Luminal A), and having received radiotherapy were significantly associated with a higher risk of recurrence or death (Table 6). In multivariable analyses, pT, pN, and subtype remained significantly associated with a higher risk of recurrence or death: pT2/3/4 vs. pT1 HR 1.57 (95% CI 1.04–2.38), pN2/3 vs. pN0 HR 1.99 (95% CI 1.18–3.36), HER2 positive or triple-negative subtype vs. Luminal A subtype HR 5.25 (95% CI 1.69–16.3; Table 6).

Table 3 Distribution of tumor characteristics and treatments

	Invasive N = 375		DCIS N = 28		All N = 403	
	N	%	N	%	N	%
ER/PR						
Not expressed (Both 0)	6	1.6	0	–	6	1.5
Incompletely expressed (ER < 50 or PR < 50)	119	31.7	7	25.0	126	31.3
Highly expressed (ER ≥ 50 & PR ≥ 50)	244	65.1	13	46.4	257	63.8
Unknown	6	1.6	8	28.6	14	3.5
Ki67 (%)						
< 20%	120	32.0	13	46.4	133	33.0
≥ 20%	244	65.1	3	10.7	247	61.3
Unknown	11	2.9	12	42.9	23	5.7
HER2						
Negative	309	82.4	15	53.6	324	80.4
Positive	50	13.3	0	–	50	12.4
Unknown	16	4.3	13	46.4	29	7.2
Subtype						
Luminal A	99	26.4	12	42.9	111	27.5
Luminal B (Ki67 ≥ 20%)	203	54.1	3	10.7	206	51.1
Luminal B (HER2 positive)	46	12.3	0	–	46	11.4
HER2 positive	3	0.8	0	–	3	0.7
Triple negative	3	0.8	0	–	3	0.7
Unknown	21	5.6	13	46.4	34	8.4
Histotype						
Ductal	326	86.9	28	100.0	354	87.8
Lobular	6	1.6	0	–	6	1.5
Papillary	27	7.2	0	–	27	6.7
Other	8	2.1	0	–	8	2.0
Unknown	8	2.1	0	–	8	2.0
Systemic adjuvant treatment						
No adjuvant treatment	27	7.2	24	85.7	51	12.7
Only CT	13	3.5	0	–	13	3.2
Only HT	207	55.2	4	14.3	211	52.4
CT + HT	128	34.1	0	–	128	31.8
Radiotherapy						
No	202	53.9	27	96.4	229	56.8
Yes	173	46.1	1	3.6	174	43.2

CT chemotherapy, *DCIS* ductal carcinoma in situ, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *HT* hormone therapy, *PR* progesterone receptor

Discussion

Most of the knowledge regarding MBC treatment is derived from therapeutic strategies for female BC, despite significant differences between these two entities. Therefore, we conducted a multicenter study focusing on male patients with BC treated in 12 Italian breast units, providing an analysis of characteristics and survival rates at a national level. To our knowledge, this is the largest published series in our country, encompassing 403 patients.

BC incidence rates steadily increase with age in men, mirroring trends observed in women [5]. In our case series, the median age at surgery (63.8 years) is similar but slightly higher compared to that reported in the literature for women

Table 4 Overall survival and disease-free survival

	Invasive N = 375		DCIS N = 28		All N = 403	
	N	%	N	%	N	%
Median follow-up, yrs (IQR)	7.5 (3.9–12.3)		8.9 (3.3–12.3)		7.5 (3.9–12.3)	
Overall survival (OS)						
Observed deaths	82	21.9	3	10.7	85	21.1
5-yr OS (95% CI)	88.6 (84.4–91.7)		95.0 (69.5–99.3)		89.0 (85.0–92.0)	
10-yr OS (95% CI)	73.6 (67.0–79.1)		90.0 (65.6–97.4)		74.9 (68.7–80.1)	
Disease-free survival (DFS)						
Observed events, N (%)	123	32.8	6	21.4	129	32.0
Death from breast cancer	5	4.1	0	–	5	3.9
Death from non-breast cancer cause	13	10.6	2	33.3	15	11.6
Death from unknown cause	21	17.1	1	16.7	22	17.1
Distant recurrence	46	37.4	0	–	46	35.7
Invasive contralateral breast cancer	9	7.3	0	–	9	7.0
Invasive ipsilateral breast tumor recurrence	1	0.8	0	–	1	0.8
Local/regional invasive recurrence	11	8.9	2	33.3	13	10.1
Second primary invasive cancer (non-breast)	17	13.8	1	16.7	18	14.0
5-yr DFS (95% CI)	78.0 (73.0–82.2)		90.0 (65.6–97.4)		78.8 (74.0–82.8)	
10-yr DFS (95% CI)	59.9 (53.0–66.0)		75.6 (44.8–90.7)		61.1 (54.5–67.0)	

DCIS ductal carcinoma in situ, *IQR* interquartile range

(62 years). This may reflect two distinct aspects: firstly, male breast cancer is often accompanied by less awareness, and secondly, men are not included in screening policies due to the very low incidence of MBC.

Several risk factors causing breast cancer in men have been identified, including general and genetic factors. Among genetic risk factors, radiation exposure, age, and obesity are the most common. High estrogen levels are also associated with MBC, often caused by chromosomal disorders such as Klinefelter syndrome [6]. From our retrospective cohort, we observe a significant proportion of patients with mutations (27.9%) or a family history (31.3%) of malignancy. However, analyses of potential genetic mutations or associated syndromes (such as Klinefelter syndrome and obesity) have rarely been performed. This highlights the need for increased awareness and a standardized approach to this rare but important disease.

Approximately 1 in 5 men who develop breast cancer have a family history of the disease, and we found that 31.5% of all patients have a family history of malignancy in general. Therefore, the American Society of Clinical Oncology (ASCO) guidelines recommend offering genetic counseling to all men diagnosed with breast cancer. Interestingly, as reported by Yadav et al. [7], almost 20% of MBC patients are diagnosed after another tumor diagnosis, with prostate, colon, and genitourinary cancers being the most common. Among our 671 patients, 126 (18.9%) had a previous tumor (mainly genitourinary), and they were excluded from the analysis. MBC can present in several ways, with a palpable breast mass being the most common presentation. Almost 90% of patients in our series were diagnosed with early-stage disease, considering the thinness of the male mammary gland and the rapid clinical detection of palpable masses [8]. Most patients (90.9%) in our series were pT1 or pT2, confirming this observation. Additionally, half of the patients had disease without nodal involvement.

In suspected cases, men should be referred for standard imaging, often consisting of ultrasound rather than mammography, as seen in our series where breast ultrasound was performed in 68% of cases. All suspicious lesions should undergo biopsy, with core needle biopsy being the preferred method. However, cytology can provide a satisfactory specimen and could be considered a reasonable option, especially considering the low breast thickness [9]. In our cohort, both methods were performed in similar proportions.

In female BC, invasive ductal carcinoma is the most common tumor histology [10], and invasive lobular carcinoma is very infrequent, comprising less than 2% of total cases [11]. Our cohort confirms this observation,

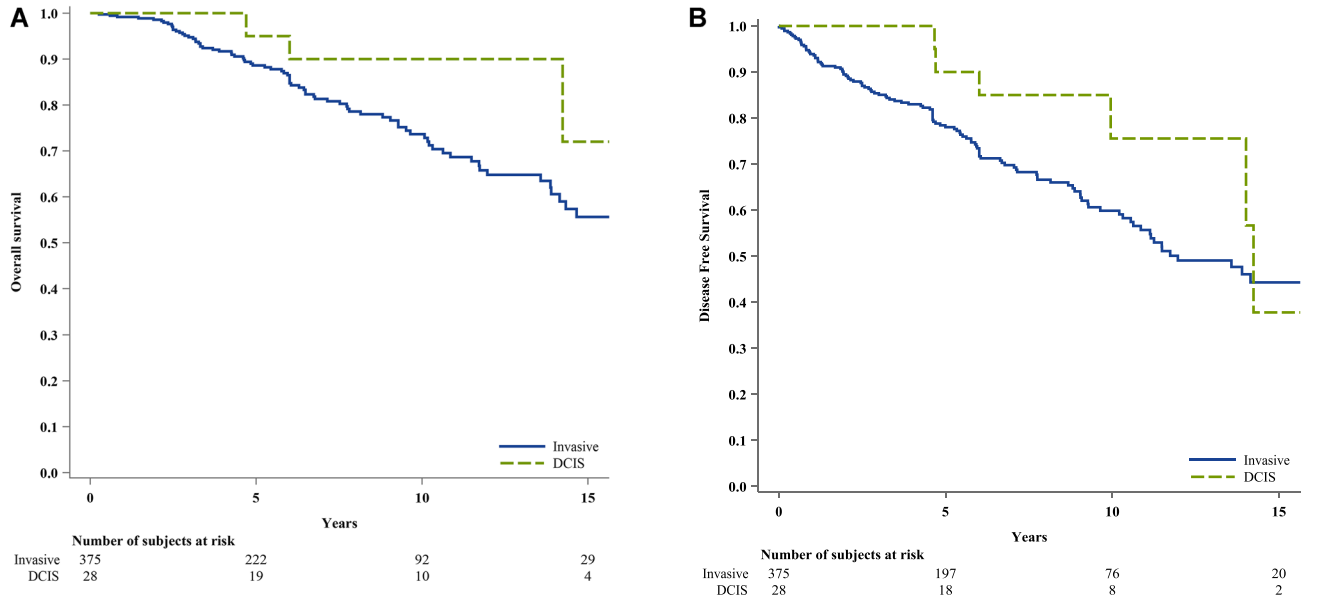

Fig. 2 Kaplan–Meier curves for overall survival (OS; panel A) and disease-free survival (DFS; panel B) according to tumor invasion

with 86.9% of cases being invasive ductal carcinoma and 1.5% invasive lobular carcinoma. This could be partially explained by the occasional formation of terminal lobules in male breast tissues, associated with estrogen exposure in females [12]. The main reason for the majority of MBC being invasive (over 90% in our series) is the lack of substantial evidence supporting screening mammograms in the general male population. As widely reported in published data, the majority of male breast cancers are grade 2 [13, 14]. Most of them are ER and PR receptor positive and HER2 negative [7, 15]. Our series confirms this, with G2 neoplasia reported in 51.4% of cases and high expression of ER and PR in 63.8% of cases. In more than 80% of cases, we had HER2-negative cancers.

In a large international MBC program consortium, Cardoso F et al. [16] retrospectively evaluated 1483 patients from 1990 to 2010 and found that 99% of patients were ER+, 82% PR+, 8.7% HER2 negative, and only 0.3% triple-negative.

Triple-negative cancers were extremely rare in our series, occurring in only 3 cases. The majority of patients showed a high rate of Ki67 (61.3%), considering the cut-off of 20% as established by the 2013 St. Gallen consensus guidelines [17]. Currently, the treatment of MBC is based on standard care developed for female breast cancer, with no prospective randomized studies available to date for the management of MBC.

Surgical treatment is usually the first therapeutic approach, and mastectomy is the intervention of choice [18]. One of the most important effects of non-special type (NST) regards the downstaging of tumor size, allowing for breast conservative surgery with aesthetic and functional advantages. However, this objective is less relevant in MBC patients, as more than two-thirds of them underwent mastectomy, considering different goals in cosmetic outcomes. Additionally, due to anatomical conditions (the male areola almost totally corresponds to the glandular residue), modest aesthetic value, and poor psychosocial implications, mastectomy is the most frequently performed surgery [18]. Despite this evidence, some authors [19, 20] suggest considering less aggressive approaches in the future, such as BCS or different conservative mastectomies.

Although no randomized clinical trial has been conducted on the use of sentinel lymph node biopsy (SLNB), this procedure can be applied with the same indications and technique as axilla management in female BC [21]. We performed SLNB in almost half of our patients and axillary dissection in 51.4%. As in women, the standard treatment option for men with early-stage breast cancer is surgery followed by adjuvant hormone therapy (HT), chemotherapy (CT), or radiation therapy (RT), depending on surgical outcomes, hormone receptor status, and prognostic factors [18].

No prospective data about adjuvant CT in males are available, but several observational studies showed better outcomes in terms of mortality rates and recurrence in men treated with adjuvant CT, especially in those with nodal involvement disease [18].

Table 5 Univariable and multivariable Cox regression model for overall survival (OS) in patients with invasive breast cancer (N = 375)

	Number of patients	Number of events	Univariable		Multivariable	
			OS-HR (95% CI)	*p-value*	OS-HR (95% CI)	*p-value*
Grade						
G1	26	4	1.00	–	1.00	–
G2	196	45	2.19 (0.79–6.11)	*0.134*	1.49 (0.43–5.21)	*0.529*
G3	139	32	3.10 (1.09–8.82)	*0.034*	1.34 (0.35–5.05)	*0.667*
pT						
pT1	224	31	1.00	–	1.00	–
pT2/3/4	140	47	3.81 (2.37–6.12)	*<.001*	3.14 (1.83–5.39)	*<.001*
pN						
pN0	174	28	1.00	–	1.00	–
pN1	111	19	1.24 (0.69–2.23)	*0.478*	0.79 (0.42–1.49)	*0.469*
pN2/3	72	27	2.86 (1.67–4.88)	*<.001*	1.50 (0.80–2.80)	*0.207*
Subtype						
Luminal A	99	18	1.00	–	1.00	–
Luminal B (Ki67 ≥ 20%)	203	48	1.77 (1.03–3.06)	*0.039*	1.37 (0.75–2.48)	0.303
Luminal B (HER2 positive)	46	8	1.13 (0.49–2.59)	*0.779*	0.78 (0.32–1.91)	0.586
HER2 positive/triple negative	6	3	2.57 (0.76–8.77)	*0.130*	4.76 (1.26–18.1)	0.022
Systemic adjuvant treatment						
No adjuvant treatment	27	7	1.00	–		
Only CT	13	7	2.09 (0.73–5.98)	*0.167*		
Only HT	207	36	0.52 (0.23–1.18)	*0.117*		
CT + HT	128	32	0.91 (0.40–2.06)	*0.819*		
Radiotherapy						
No	202	34	1.00	–		
Yes	173	48	1.63 (1.05–2.54)	*0.031*		
Year of surgery						
1992–1999	26	11	1.00	–		
2000–2009	133	46	1.13 (0.56–2.30)	*0.726*		
2010–2019	216	25	1.23 (0.55–2.75)	*0.607*		

CT chemotherapy, *DCIS* ductal carcinoma in situ, *HER2* human epidermal growth factor receptor 2, *HT* hormone therapy

The impact of adjuvant RT on overall survival in MBC is greater than in females [22, 23]. The indications for RT come from the guidelines for females, and all men with BCS should undergo adjuvant RT [22]. Post-mastectomy radiation is more controversial in MBC, but several retrospective analyses showed improved outcomes in terms of local recurrence in post-mastectomy RT, particularly in node-positive disease [23].

The 10-year overall survival (OS) for the entire cohort stood at 74.9%. Mortality risk showed a significant increase in patients with G3 tumor grade, pT2/3/4, pN2/3, and Luminal B with Ki67 ≥ 20%. These findings align with results from other published studies [24].

The risk of recurrence can be quantified by gene recurrence scores such as Oncotype DX and MammaPrint, widely used in female breast cancer treatment [25]. The most used chemotherapeutic schemes are usually CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) and FAC (anthracycline, 5-fluorouracil, and methotrexate).

Early diagnosis is particularly crucial, especially in patients with a family history and genetic predisposition. For those with a high genetic and familial predisposition, it is recommended to consider at least an annual breast ultrasound [26, 27].

Our study is constrained by its retrospective design, which prevented the collection of comprehensive data for all patients, such as information on risk factors and mutations.

One of the primary limitations of the study is the extended observation period of the involved patients, which

Table 6 Univariable and multivariable Cox regression model for disease-free survival (DFS) in patients with invasive breast cancer ($N=375$)

	Number of patients	Number of events	Univariable		Multivariable	
			OS-HR (95% CI)	*p-value*	OS-HR (95% CI)	*p-value*
Grade						
G1	26	7	1.00	–	1.00	–
G2	196	65	1.65 (0.76–3.62)	*0.208*	1.39 (0.53–3.67)	*0.507*
G3	139	48	2.34 (1.05–5.19)	*0.037*	1.36 (0.48–3.86)	*0.560*
pT						
pT1	224	60	1.00	–	1.00	–
pT2/3/4	140	59	2.05 (1.43–2.96)	*<.001*	1.57 (1.04–2.38)	*0.033*
pN						
pN0	174	41	1.00	–	1.00	–
pN1	111	36	1.61 (1.02–2.52)	*0.039*	1.30 (0.81–2.10)	*0.273*
pN2/3	72	35	2.58 (1.64–4.07)	*<.001*	1.99 (1.18–3.36)	*0.010*
Subtype						
Luminal A	99	27	1.00	–	1.00	–
Luminal B (Ki67 ≥ 20%)	203	74	1.65 (1.06–2.57)	*0.026*	1.35 (0.83–2.20)	*0.222*
Luminal B (HER2 positive)	46	12	1.04 (0.53–2.05)	*0.912*	0.89 (0.43–1.83)	*0.751*
HER2 positive/triple negative	6	4	2.88 (1.00–8.24)	*0.049*	5.25 (1.69–16.3)	*0.004*
Systemic adjuvant treatment						
No adjuvant treatment	27	8	1.00	–		
Only CT	13	8	2.51 (0.94–6.70)	*0.065*		
Only HT	207	60	0.80 (0.38–1.67)	*0.550*		
CT + HT	128	47	1.23 (0.58–2.60)	*0.591*		
Radiotherapy						
No	202	50	1.00	–		
Yes	173	73	1.82 (1.27–2.62)	*<.001*		
Year of surgery						
1992–1999	26	14	1.00	–		
2000–2009	133	58	0.88 (0.48–1.61)	*0.667*		
2010–2019	216	51	1.15 (0.61–2.19)	*0.663*		

CT chemotherapy, *DCIS* ductal carcinoma in situ, *HER2* human epidermal growth factor receptor 2, *HT* hormone therapy

needs to be juxtaposed with the diagnostic and therapeutic changes that have transpired over the years (1999–2019).

However, to our knowledge, this is the largest cohort ever analyzed in our country. Future studies should prospectively assess the role of neoadjuvant and adjuvant treatments and consider secondary aspects such as emotional consequences, sexual dysfunction, or fertility preservation strategies.

Conclusion

Male breast cancer is a rare disease, and a better understanding is essential for a more effective diagnostic and therapeutic approach. Our study, with its extensive cohort, can contribute to enhancing the management of patients with male breast carcinoma.

Appendix

Participating centers and principal investigators

Bologna—Ospedale Bellaria Carlo Alberto Pizzardi; C. La Tessa

Bologna—Policlinico di Sant'Orsola (Bologna); S. Zanotti

Milano—Istituto Europeo di Oncologia; xxx

Milano—Istituto Nazionale dei Tumori; S. Folli, V. Capizzi

Piacenza—Breast Unit; M. Gardani

Reggio Emilia—AUSL-IRCCS; G. Falco

Roma—Istituti Fisioterapici Ospitalieri e Istituto Tumori Regina Elena; A. Fabi

Siena—Azienda ospedaliero-universitaria Senese; A. Neri

Torino—Ospedale Cottolengo; R. Bussone

Trieste—Ospedale di Cattinara; xxx

Verona—AOUI Azienda Ospedaliera Universitaria Integrata; F. Pellini

Viterbo—Ospedale di Belcolle; C. Sensi

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10549-024-07380-0.

Author contributions G.L and L.N: writing the Main manuscript; V.B; C.O; E.P: statistical analysis; V.G and P.V: supervision and resources. All authors: review and editing.

Funding The authors have not disclosed any funding.

Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests The authors declare no competing interests.

References

1. Konduri S, Singh M, Bobustuc G, Rovin R, Kassam A (2020) Epidemiology of male breast cancer. Breast 54:8–14. https://doi.org/10.1016/j.breast.2020.08.010
2. Wang F, Shu X, Meszoely I et al (2019) Overall mortality after diagnosis of breast cancer in men vs women. JAMA Oncol 5(11):1589–1596. https://doi.org/10.1001/jamaoncol.2019.2803
3. Vasconcelos I, Hussainzada A, Berger S, Fietze E, Linke J, Siedentopf F, Schoenegg W (2016) The St. Gallen surrogate classification for breast cancer subtypes successfully predicts tumor presenting features, nodal involvement, recurrence patterns and disease free survival. Breast 29:181–185. https://doi.org/10.1016/j.breast.2016.07.016
4. Mittendorf EA, Bartlett JMS, Lichtensztajn DL, Chandarlapaty S (2018) Incorporating biology into breast cancer staging: American joint committee on cancer revisions and beyond. Am Soc Clin Oncol Educ Book 38(38):46. https://doi.org/10.1200/EDBK_200981
5. Liu N, Johnson KJ, Ma CX (2018) Male breast cancer: an updated surveillance, epidemiology, and end results data analysis. Clin Breast Cancer 18(5):e997–e1002. https://doi.org/10.1016/j.clbc.2018.06.013
6. Korde LA, Zujewski JA, Kamin L, Giordano S, Domchek S, Anderson WF, Bartlett JM, Gelmon K, Nahleh Z, Bergh J, Cutuli B (2010) Multidisciplinary meeting on male breast cancer: summary and research recommendations. J Clin Oncolo. https://doi.org/10.1200/JCO.2009.25.5729
7. Yadav S, Karam D, Bin Riaz I et al (2020) Male breast cancer in the United States: treatment patterns and prognostic factors in the 21st century. Cancer 126(1):26–36. https://doi.org/10.1002/cncr.32472
8. NCCN Guidelines Insights: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 1.2020 in: Journal of the National Comprehensive Cancer Network Volume 18 Issue 4 (2020). https://jnccn.org/view/journals/jnccn/18/4/article-p380.xml. Accessed 15 Oct 2021
9. Joshi A, Kapila K, Verma K (1999) Fine needle aspiration cytology in the management of male breast masses nineteen years of experience. Acta Cytol 43(3):334–338. https://doi.org/10.1159/000331077
10. Sarmiento S, McColl M, Musavi L et al (2020) Male breast cancer: a closer look at patient and tumor characteristics and factors that affect survival using the National Cancer Database. Breast Cancer Res Treat 180(2):471–479. https://doi.org/10.1007/s10549-020-05556-y
11. Leon-Ferre RA, Giridhar KV, Hieken TJ et al (2018) A contemporary review of male breast cancer: current evidence and unanswered questions. Cancer Metastasis Rev 37(4):599–614. https://doi.org/10.1007/s10555-018-9761-x
12. Michaels BM, Nunn CR, Roses DF (1994) Lobular carcinoma of the male breast. Surgery 115(3):402–405
13. Humphries MP, Sundara Rajan S, Honarpisheh H et al (2017) Characterisation of male breast cancer: a descriptive biomarker study from a large patient series. Sci Rep 7(1):45293. https://doi.org/10.1038/srep45293
14. Piscuoglio S, Ng CKY, Murray MP et al (2016) The genomic landscape of male breast cancers. Clin Cancer Res Off J Am Assoc Cancer Res 22(16):4045–4056. https://doi.org/10.1158/1078-0432.CCR-15-2840
15. Ruddy KJ, Winer EP (2013) Male breast cancer: risk factors, biology, diagnosis, treatment, and survivorship. Ann Oncol Off J Eur Soc Med Oncol 24(6):1434–1443. https://doi.org/10.1093/annonc/mdt025
16. Cardoso F, Bartlett JMS, Slaets L et al (2018) Characterization of male breast cancer: results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. Ann Oncol Off J Eur Soc Med Oncol 29(2):405–417. https://doi.org/10.1093/annonc/mdx651
17. Harbeck N, Thomssen C, Gnant M (2013) St. Gallen 2013, brief preliminary summary of the consensus discussion. Breast Care (Basel) 8(2):102–109. https://doi.org/10.1159/000351193
18. Fields EC, DeWitt P, Fisher CM, Rabinovitch R (2013) Management of male breast cancer in the United States: a surveillance, epidemiology and end results analysis. Int J Radiat Oncol Biol Phys 87(4):747–752. https://doi.org/10.1016/j.ijrobp.2013.07.016
19. Golshan M, Rusby J, Dominguez F, Smith BL (2007) Breast conservation for male breast carcinoma. Breast 16(6):653–656. https://doi.org/10.1016/j.breast.2007.05.012
20. Schnitt SJ, Hayman J, Gelman R, Eberlein TJ, Love SM, Mayzel K, Osteen RT, Nixon AJ, Pierce S, Connolly JL, Cohen P, Schneider L, Silver B, Recht A, Harris JR (1996) A prospective study of conservative surgery alone in the treatment of selected patients with stage I breast cancer. Cancer 77(6):1094–1100
21. Flynn LW, Park J, Patil SM, Cody HS, Port ER (2008) Sentinel lymph node biopsy is successful and accurate in male breast carcinoma. J Am Coll Surg 206(4):616–621. https://doi.org/10.1016/j.jamcollsurg.2007.11.005
22. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P et al (2011) Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet Lond Engl 378(9804):1707–1716. https://doi.org/10.1016/S0140-6736(11)61629-2
23. Abrams MJ, Koffer PP, Wazer DE, Hepel JT (2017) Postmastectomy radiation therapy is associated with improved survival in node-positive male breast cancer: a population analysis. Int J Radiat Oncol Biol Phys 98(2):384–391. https://doi.org/10.1016/j.ijrobp.2017.02.007

24. Masci G, Caruso M, Caruso F et al (2015) Clinicopathological and immunohistochemical characteristics in male breast cancer: a retrospective case series. Oncologist 20(6):586–592. https://doi.org/10.1634/theoncologist.2014-0243
25. Fan M, Cui Y, You C, Liu L, Gu Y, Peng W, Bai Q, Gao X, Li L (2022) Radiogenomic signatures of oncotype DX recurrence score enable prediction of survival in estrogen receptor-positive breast cancer: a multicohort study. Radiology 302(3):516–524. https://doi.org/10.1148/radiol.2021210738
26. Nicosia L, Lissidini G, Sargenti M, Bozzini AC, Farante G, Vila J, Oriecuia C, Pagan E, Bagnardi V, Lazzeroni M, Pesapane F, Sangalli C, Galimberti V, Cassano E, Veronesi P (2022) Ductal carcinoma in situ of the male breast: clinical radiological features and management in a cancer referral center. Breast Cancer Res Treat. https://doi.org/10.1007/s10549-022-06689-y
27. Nicosia L, Mariano L, Bozzini AC, Pesapane F, Bagnardi V, Frassoni S, Oriecuia C, Dominelli V, Latronico A, Palma S, Venturini M, Fontana F, Priolo F, Abiuso I, Sangalli C, Cassano E (2024) Radiological features of male breast neoplasms: how to improve the management of a rare disease. Diagnostics (Basel) 14(1):104. https://doi.org/10.3390/diagnostics14010104

Authors and Affiliations

Germana Lissidini[1] · Luca Nicosia[2] · Manuela Sargenti[1] · Maria Cristina Cucchi[3] · Alessandra Fabi[4] · Giuseppe Falco[5] · Marco Gardani[6] · Greta Grilz[7] · Ilaria Maugeri[8] · Roberto Murgo[9] · Alessandro Neri[10] · Francesca Pellini[11] · Cristiana Sensi[12] · Serena Scomersi[13] · Mario Taffurelli[14] · Vincenzo Bagnardi[15] · Chiara Oriecuia[16,17] · Eleonora Pagan[15] · Claudia Sangalli[18] · Massimo Dessena[19] · Paolo Veronesi[1,20] · Viviana Galimberti[1]

✉ Luca Nicosia
luca.nicosia@ieo.it

[1] Division of Breast Surgery, IEO, European Institute of Oncology IRCCS, 20141 Milan, Italy

[2] Division of Breast Radiology, IRCSS, IEO European Institute of Oncology, 20141 Milan, Italy

[3] Breast Surgery Unit, Bellaria-Maggiore Hospital, Bologna, Italy

[4] Precision Medicine Unit in Senology, Fondazione Policlinico Universitario A. Gemelli IRCCS Rome, Rome, Italy

[5] Breast Surgery Unit AUSL-IRCCS, Reggio Emilia, Italy

[6] Department of Surgery, Breast Unit Piacenza, Guglielmo da Saliceto Hospital, Piacenza, Italy

[7] Breast Surgery Unit Chirurgia Senologica Breast Unit Ospedale Cottolengo, Turin, Italy

[8] Breast Surgery Unit, Fondazione IRCCS Istituto Nazionale Tumori Di Milano, Milan, Italy

[9] Breast Surgery Unit, IRCCS Ospedale Casa Sollievo Della Sofferenza, San Giovanni Rotondo, Foggia, Italy

[10] Department of Medicine, Surgery and Neuroscience, University of Siena, Siena, Italy

[11] Complex Operative Unit (UOC) Breast Surgery, Breast Unit, Oncology Department Azienda Ospedaliera, Universitaria Integrata (AOUI) Verona, Verona, Italy

[12] Breast Surgery Unit, Ospedale Belcolle, Viterbo, Italy

[13] Division of General Surgery, Breast Unit, Hospital of Cattinara, Azienda Sanitaria Universitaria Giuliano Isontina, Trieste, Italy

[14] Breast and General Surgery Unit, IRCCS Azienda Ospedaliero-Universitaria Di Bologna, Bologna, Italy

[15] Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy

[16] Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

[17] Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy

[18] Clinical Trial Office, European Institute of Oncology IRCCS, 20141 Milan, Italy

[19] Breast Surgery Unit, Azienda Ospedaliero-Universitaria Di Cagliari, Cagliari, Italy

[20] Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy