



Prognosis of Male Breast Cancer: A Systematic Review of the Literature

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Authors' contributions

Authors PB and CRC managed the literature searches, collected the data, performed the statistical analysis, checked the analyses, drafted and revised the manuscript. Authors AB and LCST conceived the idea and its analytic strategy, checked data extraction and analyses, interpreted the findings, drafted and revised the manuscript. All authors read and approved the final manuscript.

Review Article

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ABSTRACT

Objective: to discuss disease-free survival, overall survival, cancer specific survival, mortality and potential complications of the surgical treatment of breast cancer in men. **Methods:** a systematic review of studies identified in the databases PubMed and Lilacs, using the keywords "breast cancer in men" in combination with the terms "treatment" and "complications", published from 2006 to 2011. **Results:** the review included 20 studies sourced from all continents except Latin America and Oceania. The selected studies included 9,634 cases of male breast cancer diagnosed and treated between 1969 and

2009. Several authors have shown that men and women with breast cancer have similar clinical patterns, and that the treatment of male breast cancer persists as an extrapolation of female breast cancer. In primary studies, male survival rates 5 years after surgery ranged from 42% to 100% and, after 10 years, from 43% to 83%. In secondary studies, cancer specific survival at 5 years was 59% and at 10 years was 34%. There was no information regarding complications of surgical treatment. Conclusion: a wide variation in the rates of disease-free survival and overall survival was observed. Further studies should address this specific group, focusing mainly on its biological nature, therapeutic approaches and post-operative complications.

Keywords: Breast cancer; men; treatment; survival; complications.

1. INTRODUCTION

The American Cancer Society (ACS) estimates that each year 1.4 million women are diagnosed with breast cancer (BC) in the world [1] and, for 2012, an incidence of 2,190 cases of male BC (MBC) was expected with 410 deaths from the disease [2]. In Brazil, for the year 2013, according to the National Cancer Institute/Ministry of Health, 52,680 new cases of female BC (FBC) were expected. Although there are no estimates of the incidence for males, among the 12,852 deaths from BC in 2010, 147 were men [3]. These figures have important implications for Public Health because 15% to 20% of men with breast cancer have blood relatives with a history of the disease [4,5]. Giordano et al., in a population-based study in the U.S., revealed that between 1973 and 1998 the incidence of MBC increased by 26% while FBC increased by 52% [6].

The scarcity of cases of breast cancer in men prevents the realization of randomized, controlled trials in order for there to be formal recommendations regarding specific diagnosis and treatment; extrapolation thus has to be made from studies with FBC. Furthermore, the rarity of the disease has led to delays in diagnosis, with more than 40% of patients diagnosed at stages III or IV; this results in an adverse prognosis, lower life expectancy related to older age at diagnosis, and the consequent impact of comorbidities and other neoplasms, entailing not only less favourable outcomes but also inducing biases in comparative studies. Lack of awareness in the medical community as well as in the general population also contributes to poor results [7-12].

The aim of this systematic review was to discuss disease-free survival (DFS), overall survival (OS), disease specific survival (DSS), mortality and potential complications of the surgical treatment of breast cancer in men.

2. MATERIALS AND METHODS

2.1 Strategy for the Identification of Studies

An online survey was conducted in the databases PubMed and Lilacs, using the keywords "breast cancer in men" in combination with the terms "treatment" and "complications", covering the period from 2006 to 2011. The languages used for selection were Spanish, French, English and Portuguese.

2.2 Criteria for Selection of Studies

2.2.1 Inclusion

Studies of human beings, conducted in the male population diagnosed with breast cancer, with a summary available in the database, with observational design (cohort, case-control and transversal), having the outcomes of interest: complications, survival (DFS, OS and DSS) and mortality.

2.2.2 Exclusion

Case reports or case series with less than 10 cases in men, studies with qualitative analysis, studies of risk factors for breast cancer as the primary outcome, studies involving other types of cancer, duplicate publications.

2.3 Methods of Revising the Eligibility Criteria for Studies

We identified 178 studies (170 PubMed and 9 Lilacs; 1 study was simultaneously documented in the two databases). Two reviewers evaluated the eligibility criteria in an open manner (unblinded). When there was no agreement among the reviewers regarding the eligibility criteria, a third reviewer was consulted, establishing a consensus.

The first review was conducted by reading the titles and abstracts; however, 150 studies were excluded: 29 descriptive reviews of the literature; 41 case reports; 2 qualitative studies; 34 studies assessing risk factors, family and genetic aspects; 31 studies involving other types of cancers and diseases; 3 studies of basic/experimental research and 10 diagnostic studies. For the second stage of the review, 28 studies were obtained in full in order to read the methodology and final assessment according to the eligibility criteria defined for this systematic review; excluded at this stage were: 4 studies which did not incorporate the outcomes of interest; 2 studies regarding diagnostic method; 1 case report; and 1 study which was common to the two publications. This systematic review includes, therefore, the critical evaluation of 20 studies (Fig. 1).

2.4 Extraction and Synthesis of Data

Data extracted from the studies included in this review were stored in tables, including information related to the following characteristics:

2.4.1 Identification and methodology

Main author; country where the study was performed; year of publication; period of inclusion of patients; type of study; source of data (primary or secondary); total number of patients included; distribution of patients according to gender; duration of follow-up.

2.4.2 Characteristics of the patients

Age; ethnicity; clinical and pathological staging; pathological nodal status; histological grade; hormone receptor; HER2 receptor.

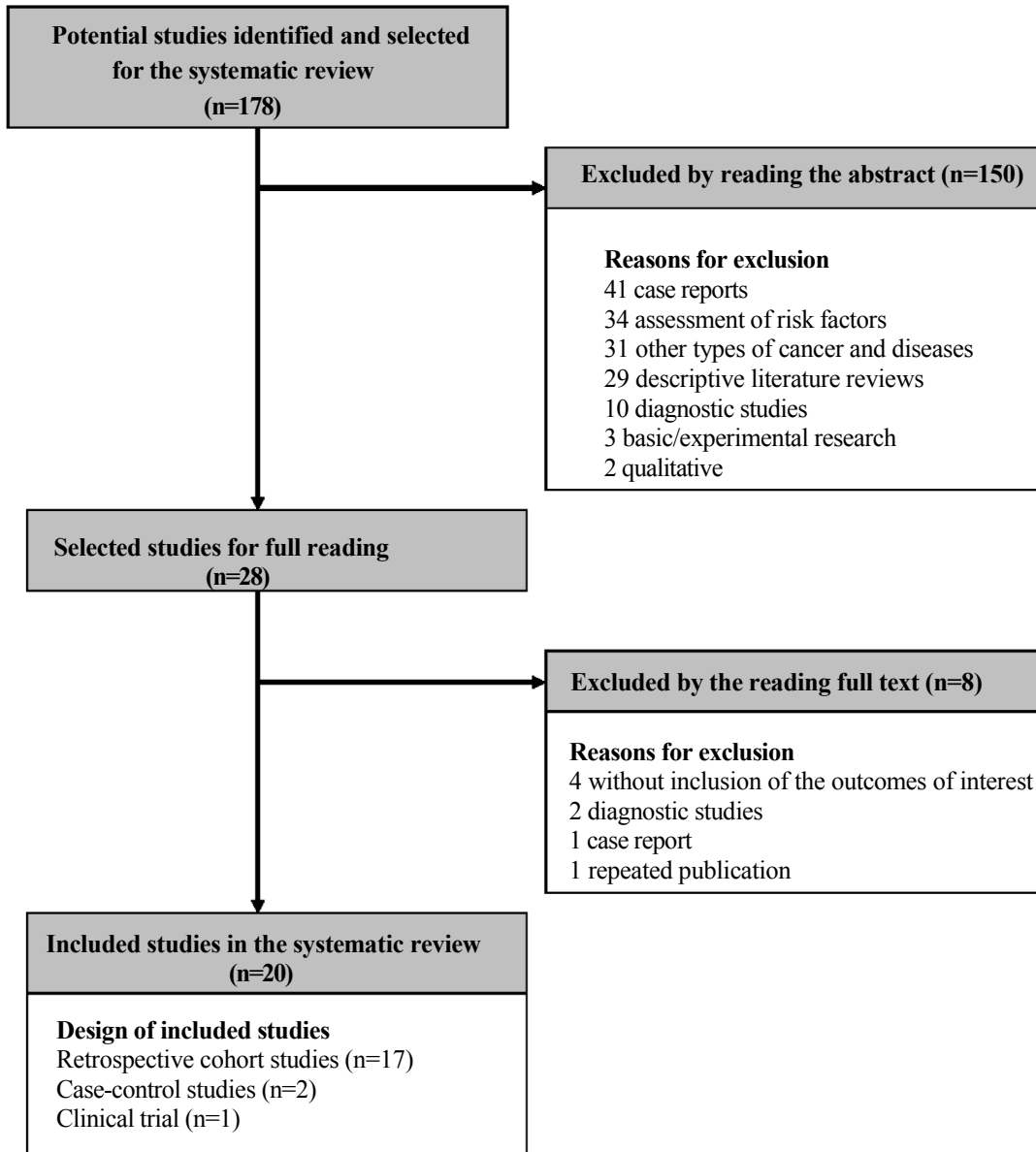


Fig. 1. Criteria of eligibility for articles identified for systematic review

2.4.3 Treatments performed

Type of breast surgery; type of axillary surgery; radiation therapy; hormone therapy; chemotherapy; other treatments performed.

2.4.4 Outcomes

DFS, OS, DSS, mortality and complications of surgical treatment for breast cancer in men.

The data were presented as absolute numbers and percentages were calculated based on valid data.

3. RESULTS

3.1 Design and General Characteristics of the Included Studies

The data on the characteristics of the studied population and the methods used in the studies identified for this review are described in Table 1. The 20 selected studies represented all continents except Latin America and Oceania, seven of them were from the United States, three from France and two each from China and Turkey. Sweden, Finland, Korea, India, Japan and Libya had one publication each. The selected studies included 9,634 cases of male breast cancer diagnosed and treated between 1969 and 2009. Nine studies analysed female breast cancer cases as well. Primary databases were used exclusively for 8 studies, while 10 studies analysed only secondary databases; 2 studies used both types of data. In relation to the origin of the patients, 8 studies were multicentric and 12 were from a single institution.

The studies were predominantly of retrospective cohorts (85%). We also identified two matched case-control studies [13,14]. The study by Walshe et al. [15], although described as a prospective clinical trial, presented data that suggested a prospective cohort that was later compared with secondary data from the National Cancer Institute Surveillance, Epidemiology and End Results (NCI SEER).

3.2 Primary Studies (n=10 studies)

Ten primary studies comprised 888 men with breast cancer whose ages ranged from 22 to 94 years. Regarding ethnicity, only two authors analysed this feature. Walshe et al. [15] described 10% of African Americans in their study while Shaub et al. [19] showed a range between 54% and 61% of African Americans in the 2 analysed cohorts.

In 4 studies [16-19] the distribution by clinical staging comprised 606 patients; for 76 (13%) of these, no stage was provided. In those with a known stage, 67% of the cases were stage II to IV (stage II= 53%, stage III= 12% and stage IV= 2%), in other words, they had advanced tumours larger than 2 cm; stage I was described in 33% of the patients. Nine studies [15-23] described the histological type (n=780) and the predominant type was invasive ductal carcinoma, representing 96% of the analysed data. Ductal carcinoma *in situ* (DCIS) accounted for only 2% of tumours, according to available information.

Relative to nodal status, Walshe et al. [15] only selected patients with positive lymph nodes exposed to adjuvant chemotherapy to determine overall long term survival. In the other studies, the proportion of patients with axillary impairment ranged from 19% (6 of 32 patients) [12] to 94% (74 of 79 patients) [24].

Table 1. Methodological characteristics of included studies (n=20)

Author	Country	Year of publication	Period	Type of study	Database	Patients total	Cases of MBC	% of MBC	Follow up (years)
Anderson et al. [27]	USA	2010	1973-2005	RC	S/M	841299	5494	0.65	-
Atahan et al. [31]	Turkey	2006	1994-2001	RC	S	42	42	100	2
Crew et al. [25]	USA	2007	1991-2002	RC	S/M	510	510	100	5
Cutuli et al. [16]	France	2010	1990-2005	RC	P/M	489	489	100	5
El Habbash et al. [17]	Libia	2009	1990-2008	RC	P	1568	22	1.4	-
Fogh et al. [20]	USA	2011	1990-2003	RC	P/M	42	42	100	8
Gnerlich et al. [26]	USA	2011	1988-2003	RC	S/M	246,059	1,541	0.6	-
Ioka et al. [29]	Japan	2006	1975-1997	RC	S/M	19,869	97	0.5	-
Lara et al. [21]	France	2008	1980-2004	RC	P/S	52	52	100	7*
Liukkonen et al. [22]	Finland	2010	1981-2006	RC	P	58	58	100	5*
Marchal et al. [13]	France	2009	1980-2002	CC	S	174	58	33.3	10
Mitra et al. [24]	India	2007	1994-2003	RC	P	3176	79	2.5	6*
Nahleh et al. [32]	USA	2007	1995-2005	RC	S/M	3,025	612	20.2	-
Park et al. [23]	Korea	2008	1985-2007	RC	P	4,668	20	0.4	-
Shaub et al. [19]	USA	2008	A: 1972-1991	RC	P	28	28	100	-
			B: 1992-2005			28	28	100	-
Thalib et al. [28]	Sweden	2009	1970-1997	RC	S/M	30,280	269	0.9	-
Walshe et al. [15]	USA	2007	1974-1988	CT	P/S	960	31	3.2	23
Xia et al. [14]	China	2010	1969-2004	CC	S	A: 105	A: 35	33.3	-
						B: 54	B: 18		
Yoney et al. [18]	Turkey	2009	1996-2004	RC	P	39	39	100	5*
Zhou et al. [30]	China	2010	A: 1969-1997	RC	S	A: 35	A: 35	100	A: 8
			B: 1998-2009			B: 35	B: 35	100	B: 4

* Average time, Legend: P= primary study; S= secondary study; M= multicentric study; RC= retrospective cohort; CC= case-control; CT= clinical trial; MBC= male breast cancer; FBC= female breast cancer

The degree of tumour differentiation was reported in only 50% of the studies involving 661 patients with valid data; 261 cases (29%) had no known classification [16,20-23]. It was observed that 54% were classified as G2 (moderately differentiated). The remaining cases were well-differentiated (G1 - 22%) or poorly differentiated (G3 - 24%); 9 cases (2%) were classified as G2/G3. Of the 719 tumours assayed for estrogen receptors, 91% were positive and 9% were negative. Only three authors described the pathological staging in their series, totaling 518 cases [16,20,23]. The majority of cases were classified as stage I (46%), followed by stage III and IV (30%) and stage II (23%). In turn, HER2 biomarker research was performed on a cohort of Shaub et al. and in the study of Liukkonen et al. [19,22] with a very uneven distribution: 60% (3 positive out of 5 cases) and 11% (2 positive out of 19 cases), respectively.

The studies reported therapeutic modalities employed in 759 men with breast cancer, prevailing radical mastectomy (86%). Conservative surgery and simple mastectomy were performed in 8% and 5% of cases, respectively. Axillary lymphadenectomy was performed in 90% and sentinel node biopsy in 4%. In only 1% of cases, surgical treatment was not performed. Adjuvant treatments comprised radiotherapy (72%), chemotherapy (40%) and hormone therapy (65%); 9 cases were treated with orchiectomy and 1 with trastuzumab [15-24].

3.3 Secondary Studies (n=10 studies)

Ten selected secondary studies covered 8,746 cases of male breast cancer, which the authors obtained data from: national databases such as the SEER (Surveillance, Epidemiology, and End Results) in the United States [25-27], and the Swedish Cancer registration database [28]; regional databases such as the Osaka Cancer Registry in Japan [29], and the Lorraine Comprehensive Cancer Centre in France [13]; and institutions such as the Cancer Center of the University of Sun Yat-Sen [14-30], the Department of Radiology of the Hacettepe University in Turkey [31] and the Veterans' Central Cancer Registry in the United States [32]. The number of cases included per centre ranged from 42 [31] to 5,494 [27].

In the distribution of the tumours according to staging (n=8,078), stage I predominated, accounting for 39% of cases, followed by ill-defined stages (26%), stage II with 15% and cases in situ with 9%, stages III 4% and IV 7%. The unknown stage was 8% of cases. Regarding nodal status among the known cases (n=5,677), there was a predominance of negative axillary nodal status (58%), followed by axillary lymph node involvement (42%). In over a third of cases (35%), this aspect was not known or was not provided. There was some heterogeneity in the classification of histological grade (n=5,624): 62% were well or moderately differentiated (G1 or G2), 38% poorly differentiated (G3); in 34% of cases, the histological grade was unknown or not provided. The study of estrogen receptors in these series showed that, of the known cases, approximately 93% were positive; in 47% (n=4,110) of cases, this information was unknown or not considered. The identification of HER2 was performed in only 9 cases, 2 of which were positive.

In 75% of the cases from the secondary studies, the surgical treatment adopted was not reported. In the reported studies (n=2,162), radical mastectomy was the predominant procedure in 82% of the cases, followed by conservative surgery (14%). In only one case a simple mastectomy was performed and no surgical treatment was undertaken in 4% of patients [14,25,26,30,31]. However, information regarding the axillary status confirmed 5,877 cases (95%) with lymphadenectomy versus 334 cases (5%) without lymphadenectomy, and

sentinel lymph node research was not mentioned. Radiation therapy, chemotherapy and hormone therapy were applied in 18%, 16% and 13% of cases respectively. Treatments such as orchiectomy and the use of trastuzumab were not performed.

3.4 Survival and Mortality

Regarding survival time (Table 2), in the primary studies, five authors contemplated the DFS in their analyses, ranging from 42% to 100% and from 43% to 83%, at 5 and 10 years respectively [16,18,20,23,24]. This last value (DFS 83% in 10 years) was registered in the group of patients who received a combination of radiotherapy and adjuvant hormone therapy [20]. In the series by Mitra et al. [24], the DFS ranged from 54% to 71% in five years, when patients were stratified according to the presence of lymph node involvement. OS at 5 years was 43% (1972 to 1991) and 51% (1992-2005) in the two cohorts studied by Shaub et al. [19], reaching 100% in the Fogh et al. [20] series of radiotherapy and adjuvant hormone therapy studies. The Lara et al. [21] series presented the worst OS result at 10 years (32%), while the cohort of radiotherapy and adjuvant hormone therapy of Fogh et al. [20] and the post-menopausal cohort of Xia et al. [14] reached 100%. Walshe et al. [15] showed in their series a probability of OS at 10 years of approximately 65%; 52% at 15 years and 42% at 20 years. A multicentric study, which included 489 patients, presented an OS of 81% and 59% at 5 and 10 years, respectively, and a DSS of 89% and 72%, at 5 and 10 years respectively [16].

In secondary studies, only one author contemplated OS, DSS and DFS at 5 and 10 years, observing values of 59% and 34%, 73% and 55%, and 67% and 46%, respectively [13]. For the series described by Atahan et al. [31], the OS was 77% and DFS 42%, both in 5 years. Thalib et al. [28] describe the OS at 5 and 10 years with values of 79% and 75%. Crew et al. [25] analysed survival by race and found 66% and 90% OS at 5 years for blacks and whites respectively. Nahleh et al. [32] showed a median OS at 7 years for cases of MBC significantly lower than the 10 years described for the population with FBC. Finally, the total number of deaths from breast cancer in the series described by Gnerlich et al. [26] was 16% for men while for women this percentage was 13%.

For Anderson et al. [27] specific mortality was 16% in both men and women. Ioka et al. [29] described the DSS at 5 years of 71%. Comparing radical mastectomy and modified radical mastectomy, Zhou et al. [30] studied two cohorts of 35 men, and found 69% and 80% of OS at 5 years. The study by Xia et al. [14] that compared men and women with breast cancer showed that the OS at 5 and 10 years was higher in women; in a second group which compared men with post-menopausal women with breast cancer, a similar prognosis was observed between men and women.

Table 2. Survival in included studies (n=20)

Author	DFS (%) 5 years	DFS (%) 10 years	OS (%) 5 years	OS (%)10 years	Other analyzed outcomes
Anderson et al. [27]	-	-	-	-	SM: 16%
Atahan et al. [31]	42	-	77	-	-
Crew et al. [25]					
Blacks	-	-	66	-	-
Whites	-	-	90	-	-
Cutuli et al. [16]	-	-	81	59	DSS 5 years: 89%; 10 years: 72%
El Habbash et al. [17]	-	-	57	-	
Fogh et al. [20]					
HT adjuvant 5 years	100	90	100	83	-
HT adjuvant < 5 years	79	62	83	71	-
RT adjuvant	90	75	90	90	-
RT+ HT adjuvant	100	83	100	100	-
QT adjuvant	80	64	83	78	-
No adjuvant	81	68	85	65	-
Gnerlich et al. [26]	-	-	-	-	SM: 16%
Ioka et al. [29]	-	-	-	-	DSS 5 years: 71%
Lara et al. [21]	-	-	69	32	
Liukkonen et al. [22]	-	-	75	-	
Marchal et al. [13]	66.5	46	59	34	DSS 5 years: 73%; 10 years: 55% SM 5 years: 67%; 10 years: 46%
Mitra et al. [24]					
LN positive	54	-	67	-	-
LN negative	71	-	78,5	-	-
Nahleh et al. [32]	-	-	-	-	OS: 7 years (median)
Park et al. [23]	98	82	86	76	
Shaub et al. [19]					
A	-	-	43	-	-
B	-	-	51	-	-

Table 2 Continued in next page.....

Author	DFS (%) 5 years	DFS (%) 10 years	OS (%) 5 years	OS (%)10 years	Other analyzed outcomes
Thalib et al. [28]	-	-	79	75	AMR: 2,31%
Walshe et al. [15]	-	-	-	64.5	OS 15 years: 52%; 20 years: 42%
Xia et al. [14]					
A	-	-	82	60	-
B	-	-	86	66	-
Yoney et al. [18]	66	-	80	-	-
Zhou et al. [30]					
A	-	-	68	-	-
B	-	-	80	-	-

Legend: DFS= disease-free survival; OS= overall survival; SM= specific mortality; DSS= Disease-specific survival; AMR= annual mortality rate; HT= hormone therapy; CT= chemotherapy; RT= radiotherapy; LN= lymph nodes

4. DISCUSSION

The increasing incidence of MBC has raised interest in this pathology. Among the risk factors for developing the disease are age, genetic factors mainly related to the BRCA 2 mutations, circumstances in which there is a change of sex hormone levels with hyperestrogenism such as testicular abnormalities, Klinefelter syndrome, obesity, use of exogenous estrogen and testosterone and liver diseases, among others. It is doubtful whether there is an association between gynecomastia and an increased risk of breast cancer [8,33].

In men, the painless tumour, which usually manifests as a retroareolar mass, is found in more advanced stages than in women [21,32]. There is a predominance of invasive ductal carcinoma, well differentiated tumours, and estrogen receptor is positive [21]. Overexpression of HER2 is between 11% and 15% of cases and does not seem to represent an isolated prognostic factor in OS [9,34,35]. However, data on HER2 are extremely limited for drawing any conclusions. Multivariate analysis of the series shows that the nodal involvement and tumour size are isolated prognostic factors for OS [16,18,21]. In the studies by Park et al. [23], whose sample consisted of 20 men, nodal involvement, tumour size, hormone receptor status and tumour differentiation were associated with lower OS, but without statistical significance.

Modified radical mastectomy was the predominant surgical treatment on primary and secondary baseline studies, with a value of 100% in the series of Xia et al. [14], without a worsening in OS when compared with radical mastectomy. Conservative surgery does not play a major role in the treatment of breast cancer in men, since it is significantly associated with worse local disease control [36]. Marchal et al. [13] report in their series that the risk of local recurrence was higher in men than in women because of the small volume of breast tissue, with easy access to the lymphatic network and direct extension to the wall muscles of the chest.

Lymphadenectomy is the axillary standard approach. However, for clinically negative axilla, adoption of the sentinel lymph node (SLN), which is well established in the investigation of lymph node involvement in women who felt less pain, paresthesia, edema, and better arm mobility when submitted only to the SLN, is proposed as an ideal approach in men, in well selected cases - T1 N0 [10,12,16,22].

Adjuvant therapy, which has never been evaluated in randomised prospective clinical trials, predominantly consisted of hormone therapy, radiation therapy and chemotherapy. Aromatase inhibitors, trastuzumab and orchiectomy were rarely used. Fogh et al. [20] show in their studies that the best results in OS at 5 and 10 years were obtained with the association of hormone therapy for 5 years and radiation therapy ($P=0.03$), suggesting the potential benefit of this therapeutic association [].

In regard to complications, there are no specific data for the male population undergoing surgical treatment, and approaches are extrapolated from experiences with women with breast cancer. Only Mitra et al. [24] note that the two most common late effects found were arm edema and restriction of shoulder movements.

Gender was not a significant predictor of survival after adjusting for other variables [13,14,37]. However, Gnerlich et al. [26] describe in their series higher cancer-specific mortality only for male breast cancer stage I, although with no clinical significance.

Due to the relative scarcity of studies, the treatment of breast cancer among men persists as an extrapolation of female breast cancer. The ideal disease management in men remains unknown as well as their biological peculiarities. Inter-institutional efforts should be encouraged in order to undertake more clarifying studies.

However, this systematic review is mainly limited by the fact that the data are related to patients diagnosed and treated between 1969 and 2009. During this period, important changes were introduced in medical practice, which makes it difficult to compare studies and extrapolate the results to today's world. However, the results allow us to understand the magnitude of breast cancer in men, by aggregating information from different populations.

5. CONCLUSION

The review included 20 studies, the majority (n=17) with retrospective design. The analysed studies contemplated the inclusion of 9,634 men (1%) and 1,142,032 women (99%) diagnosed and treated between 1969 and 2009. In primary studies, male survival at 5 years ranged from 42% to 100% and in 10 years, from 43% to 83%. In secondary studies, DSS at 5 years was 59% and at 10 years was 34%. Several authors have shown that, while men and women with breast cancer have similar clinical patterns, the treatment of male breast cancer persists as an extrapolation of female breast cancer. However, further studies should address this specific group, focusing mainly on its biological nature, therapeutic approaches and post-operative complications.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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