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Critical Reviews in Oncology/Hematology 73 (2010) 141–155

Hematology
Incorporating Geriatric Oncology

www.elsevier.com/locate/critrevonc

Male breast cancer

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Accepted 1 April 2009

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doi:10.1016/j.critrevonc.2009.04.003

Abstract

Male breast cancer (MaleBC) is a rare disease, accounting for <1% of all male tumors. During the last few years, there has been an increase in the incidence of this disease, along with the increase in female breast cancer (FBC). Little is known about the etiology of MaleBC: hormonal, environmental and genetic factors have been reported to be involved in its pathogenesis. Major risk factors include clinical disorders carrying hormonal imbalances, radiation exposure and, in particular, a positive family history (FH) for BC, the latter suggestive of genetic susceptibility. Rare mutations in high-penetrance genes (*BRCA1* and *BRCA2*) confer a high risk of BC development; low-penetrance gene mutations (i.e. *CHEK-2*) are more common but involve a lower risk increase.

About 90% of all male breast tumors have proved to be invasive ductal carcinomas, expressing high levels of hormone receptors with evident therapeutic returns.

The most common clinical sign of BC onset in men is a painless palpable retroareolar lump, which should be evaluated by means of mammography, ultrasonography and core biopsy or fine needle aspiration (FNA).

To date, there are no published data from prospective randomized trials supporting a specific therapeutic approach in MaleBC. Tumor size together with the number of axillary nodes involved are the main prognostic factors and should guide the treatment choice. Locoregional approaches include surgery and radiotherapy (RT), depending upon the initial clinical presentation. When systemic treatment (adjuvant, neoadjuvant and metastatic) is delivered, the choice between hormonal and or chemotherapy (CT) should depend upon the clinical and biological features, according to the FBC management guidelines. However great caution is required because of high rates of age-related comorbidities.

Keywords: Male breast cancer; Genetics; Therapy; Surgery; Radiotherapy; Chemotherapy; Hormonal treatment; Survival; Local recurrence

1. Introduction

Male breast cancer (MaleBC) is a rare disease, showing an increasing incidence trend rising along with that of female breast cancer (FBC). Even if male and female breast cancers seem to be similar, with regard to epidemiological aspects, they deeply differ because of the lower incidence and later onset of the former. Little is known about the etiology of MaleBC: hormonal, environmental and genetic factors are involved in the pathogenesis of breast cancer in men as well as in women. The major risk factor related to MaleBC is a positive family history for breast cancer, which indicates a relevant genetic component. In fact, MaleBC susceptibility can result from rare mutations in high-penetrance genes conferring a high risk, or from more common low-penetrance genes giving a lower risk increase.

From the clinical and biological point of view, male and female breast cancers differ mainly in the frequency of their histological types and in the expression of hormone receptors and of epidermal growth factor receptor 2 (HER2).

In the lack of randomized controlled trials, principles of management of MaleBC are mainly derived from randomized trials in female patients (pts). Since it is often late diagnosed, MaleBC remains a substantial cause of morbidity and mortality in men. This last consideration together with the increasing incidence made it urgent to comprehensively review the epidemiological, genetic, histopathological and clinical aspects of MaleBC, including the diagnosis, prognosis and treatment of the disease.

2. Epidemiology

In Western countries, MaleBC accounts for <1% of all cancers in men but its incidence varies greatly in different geographical areas and ethnic groups [1,2]. The worldwide variation of MaleBC resembles that of FBC, with higher rates in North America and Europe and lower rates in Asia. A substantial high proportion of MaleBC cases have been reported in Africa [3]. Although scarce, data from this continent have shown annual MaleBC incidence rates ranging from 5 to 15% [4–6]. These relatively high rates have been attributed to endemic infectious diseases, such as bilharziosis and hepatitis B/C that, by chronic liver infection, may cause liver damage leading to hyperoestrogenisms. By contrast, the annual incidence of MaleBC in Japan is significantly lower (5 per 1,000,000) than the average incidence, comparable to the lower than average incidence of FBC in this country [7]. Recent epidemiological studies indicate that MaleBC incidence is rising [8]. The incidence of MaleBC increases with age and the bimodal age distribution seen in women is absent in men, with a peak incidence in the sixth decade [3]. Overall, due to the absence of screening programs in men, MaleBCs are diagnosed at a more advanced age and with a more severe clinical presentation than in women, with greater tumor size and a more frequent lymphonodal involvement. The mean age at breast cancer diagnosis in males is 63.4 years [9]; in the SEER data, the median ages at diagnosis of breast cancer were 67 and 62 years in males and females, respectively [3]. The mortality rates for MaleBC have been shown to remain stable [1], however, survival rates differ significantly according to race/ethnicity [10] and are not significantly different from those observed in women [3]. In general, the prognosis for male and female patients with breast cancer is similar. Overall survival rates are lower for men, but this is due to an older age at diagnosis and more advanced stage at presentation [11]. Disease-specific survival rates are higher than overall survival rates due to the older average age and deaths from other comorbid diseases [12].

Table 1
Risk factors for male breast cancer.

High risk	Hormonal imbalance Testicular or liver damage Oestrogen intake	*BRCA2*
	Radiation exposure	Klinefelter's syndrome Breast cancer family history
Moderate/Low risk	Occupational exposure Heat	*BRCA1*
	Obesity	*CHEK2* Cowden syndrome
Suspected risk	Occupational exposure Exhaust emissions Magnetic fields	*AR*
	Alcohol intake	*CYP17*

3. Risk factors

Similar to breast cancer in women, MaleBC is likely to be caused by the concurrent effects of different risk factors, including clinical disorders relating to hormonal imbalances, certain occupational and environmental exposures, and genetic risk factors, for instance a positive family history (FH) of breast cancer (BC) and mutations in BC predisposing genes, such as *BRCA* genes, and possibly others. Environmental factors, particularly occupational carcinogen exposure, might well contribute to MaleBC risk by interacting with genetic factors. We reported a strong association between a specific occupation (truck driving) and breast cancer risk in male carriers of *BRCA1/2* mutations [13]. Risk factors for MaleBC are summarized in Table 1.

3.1. Hormonal risk factors

As is the case in female BCs, MaleBCs are highly sensitive to hormonal changes. In particular, hormonal imbalance between an excess of estrogen and a deficiency of testosterone increases the risk of the disease. This imbalance may occur endogenously due to testicular abnormalities, including, undescended testes, congenital inguinal hernia, orchitis, orchiectomy and testicular injury [14]. Liver diseases, such as cirrhosis, may also result in a hyperestrogenic state [15]. In general, liver damage and disease, caused by the effects of several drugs or their metabolites, may affect hepatic functions and lead to hyperestrogenism.

Obesity is one of the most common causes of hyperoestrogenization in men because of increased peripheral aromatization of androgens. Obesity, in fact, doubles the risk of breast cancer in men [16–18]. Recently it has been reported that first-born male children have a 1.71 times higher risk of MaleBC than their younger brothers, possibly because they have been exposed to higher levels of intrauterine estrogen [19].

Klinefelter's syndrome, characterized by 47XXY karyotype, testicular dysgenesis, gynecomastia, low testosterone concentrations and increased gonadotrophins, is strongly associated with MaleBC risk. Individuals with this syndrome have a 20–50 times higher risk over the general male population [20].

An upset in estrogen or androgen balance is a causal factor in gynecomastia, which is extremely common in pubescent boys, may occur in men over the age of 50 and is found in 6–38% of male pts affected by BC. However, the incidence of gynecomastia in MaleBC pts is no higher than in the general male population [6]; gynecomastia, therefore, does not in itself seem to represent a risk factor for MaleBC [17,21]. Conditions increasing exposure to estrogen or decreasing exposure to androgen, such as the exogenous administration of estrogen to trans-sexuals or the long-term use of antiandrogens and estrogens in the treatment of prostate cancer, have also been implicated as causative factors for MaleBC [22–24].

3.2. Occupation and environmental risk factors

As in women, ionizing radiations have been considered as possible causal cofactors in the etiology of MaleBC [25], with a modest positive trend with the increasing number of X-ray examinations performed on chest and adjacent body areas and with an induction period of at least 20–25 years, with a subsequent decrease of risk after the 30 or 40 years subsequent to the last exposure.

Occupational exposure to heat and electromagnetic radiation are postulated to be linked to MaleBC risk. A higher frequency of breast cancer is reported in men who have worked in hot environments, such as blast furnaces, steel works, rolling and finishing mills [26], possibly because long-lasting exposure to high ambient temperatures can lead to testicular failure. An increased MaleBC risk has been observed in men exposed to high electromagnetic fields [2] and a 1.31 relative risk in men with an exposure above the first quartile has been reported, although no clear trend of exposure and risk has emerged [27].

In a few studies, a certain degree of risk has been found to be associated also to polycyclic aromatic hydrocarbons (PAHs) [2], but the evidence is still too inadequate to draw any valid conclusions. Moreover, PAHs are usually found in environments contaminated by other pollutants with mutagenic effects, such as nitrogen oxides, nitrosamines and exhaust fumes, making it very difficult to disentangle the effect of any single pollutant.

3.3. Dietary risk factors

As for women, alcoholic beverages seem to represent a risk factor for the development of MaleBC, with an increase of 16% for each increase of 10 g/day of alcohol intake. Moreover, strong consumers of alcoholic beverages (more than 90 g/day) present a 6-fold increased OR to develop MaleBC

when compared to light consumers (<15 g/day) [28]. The available evidence for other components of diet is rather scarce. The consumption of animal fats and in particular red meat in relation to the risk of MaleBC has been investigated in several studies, but the results are still not clear. Inconsistent findings have also been provided by the evaluation of the effect of fruit and vegetable intake [28]. Overall, with the exception of alcohol consumption, dietary factors seem to play a marginal role in the etiology of MaleBC.

3.4. Family and personal history of cancer

Similar to FBC, a positive FH of BC is associated with increased risk of MaleBC. Data from population-based studies have shown that about 20% of all MaleBC pts have a history of BC in a first-degree female relative [17,18,29–31]. In general, a positive FH of either female or male breast cancer among first-degree relatives confers a 2–3-fold increase in MaleBC risk [17,32–34]. The risk increases with increasing numbers of first-degree relatives affected and with early onset in affected relatives. In addition to BC families, MaleBC cases have also been reported in families with the hereditary non-polyposis colorectal cancer (HNPCC) syndrome [35] and Cowden syndrome [36].

A personal history of a second primary tumor is reported in more than 11% of MaleBC pts [37]. Men diagnosed with a first primary breast cancer have a 16% increased risk of developing a second primary cancer in comparison with the general male population [37]. Data from the SEER program from the National Cancer Institute show that a history of MaleBC is associated with a 30-fold increased risk of breast cancer on the contralateral side [38], which is much higher than the 2–4-fold increase observed in women [39]. The risk of a second site-specific cancer is elevated also for gastrointestinal cancer, pancreas and prostate carcinomas, melanoma and non-melanoma skin tumors [37,40].

3.5. BRCA1 and BRCA2

MaleBC predisposition can result from germ-line mutations in the high-penetrance *BRCA2* (OMIM #6600185) and, with lower frequency, *BRCA1* (OMIM #113705) genes. The presence of MaleBC within high-risk BC families indicates a high likelihood of *BRCA2* mutations with a frequency ranging from 60 to 76%, whereas *BRCA1* mutations frequency ranges from 10 to 16% [41,42]. The frequency of *BRCA1* and *BRCA2* mutations are extremely different in ethnically diverse population- and clinic-based MaleBC series, ranging from 4 to 40% for *BRCA2* and up to 4% for *BRCA1* (Table 2), and resulting higher in the presence of founder effects [12,43]. *BRCA1* and *BRCA2* founder mutations have been identified in specific countries or ethnic groups, particularly in genetically isolated populations such as the Icelanders and Ashkenazi Jews. In Iceland, the *BRCA2* 999del5 founder mutation is involved in 40% of all MaleBC cases [44]. In Ashkenazi Jews the *BRCA1* 185delAG and the *BRCA2* 6174delT founder mutations found in women are also frequent in men. In fact, the combined prevalence of the *BRCA1* and *BRCA2* founder mutations among Askenazi Jewish men is slightly higher than for women, due to the higher frequency of *BRCA2* mutations [45]. However, even in heterogeneous countries, such as Italy, there is evidence of founder *BRCA1* and *BRCA2* mutations in regions that show a micro-homogeneity [46–50]. *BRCA2* mutations are currently considered as the major genetic risk factor for MaleBC, however, there is no evidence for a correlation between the location of the mutation within *BRCA2* gene and risk of MaleBC. The median age at BC diagnosis among *BRCA2* mutation carriers is earlier (median, 58.8 years) than that of negative cases (median, 67.9 years) [29]. Overall, *BRCA1* and *BRCA2* mutations are more prevalent in men with a positive first-degree FH compared with those without [29,51,52]. Since mutations are also identified in MaleBC cases without

Table 2
BRCA1 and *BRCA2* mutations prevalence from studies of male breast cancer patients.

Study	Center	*n* tested	*BRCA1* mutation *n* (%)	*BRCA2* mutation *n* (%)
Couch et al. Nat Genet 1996 [169]	Philadelphia, PA	50	ne	7 (14)
[a]Friedman et al. Am J Hum Genet 1997 [170]	Southern California	54	0	2 (4)
[a,§]Thorlacius et al. Am J Hum Genet 1997 [44]	Iceland	30	ne	12 (40)
Mavraki et al. Br J Cancer 1997 [171]	Leeds, UK	28	ne	2 (7.1)
Haraldsson et al. Cancer Res 1998 [172]	Sweden	34	ne	7 (21)
Csokay et al. Cancer Res 1999 [173]	Hungary	18	0	6 (33)
Tirkkonen et al. Genes Chrom Cancer 1999 [174]	Sweden	26	0	5 (19)
§Sverdlov et al. Genet Test 2000 [175]	Israel	31	1 (3)	1 (3)
Kwiatkowska et al. Hum Mut 2001 [176]	Poland	37	ne	4 (11)
[a]Basham et al. Breast Cancer Res 2002 [29]	Cambridge, UK	94	0	5 (5)
Frank et al. J Clin Oncol 2002 [42]	USA	76	8 (10)	14 (18)
Evans et al. Familial Cancer 2008 [51]	Manchester, UK	64	4 (6)	17 (27)
§Chodick et al. Eur J Med Genet 2008 [45]	Israel	261	8 (3)	21 (8)
[a]Ottini et al. Breast Cancer Res 2008 [86]	Italy	108	2 (2)	8 (7)

ne: not evaluated.
[a] Population-based study.
§ Mutational analysis limited to founder mutations.

FH, from a clinical point of view, predictive genetic testing is not only beneficial in men from high-risk families but also among isolated MaleBC cases.

3.6. CHEK2

There is evidence supporting the implication of *CHEK2* (OMIM #604373), a cell cycle checkpoint kinase that along with *BRCA1* and *BRCA2* plays a role in DNA repair, in inherited MaleBC predisposition. In particular, it has been estimated that the *CHEK2* 1100delC mutation accounts for 9% of MaleBC cases and confers approximately a 10-fold increase of BC risk in men lacking *BRCA1* and *BRCA2* mutations [53]. Although this mutation has been strongly associated with the increased MaleBC risk in high-risk BC families, this association is not so clear in MaleBC cases unselected for FH [54–57]. Furthermore, there is evidence that the contribution of the *CHEK2* 1100delC variant to MaleBC predisposition varies from one ethnic group and from one country to another [58].

3.7. AR

AR gene (OMIM # 313700), the gene encoding the androgen receptor, has been suggested to play a role in MaleBC predisposition. Germ-line mutations of *AR* and variation of the polyglutamine (CAG) repeat within *AR* exon 1 were found in MaleBC cases [59], However, these results were not supported by additional studies [60]. Overall, *AR* gene mutations do not seem to contribute significantly to the risk of MaleBC.

3.8. CYP17

The *CYP17* gene encodes for the cytochrome P450c17α enzyme that is involved in the synthesis of estrogens and androgens. A germ-line variant in the *CYP17* promoter region was found to be associated with an increased MaleBC risk [61]. Overall, a possible role for the *CYP17* promoter polymorphism in MaleBC risk may be suggested although studies are not conclusive because of the small sample size analyzed.

4. Lifetime risk for male breast cancer

Male carriers of *BRCA2* germ-line mutations have a higher risk of developing BC than men in the general population. Male *BRCA2* mutation carriers have been estimated to have a lifetime risk of 6.9% for developing BC, which is approximately 80–100 times higher than in the general population [62]. The association between *BRCA1* germ-line mutations and MaleBC risk has proved to be less clear. In a clinically based study of *BRCA1* mutation carriers, a lifetime risk of 5.8% for MaleBC has been estimated [63]. Recently, the risk of developing breast cancer for male *BRCA1* and *BRCA2* mutation carriers has been evaluated in the US population by means of an analysis of data from 1939 families collected within the National Cancer Institute's Cancer Genetics Network [64]. Data from this large study show that at all ages, the cumulative risks of MaleBC are higher in both *BRCA1* and *BRCA2* mutation carriers than in non-carriers (Table 3). The relative risk of developing BC is highest for men in their thirties and forties and decreases with increasing age. In particular, in *BRCA2* mutation carriers the relative risk at age 30 is 22.3 times that at age 70. Both the relative and cumulative risks are higher for *BRCA2* mutation carriers than for *BRCA1* mutation carriers. In particular, the estimated cumulative risk of MaleBC at age 70 is 1.2% for *BRCA1* mutation carriers and 6.8% for *BRCA2* mutation carriers (Table 3). Overall, these observations demonstrate that *BRCA1* mutations are associated with an increased risk of MaleBC, but such risks are substantially lower than those in *BRCA2* mutation carriers.

Table 3
Age-specific cumulative risk of developing breast cancer for general male population and male *BRCA1* and *BRCA2* mutation carriers (%)[a].

Age, year	General population	*BRCA1* carrier	*BRCA2* carrier
30	1.2×10^{-4}	1.7×10^{-2}	0.18
40	1.9×10^{-3}	0.12	1.2
50	8.5×10^{-3}	0.3	2.7
60	2.7×10^{-2}	0.62	4.7
70	6.7×10^{-2}	1.2	6.8
80	0.12	1.8	8.3

[a] Modified by Tai et al. [64].

Male carriers of *BRCA1* and *BRCA2* mutations are at increased risk of developing several cancer types, including prostate and pancreatic cancer. The prostate is the most consistently reported site for cancer susceptibility in male *BRCA1* and *BRCA2* mutation carriers, although the association between prostate cancer risk and *BRCA2* mutation is more consistent. A relative risk (RR) of 1–3 and of 2–5 has been estimated for *BRCA1* and *BRCA2* mutation carriers, respectively, and the RR risk has proved to be greater for men under 65 years of age [65,66]. Intriguingly, mutations in the ovarian cancer cluster region (OCCR), the central part of the *BRCA2* gene associated with a higher risk of ovarian cancer compared with breast cancer, are associated with a lower risk of prostate cancer than mutations outside the OCCR (19.2% vs. 33.6% before the age of 80) [62]. Pancreatic cancer is an established feature of the *BRCA2* phenotype. A significant increased risk of pancreatic cancer is reported also in relatives of *BRCA1* mutation carriers [63,67]. Overall, a RR of 2–3 and of 2–8 has been estimated for *BRCA1* and *BRCA2* mutation carriers, respectively [63,65,67]. Male carriers of *BRCA1* and *BRCA2* mutations are also at risk of developing colon and gastric carcinomas, melanoma and non-melanoma skin cancer. However data to determine the magnitude of excess cancer risk at these sites are limited [66].

Overall, these observations indicate that the total cancer risk to male carriers of *BRCA1* and, particularly, *BRCA2* mutations, is high before the age of 65 and consists mainly in breast, prostate and pancreatic cancers.

5. Oncogenetic counseling for men at increased breast cancer risk

At present, oncogenetic counseling is available to women at increased risk of breast and ovarian cancer. These women usually have a first-degree FH of cancer and are offered screening for *BRCA1* and *BRCA2* mutations. *BRCA1/2* genes testing is an example of susceptibility testing, which is the assessment of the future risk determination in an asymptomatic individual. To date, attention has focused mainly on the women belonging to *BRCA1* and *BRCA2* families and little is known about the impact of genetic testing on men.

No universal guidelines have been established to determine the population of pts who should be tested for *BRCA* mutations. General adopted criteria consider families as eligible for *BRCA* mutations testing if they meet any of the following classifications: multiple pre-menopausal first or second-degree relatives with BC, bilateral BC, ovarian cancer and MaleBC. The criteria for testing of men should be similar to genetic testing criteria for women [66], and the following individuals should therefore be eligible for testing:

- men without cancer, if they have a FH of breast or ovarian cancer in first- or second-degree relatives with BC diagnosed before the age of 50;
- men with a diagnosis of breast cancer regardless of FH;
- men with a diagnosis of prostate cancer if they have a FH of breast or ovarian cancer in first- or second-degree relative with BC diagnosed before age 50;
- men of Ashkenazi Jewish descent, since the *BRCA* genes mutation prevalence is 2.5% in the general Ashkenazi Jewish population.

To date, fewer men than women have pursued *BRCA1* or *BRCA2* testing, most likely due to the misinformation about cancer risk in men. Generally, men have a clear understanding of genetic testing and often, rather than for their own cancer risk, their principal motivation for seeking it is concern for their families and children, specifically for their daughters [68]. In fact, male carriers of *BRCA1* and *BRCA2* mutations have an increased risk of developing breast, prostate and other cancers [66]. There are therefore important management implications for male *BRCA* carriers and there is a need to promote cancer screening recommendations, particularly with regard to breast and prostate cancer, to male carriers of *BRCA* mutations who are undergoing genetic counseling.

6. Histopathological features

About 90% of all male breast tumors prove to be invasive ductal carcinomas [11]. Since the male breast lacks terminal lobules, unless it is exposed to high doses of endogenous and/or exogenous estrogens, the lobular histotype accounts for only 1.5% of invasive cancers, whereas in women more than 10% of all breast carcinomas are lobular [11,12]. The lobular histotype has been reported in association with Klinefelter's syndrome [69]. In situ ductal and lobular in situ carcinomas account for almost 10% of all male breast carcinomas [11,70,71]. The vast majority of MaleBCs are low grade (68–78% G1–2) [72].

In large studies MaleBC has been found to express high levels of hormone receptors. The estrogen receptors are more likely to be positive in MaleBC than in FBC (80–90% vs. 75%) as are the progesterone receptors (73–81% vs. 65.9%), with evident therapeutic returns [73–77]. The proportion of hormone-receptor-expressing tumors increases with age, as occurs in post-menopausal women [11]. The expression of androgen receptors ranges from 39 to 95% according to the various reports in literature [1,78,79].

With regard to the over-expression of the proto-oncogene HER2/neu, it should be borne in mind that it is less likely to be present in MaleBC (about 5%) than in FBC (about 15%) [80,81]. Even though previous studies have reported equivalent over-expression rates for both sexes, it should be noted that they were performed prior to the standardization of the assessment method, thus leading to a possible overestimation of the findings [82,83]. Recently, an immunohistochemical HER2 expression has been found in about 15% of MaleBCs, confirmed by FISH in all cases presenting a 3+ Herceptest [84]. Furthermore, it has been observed that the HER2/neu status of the metastatic lesions may differ from that of the original primary tumor [85].

At present, little is known of the immunophenotypic characteristics of MaleBCs stratified according to *BRCA1* and *BRCA2* mutation status. *BRCA2*-related MaleBCs seem to show a significant association with HER2 over-expression and have higher histological grades [86]. These data suggest that specific phenotypic characteristics, indicative of aggressive behavior, could be associated with *BRCA2*-linked MaleBCs.

7. Clinical characteristics and diagnostic work-up

The most common clinical sign of breast cancer onset in men is a painless palpable retroareolar lump [87]. Other initial symptoms may include nipple involvement, with retraction and/or ulceration and/or bleeding, and axillary lymphoadenopathies [74,77,87–90]. The association between gynecomastia and MaleBC has been studied and a similar incidence has been found in MaleBC pts when compared to the general population [6,91].

The majority of pts (over 40%) presents with stage III/IV disease [1], often due to an early chest wall spread, not only as a consequence of low public awareness, but also with the scarcity of male breast parenchyma. It is interesting to note that the proportion of advanced stage disease reaches 50–60% when North African series are involved [92].

Clinically suspicious lesions referred for imaging should first be evaluated with mammography and with ultrasonography scans to select pts who will undergo to FNA or core biopsy (Fig. 1). Mammography can identify malignant breast

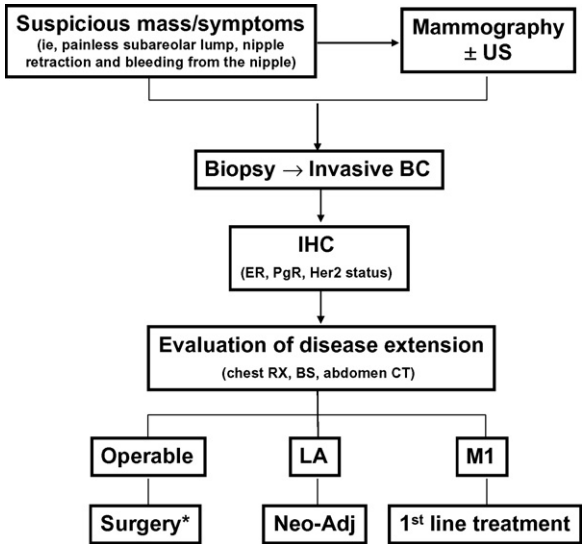

Fig. 1. Algorithm for the management of suspicious male breast mass. US = ultrasonography; BC = breast cancer; IHC = immunohistochemistry; ER = estrogen receptor; PgR = progesterone receptor; BS = bone scan; LA = locally advanced disease; Neo-Adj = neo-adjuvant treatment; M1 = metastatic disease; * = post-op treatment in Fig. 2.

tumors with a sensitivity of 92–100% and a specificity of 90% [93–95]. US of the axillary region could be helpful for staging as long as more than 50% of pts have positive axillary nodes at diagnosis [74].

8. Prognostic evaluation

Overall, men experience a worse prognosis than women [96], probably due to an advanced stage at diagnosis together with the higher age of male patients often leading to the coexistence of serious comorbidities. The overall 5- and 10-year survival rate of MaleBC patients are around 60 and 40%, respectively [11]. Nevertheless, when male or FBC pts are matched with respect to age and stage, no significant difference in terms of DFS or OS between the sexes is observed [97].

The number of histologically positive axillary nodes and the tumor diameter are significant prognostic factors [11]. The higher the number of lymph node metastases, the more unfavorable the prognosis will be. In fact, the survival rates at 5 years has been reported to be 90% for patients with node negative disease, 73% for those with 1–3 positive nodes and 55% for the group with 4 or more involved nodes [98]. It has to be mentioned that axillary nodes involvement has been reported in about the 50–60% of cases [99].

Another negative prognostic factor is the advanced age at the time of diagnosis, since the increased presence of comorbidities may limit the possibility of treatment [77,100]. Thus, the disease-specific survival (DSS) rates should be considered [74,98]. In a large French series, 5- and 10-year OS rates of 65 and 38%, respectively, were reported, whereas the DSS rates were 74 and 51%, respectively. In fact, only 113 (60.5%) out of the 187 deceased pts, died of breast cancer [74].

9. Locoregional treatments for male breast cancer

To date there are no published data from prospective randomized trials supporting a specific therapeutic approach in MaleBC. Most of the information regarding locoregional treatment derives from retrospective studies or those performed by individual institutions, with all the potential biases deriving from an analysis of data collected over a time span of several decades. This means, therefore, that almost all the treatment strategies that have been progressively adopted in MaleBC are based upon data resulting from female studies. A review of literature clearly shows that changes in treating MaleBC mirror the evolution of FBC care.

9.1. Surgery

Surgery is the cornerstone of treatment of MaleBC pts [75]. Until the 1970s, as for FBC, radical mastectomy was the treatment of choice for MaleBC; this approach was subsequently progressively substituted by less invasive surgical procedures, such as modified radical mastectomy, according to lesion extension [75,101,102].

Initial reports suggested that a less invasive approach might possibly have little effect on the patient's outcome [103–105]. More recently, in a retrospective study with 397 MaleBC cases, this topic has been reopened by Cutuli et al., who have reported that radical mastectomy is of no more value than modified radical mastectomy in terms of local relapse [74].

Since breast conservation has become the standard for the surgical management of FBC [106–110] new interest in minimally invasive surgical procedures has also arisen in the treatment in male pts.

Conservative breast surgery followed by radiotherapy, proposed in selected pts for the treatment of small tumors, has produced encouraging results, although there may be several technical difficulties when the procedure is used in males [111]; in fact, a larger tumor size and a higher rate of chest wall infiltration are found compared to female pts [112]. Moreover the usual central or retroareolar localization of the primary tumor in men, together with the paucity of the male breast parenchyma, makes a partial resection difficult to be planned. Nevertheless, in selected situations, for example when the breast tumor is associated with gynecomastia, even a lumpectomy could be a rational approach [111].

Radical mastectomy often leads to widespread skin removal, consequently causing problems in the management of the chest wall defect. Different options have been proposed such as the use of a transverse thoracoepigastric skin flap [113]. Other authors have suggested that a transverse rectum abdomini myocutaneous (TRAM) flap may be the best choice for male breast reconstruction, not only because it is

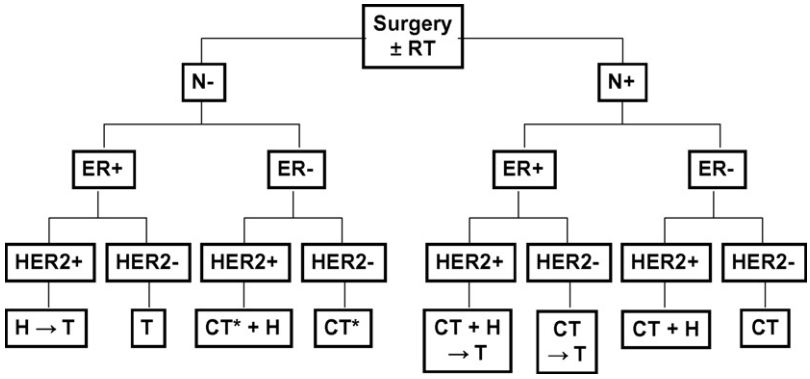

Fig. 2. Algorithm for the treatment of early male breast cancer. RT = radiotherapy; N = node involvement; ER = estrogen receptor; HER2 = epidermal growth factor receptor 2; T = tamoxifen; H = trastuzumab; CT = chemotherapy; * = consider CT according to risk level.

able to replace the missing skin and fat but also because it may be a source of hair-bearing skin similar to that of the male breast [114]. When the surgical wound is closed, the nipple can be reconstructed surgically or simply tattooed to restore the body image.

As for breast surgery, the surgical management of axillary lymph nodes has also undergone changes over the past years. Since axillary node involvement is one of the most relevant prognostic variables in MaleBC as in FBC [11], axillary lymph node dissection has been performed as part of the adjuvant treatment, but it is consistently associated with many late complications (i.e. lymphedema, paresthesias and reduced motility of the upper limb) [115].

Since several studies in FBC have shown that sentinel lymph node biopsy (SLNB) can reliably predict the status of axillary nodal involvement, so preventing useless larger dissections and ameliorating the quality of life [116], a minimally invasive approach has also became the standard treatment for men pts [117,118].

The first report regarding SLNB in a man with BC, was published by Hill et al. from the Memorial Sloan Kettering Cancer Center [119]. Larger single institution series, overall including <200 pts, have subsequently been collected by the leading American and European centers for breast cancer care, suggesting that SLNB in MaleBC pts is an extremely accurate tool providing a sentinel lymph node detection rate close to 100% [120–123]. The use of this technique could be indicated in pts with tumor size <2.5 cm and without clinical evidence of axillary node involvement [124].

9.2. Adjuvant radiotherapy

As MaleBC frequently presents at an advanced stage with early nodal involvement, locoregional relapse rates after surgery alone are quite high. In a comparative study published in the late-1990s by Scott-Conner, analyzing stage-specific differences in contemporary treatment strategies for highly comparable breast cancer pts of both sexes treated between 1985 and 1992, it was reported that radiotherapy after surgery was preferentially given to males [125].

Nevertheless, a subsequent large retrospective analysis of MaleBCs diagnosed between 1995 and 2005 have showed that, to date, male pts are more likely not to receive adjuvant radiotherapy compared to women [112].

Unfortunately, it is difficult to properly evaluate the real impact of adjuvant radiotherapy in MaleBC pts in terms of DFS and OS since most of the papers dealing with the question are statistically underpowered [96,126,127].

Notwithstanding this, several retrospective single institution studies have reported an excellent rate of local control after radiotherapy. Stranzl et al. have obtained a local control rate of 96.8% on a cohort of 31 pts who underwent postmastectomy adjuvant radiation with a 5-year DSS and DFS of 84% and 73%, respectively [128]. Similar results have been reported by Zabel et al. and Ober et al., the former with a local control rate of 96% after postoperative radiotherapy, the latter found that 5- and 10-year rates of local control were 90 and 85%, respectively, on a series of 41 pts [129,130].

Furthermore, these encouraging results concur with the two largest studies published so far. The first one by Cutuli et al. collected 690 pts coming from 20 French institutions over a time span of 30 years. In this series, the overall rate of locoregional relapse among the 496 evaluable pts was 9.5%, with a significant difference between irradiated and non-irradiated pts (7.3% vs. 13%, respectively) [131]. In the second one, on a historical cohort of 428 pts, Ribeiro et al. demonstrated a significant difference in 5-year DFS rates between pts receiving radical mastectomy alone or simple mastectomy plus radiotherapy (44.6% vs. 77.2%, respectively) [77]. Other studies have failed to show a significant impact of RT on local recurrence rates [89].

The drawbacks of all the cited studies should be borne in mind when planning the therapeutic strategy for pts treated outside controlled trials. All these retrospective data, in fact, collected over several decades, are not able to take into account the huge technical changes in RT planning and delivery. Moreover, RT can be used in association with various types of surgery on both the breast and the axilla and also with a wide range of systemic adjuvant treatments, hence the

same guidelines generally accepted for FBC can be followed [1,89,99,132–134].

Adjuvant radiotherapy should be mandatory after breast-conserving surgery and, on the chest wall, after mastectomy in cases of close or positive margins and tumors larger than 1 cm with areola, skin or pectoral muscle involvement. Moreover, histological parameters, such as lymph-vascular space invasion, high tumor proliferation rates, high grade, multifocality and nodal involvement should strongly recommend RT on primary site [124,127,135].

It has been proven that in male pts too, axillary nodal involvement is the most accurate predictor of locoregional failure [127,136] as well as of shorter DFS [75,101] and OS [89,137,138], which indicates that the fixed number of 3 involved axillary nodes requiring additional axillar irradiation in female pts might also be used for male pts [139]. Similarly, supraclavicolar area irradiation should be considered with 4 or more nodes involved.

10. Adjuvant chemotherapy

Whereas reliable data support the use of adjuvant CT in women [140], the few available data regarding men suggest that such strategy might be beneficial even in this subpopulation [141].

Great caution is required given the possibility of increased toxicities due to comorbidities and older age at diagnosis.

Several retrospective series have suggested that the use of adjuvant CT in male pts is associated with a reduced risk of relapse [142–144].

In 1987, Bagley et al. published the results of a small, prospective study involving 24 men with stage II breast carcinoma treated with adjuvant CMF and reported a 5-year survival rate of over 80% [145]. Yildirim and Berberoglu have found an increase of 5-year survival rate in 121 men treated with different regimens [144].

Since MaleBC is a rare disease, it is hardly possible to plan and carry out large randomized studies; nevertheless, given the confirmed results regarding FBC and the positive experiences in men, both men and women could share the same guidelines for adjuvant treatment [146]. So that, chemotherapy should be used in the absence or doubt about endocrine-responsiveness and the taxanes may be considered when lymph nodes are involved. Regarding the use of adjuvant trastuzumab, since no specific data exist, its use should be considered according to patients' and tumor characteristics, following FBC guidelines (Fig. 2).

11. Adjuvant hormonal therapy

As previously mentioned, MaleBC expresses hormone receptors in about 90% of cases, which makes adjuvant hormone treatment a basic part of the therapeutic management of the disease (Fig. 2). A great many retrospective studies have, in fact, evaluated the usefulness of tamoxifen, first in the metastatic setting [3], where it has proved to be extremely active, and subsequently in the adjuvant setting, where it has been associated with a reduction of the relapse and mortality rates [75,77,147,148]. Goss et al. in particular have reported a significant increase, both in DFS and OS, in a series of MaleBC pts treated with hormone therapy, even though often administered for <2 years [75]. Another study including 39 men with stage II/III BC has shown a 5-year survival rate of 61% in pts treated with adjuvant tamoxifen for 1 or 2 years, vs. 44% in the control cases [77]. Interestingly, in both these experiences the duration of the adjuvant therapy was shorter than the normal standard of 5 years; both these studies, therefore, might even have underestimated the real benefits deriving from adjuvant tamoxifen.

Moreover, in a recent British observational study, performed between 2002 and 2003 to evaluate the management of men with breast carcinoma, it has been noted that 126 pts out of the considered 161 (78%) had received adjuvant tamoxifen [149].

Tamoxifen has proved to lead to an increase in survival rates in women with hormone-responsive disease and to date is generally considered the standard adjuvant treatment for hormone-dependent MaleBC. The tolerance of the drug has not been sufficiently studied in men; its main side effects are deep venous thrombosis, reduction of libido, impotence, mood changes and hot flushes [150].

With regard to aromatase inhibitors, even fewer studies have been performed to evaluate their role in the adjuvant setting; in fact, preclinical data have led to doubts regarding their usefulness. When used in healthy male volunteers, anastrozole has not proved to bring about the complete estrogenic suppression it usually provides in women: only a 50% reduction of estradiol plasma levels associated with an increase in testosterone levels in the 58% of cases has been observed [151]. On the contrary, encouraging results have been obtained in two pts treated with letrozole for metastatic disease: an objective response has been obtained in both cases (one with complete response) [152,153].

To date, the use of aromatase inhibitors and/or GnRH analogues cannot be included in the adjuvant treatment strategy for men with breast cancer.

12. Neoadjuvant therapies

The main indications for the use of neoadjuvant treatments are the presence of an ulcerated neoplasia, its fixation to the surrounding tissues, a state of advanced lymph node involvement and the possibility of avoiding surgical treatment which would modify the body structure [134]. A further advantage is that it makes it possible to observe the drug efficacy *in vivo*: it is now known that those pts who achieve a histopathological complete response to neoadjuvant therapy generally have a more favorable prognosis. Since no specific data on this topic for MaleBC exist, FBC guidelines should be followed man-

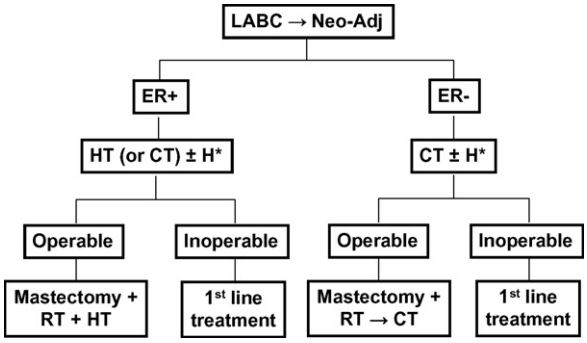

Fig. 3. Algorithm for the treatment of locally advanced inoperable male breast cancer. LABC = locally advanced breast cancer; Neo-Adj = neo-adjuvant treatment; ER = estrogen receptor; HT = hormonal therapy; CT = chemotherapy; H* = trastuzumab depending on HER2 status; RT = radiotherapy.

aging eventual peculiar situations. The choice of treatment depends essentially on the biological features of the tumor (Fig. 3).

13. Treatment of metastatic disease

In the past, the traditional management of metastatic MaleBC consisted in surgical interventions causing hormonal status modifications, such as orchiectomy, adrenalectomy or hypophysectomy, which did, in fact, lead to a positive response in 55–80% of the cases, depending on the performed procedure [1,154–158]. Obviously, these surgical approaches were effective only in the majority of pts with hormone-responsive breast carcinomas. Nowadays these methods have given way to various types of additive hormone treatment, the most important being tamoxifen, which leads to a response in about 50% of cases [159]. There have been reports of even complete response to LH–RH analogues, with or without antiandrogens [160–162]. Other possibilities to take into consideration include androgens, progestins, corticosteroids and high doses of estrogens, in order to obtain response rates ranging from 32 to 75%, according to the chosen drug [1]. The role of fulvestrant remains undetermined for MaleBC pts.

As already mentioned in the section regarding adjuvant therapy, the role of aromatase inhibitors in MaleBC has not yet been sufficiently evaluated and is therefore still not fully understood, although encouraging results have been obtained from single institution experiences [152,153,163].

In spite of the fact that the mean onset age in males is higher than in females, this alone cannot be considered as a valid criterion for excluding chemotherapeutic management; treatment choice should depend upon the clinical and biological features. At the present time, chemotherapy should be addressed to hormone-refractory disease, to young men and to cases of aggressive tumors, for example those with visceral metastases. It should be borne in mind that chemotherapy might also have a significant palliative effect [164]. Since very few reports can be retrieved from literature, there is no standard chemotherapeutic regimen, with response rates ranging from the 13% of 5-fluorouracile alone to the 67% of the combination of 5-fluorouracile, doxorubicin and cyclophosphamide [159].

With regard to male pts with HER2/neu over-expressing tumors, they should be treated with trastuzumab, on the basis of data coming from FBC both in the adjuvant and in the metastatic settings [165–168].

Practice points

- Major risk factors for the development of MaleBC include clinical disorders carrying hormonal imbalances, radiation exposure and a strong FH for BC.
- MaleBC can be linked to mutations in BRCA or in low-penetrance genes (i.e. CHEK-2).
- Men with BC should be referred for genetic counseling and potential genetic testing.
- Most MaleBCs are advanced stage ductal invasive carcinomas.
- MaleBC expresses hormone receptors in about 90% of cases and is less likely to over-express HER2/neu than FBC.
- Locoregional approaches include surgery and RT depending upon the initial clinical presentation.
- Systemic treatment must be administered according to the tumor biology:
  - Tamoxifen is the recommended therapeutic option for hormone sensitive MaleBCs, either as adjuvant or metastatic first-line treatment. Data on the efficacy of other hormonal therapies are not yet definitive, even though positive experiences have been reported.
  - CT should be prescribed in the absence or doubt about endocrine-responsiveness.
  - HER2/neu over-expressing tumors should be treated with trastuzumab.

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Acknowledgement

We thank David Andrew Boyd-Carrigan for reviewing the article.

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