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Review

Male Breast Cancer: A Systematic Review about Epidemiology, Risk Factors, Diagnosis and Therapy in a Comparative Perspective with the Female Counterpart

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Abstract: Male breast cancer (MBC) is a rare clinical entity, accounting for almost 1% of all cancers in men and less than 1% of breast cancer (BC). Risk factors for MBC include age, family history of breast cancer, estrogen use, and testicular abnormalities. Due to the limited prospective research specifically focused on MBC, its management generally follows the same approach as for female breast cancer (FBC). However, MBC differs from FBC in terms of clinical presentation and molecular features, including variations in hormone receptor expression. Notably, MBC is often diagnosed at a more advanced stage due to diagnostic delays, with approximately half of the patients presenting with at least one involved lymph node at the time of diagnosis. Also, MBCs are predominantly estrogen receptor (ERα) positive. Genetic alterations, such as pathogenetic variants in the BRCA1/2 genes, and epigenetic changes identify a subset of MBCs that may differ from FBCs and could potentially require a distinct therapeutic approach. Treatment typically involves surgery, adjuvant radiation, endocrine therapy and chemotherapy. Ongoing multinational collaborations and the inclusion of male patients in FBC trials are essential for conducting clinical studies on MBC, which will ultimately help clinicians optimize care for MBC patients.

Keywords: male; breast; cancer; diagnosis; treatment; prognosis

1. Introduction

Breast cancer remains one of the most extensively studied and complex areas in medical science, both due to its clinical significance and social implications. In contrast to female breast cancer (FBC), research on male breast cancer (MBC) management is limited and still evolving, largely due to the historical exclusion of male patients from FBC clinical trials. [1]. Furthermore, the low incidence of MBC has resulted in a scarcity of prospective clinical trials. Consequently, much of our understanding of MBC is derived from limited retrospective studies, often based on single-center experiences [2]. As a result, current therapeutic strategies for MBC are largely adapted from FBC guidelines, despite notable differences in tumor biology, hormone receptor expression, and treatment responses.

Epidemiological studies suggest that the incidence of MBC has gradually increased over recent decades, with factors such as aging populations, genetic predispositions, and environmental influences playing key roles.

According to the American Cancer Society, an estimated 2800 new cases of MBC will be diagnosed by 2025 [3]. In Italy, the annual incidence is approximately 1.7 cases per 100,000 men, with a prevalence of one affected man per 520–620 individuals [4]. MBC is typically diagnosed in men between the ages of 60 and 70; however, in recent years, there has been a noticeable increase in cases among men under 45 [5]. The lack of standardized screening

protocols further complicates early detection, often resulting in more advanced disease at the time of diagnosis. Approximately 50% of MBC cases present with lymph node involvement, compared to 30–40% in FBC, highlighting the need for enhanced diagnostic approaches [6].

Emerging research highlights both similarities and differences in treatment approaches and outcomes between men and women. For example, men are more likely to undergo mastectomy compared to women (65% of men undergo modified radical mastectomy versus 55.1% of women). Additionally, men are more likely to receive radiation therapy after mastectomy (29% of men versus 11% of women) [7]. Conversely, men are less likely to receive chemotherapy compared to women (26.7% of men versus 40.6% of women) [7]. Mortality rates among men with breast cancer are also higher than in women, with a 5-year overall survival rate of 72.9% for men compared to 83.2% for women [8]. In triple-negative breast cancer (TNBC), the 5-year overall survival rate is 68.8% for men and 74.8% for women [9].

As awareness of MBC grows, there is an increasing demand for sex-specific research to refine diagnostic tools, develop targeted therapies, and establish evidence-based management protocols tailored to male patients. This review aims to provide a comprehensive analysis of the epidemiology, diagnosis, and treatment of MBC in comparison to FBC, emphasizing the unique challenges and future directions in its clinical management.

2. Methods

This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A comprehensive literature search was carried out using the PubMed database to identify relevant studies on male breast cancer (MBC). The search strategy included the terms "male AND breast AND cancer", as well as "male breast cancer" combined with the keywords "systematic review", "treatment", "epidemiology", "risk factors", "diagnosis", and "therapy". The search was restricted to articles published in English between January 2006 and December 2024.

Studies were considered eligible if they addressed at least one of the following topics: epidemiology, risk factors, diagnosis, genetic and molecular characteristics, treatment, or prognosis of MBC. Eligible publications included original research articles, systematic reviews, meta-analyses, and clinical guidelines, with a preference for studies offering a comparative perspective with female breast cancer (FBC). Articles were excluded if they were not published in English, if they were case reports, editorials, letters, or conference abstracts lacking original data, or if they focused exclusively on FBC without reference to MBC.

The initial search yielded 1450 records. After the removal of 200 duplicates, 1250 articles remained for title and abstract screening. Of these, 1050 were excluded for not meeting the inclusion criteria. The full texts of 200 articles were then assessed for eligibility. A total of 143 studies were excluded: 60 were not specifically focused on MBC, 40 lacked original or clinically relevant data, and 43 did not include any comparative analysis with FBC. Ultimately, 57 studies were included in the qualitative synthesis. The study selection process is summarized in Figure 1 (PRISMA flow diagram).

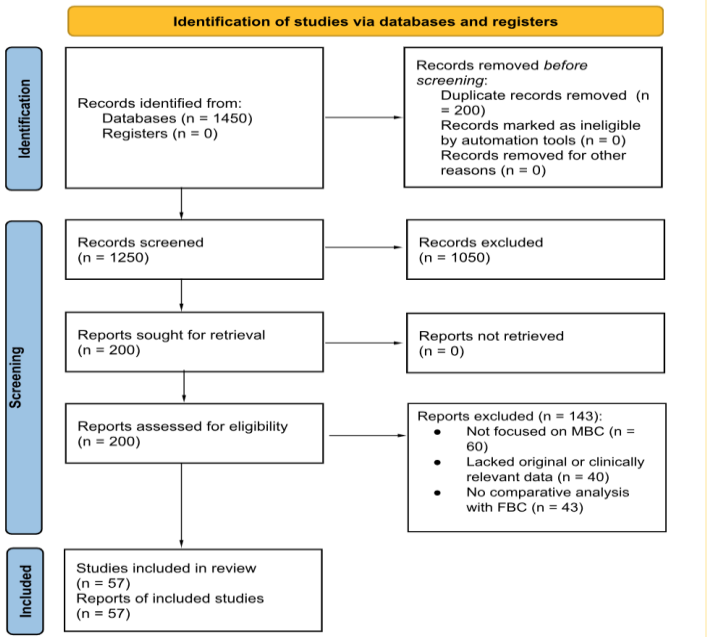

Figure 1. PRISMA 2020 flow diagram summarizing the study selection process.

The diagram illustrates the number of records identified, screened, excluded, and ultimately included in the qualitative synthesis, based on predefined inclusion and exclusion criteria.

2.1. Epidemiology

Compared to FBC, MBC is an uncommon malignancy, with a known incidence ratio of 1 male case per 100 females [3]. According to Surveillance, Epidemiology, and End Results Program (SEER) data from 2020, the incidence of invasive BC in men is 1.1:100,000, whereas it is 118.8:100,000 in women [10]. Between 1975 and 2015, the incidence of MBC increased by 40% [10], and according to the American Cancer Society [3], there will be 2800 new cases of male breast cancer by 2025 and about 510 men are projected to die from the disease. This incidence rate is significantly lower compared to women, where about 316,950 new cases are anticipated in the same year [3].

The incidence of MBC appears higher in some selected populations, such as African Americans, rather than Caucasian, Hispanic or Asian counterparts [1,11], a trend that seems to be consistent with FBC as well. One possible explanation is the higher prevalence of chronic infectious diseases in certain regions, such as schistosomiasis and hepatitis B or C, which can disrupt liver function and promote increased estrogen levels. Both hepatic dysfunction and hormonal imbalance are established contributors to elevated MBC risk [12].

Similar to women, the incidence rate of MBC widely increases as people age, but men tend to be older at the time of diagnosis, with an average age of 67 years old compared with 62 years old for women. In women, the incidence rate reaches its peak in the menopause stage, at around 55 to 60 years of age, and then gradually decreases or remains constant. In men the rate of increase in incidence does not slow after this age. This difference is probably due to hormonal changes occurring in menopause that do not happen in men [13].

2.2. Risk-Factors

Male and female BC patients share some genetic and environmental risk factors, but the majority of MBC diagnoses do not have any known risk factors other than increasing age [14]. Having a parent affected by BC determines a similar relative risk (RR) of developing BC in both sexes (RR of 1.73 in men and a RR of 1.74 in women) [2–14]. It is estimated that 15–20% of MBC patients have a positive family history for BC with at least one first degree relative affected by BC; the risk significantly rises with the number of affected family members. However, despite the elevated relative risk, the absolute risk of MBC remains low, and therefore routine screening mammography is not currently recommended for men with a family history of BC [2].

Several studies suggest that high estrogen levels rather than low androgen levels are linked to MBC [2]. Obesity has a significant effect on the pathological increase in estrogen levels because it leads to a higher proportion of androgen precursors being converted into estrogens in adipose tissue through peripheral aromatization [15]. Other causes of high levels of estrogen in men include gynecomastia and hepatic dysfunction, as they affect normal hormone metabolism. In addition, treatment with hormones, including estrogen administration for prostate cancer and gender-affirming therapy in transgender women, and testosterone treatment in hypogonadism or in transgender men, could interfere with the androgen–estrogen status, potentially leading to an increased risk of MBC [15]. Similarly, diseases like cryptorchidism, orchitis, and orchiectomy may cause an increase in the estrogen ratios due to a decrease in the amount of circulating androgens [14]. Alterations in the balance between estrogen and testosterone can also be due to Klinefelter syndrome, a genetic disease caused by an extra X chromosome (XXY genotype), which is characterized by low androgen and high levels of estrogens. Patients may exhibit gynecomastia, elevated gonadotropin levels, testicular dysgenesis, and an increased chance of developing BC [1–16]. Figure 2 underscores the multifactorial nature of MBC, with both genetic and hormonal factors playing critical roles. The horizontal bar chart illustrates various risk factors for MBC and their estimated relative impact, rated on a scale from 1 (low) to 5 (high).

2.3. Genetic-and-Epigenetic-Alterations.

BRCA1 and BRCA2 are highly penetrant autosomal dominant tumor suppressor genes strongly associated with early development of breast cancer, both in women and in men. These genes are involved in the repair of DNA double strand breaks by homologous recombination pathway and their mutation leads to the Hereditary Breast and Ovarian cancer syndrome (HBOC). Female BRCA1 carriers have a 65% lifetime risk of breast cancer, while female BRCA2 carriers have a 40% lifetime risk [17]. BRCA1 mutation has been associated with the more-aggressive triple receptor–negative tumor molecular subtype (ER negative, PR negative, and HER2 negative) and a family history of breast cancer [17].

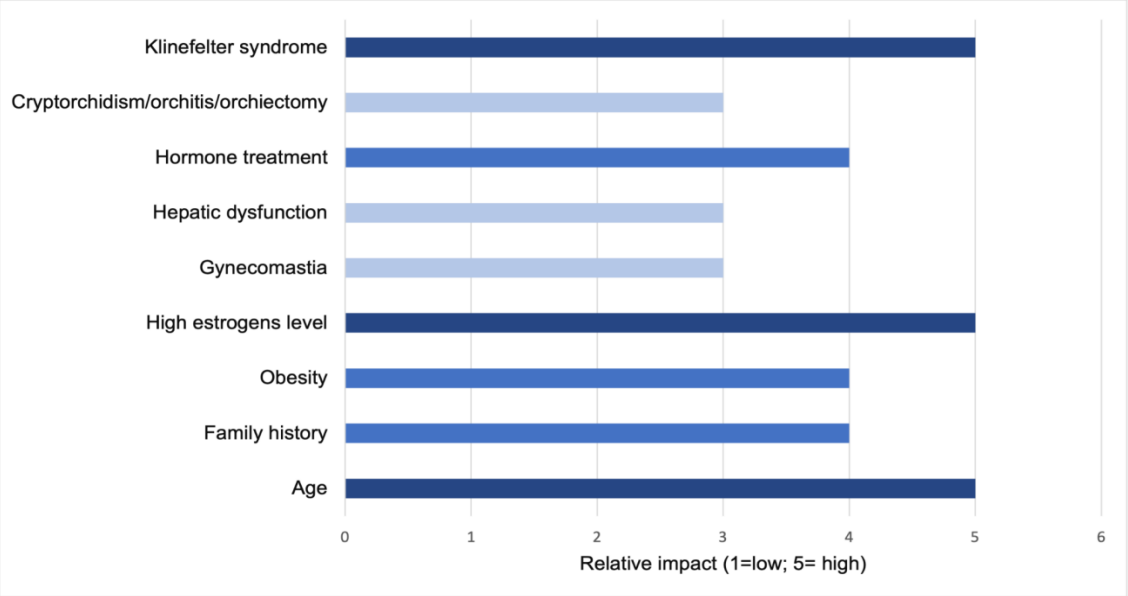

Figure 2. Relative impact of established and potential risk factors for male breast cancer (MBC) [2].

To mitigate cancer risk, women carrying BRCA1 or BRCA2 mutations typically undergo annual mammographic surveillance, and a subset elects to undergo prophylactic mastectomy and salpingo-oophorectomy. Males with pathogenetic mutations of BRCA2 have a lifetime risk of BC of 8.9%, which is 80–100 times higher than the population as a whole [18]. BRCA2 pathogenetic variation frequency in MBC ranges from 4% to 40% [18].

Germline BRCA1 pathogenic variants are less frequently observed, accounting for up to 4% of MBC cases [19]. Although male carriers of BRCA1 or BRCA2 mutations have a substantially lower absolute risk of developing breast cancer compared to female carriers, the relative increase in risk from the general population baseline is considerably higher in men—approximately 20-fold for BRCA1 and 80-fold for BRCA2—versus 4-fold and 3-fold increases in women, respectively [17]. Based on the latest guidelines from the National Comprehensive Cancer Network (NCCN), male BRCA1 or BRCA2 mutation carriers are advised to begin annual clinical breast examinations and regular breast self-examinations starting at age 35. Prostate cancer screening should start at the age of 45 [20].

Due to the limited evidence supporting the utility of imaging in men, routine mammographic screening is not currently recommended. Nonetheless, many male BRCA1 or BRCA2 mutation carriers—particularly those with a family history of breast cancer or additional risk factors—elect to undergo mammographic surveillance in consultation with their physicians. Beyond BRCA mutations, germline variants in several other cancer susceptibility genes have also been associated with prognosis and survival in MBC. A recent study involving MBC patients who underwent multigene panel testing (including eight or more common cancer-associated genes) reported that over 13.3% tested positive for at least one pathogenic mutation. Among these, the most frequently identified alterations were in BRCA2 (47%), followed by CHEK2 (31%), PALB2 (7%), BRCA1 (9%), and ATM (4%) [21].

PALB2 is a tumor-suppressor gene that encodes a protein essential for homologous re-combination in collaboration with BRCA2 during DNA double-stranded break repair [22]. In a recent study [23] with 115 instances of MBC that tested negative for BRCA2 pathogenetic variations, PALB2 pathogenetic variants accounted for 1–2% of cases. This indicates that MBC patients should undergo testing for both harmful PALB2 mutations and BRCA2, especially in families with a history of breast, pancreatic, or multiple MBCs. Yang et al. [24] found that PALB2-associated FBC tend to have an aggressive phenotype, often being hormone receptor negative, diagnosed at advanced stages, and showing high Ki67 proliferation indices.

In a recent study, PIK3CA (20%) and GATA3 (15%) were found to be the most frequently altered genes in male BC [25]. It is notable that the mutational hotspots found in PIK3CA and GATA3 in MBC appear to be different from those found in FBC, which may indicate potential differences in the biology of tumors based on sex [26–28]. The genetic predisposition to MBCs cannot be fully explained by low-penetrance (CHEK2, PALB2) or high-penetrance (BRCA1/2) genes [29].

Figure 3 summarizes key genes associated with MBC, categorized by their main biological function: DNA repair (e.g., BRCA1, BRCA2, PALB2), signal transduction (e.g., PIK3CA, GATA3), and hormone signaling pathways (e.g., ESR1, TOX3, FGFR2). Each gene is annotated with its associated level of MBC risk increase

(high, moderate, potential, or unclear) and whether the mutation exhibits specificity, such as known hotspots or sex-specific single nucleotide polymorphisms (SNPs).

GENE	MAIN FUNCTION	MBC RISK INCREASE	MUTATION SPECIFICITY
BRCA1	DNA Repair	High	No
BRCA2	DNA Repair	High	No
PALB2	DNA Repair	Moderate	No
CHEK2	DNA Repair	Moderate	No
ATM	DNA Repair	Moderate	No
PIK3CA	Signal Transduction	Unclear	Different hotspots
GATA3	Signal Transduction	Unclear	Different hotspots
ESR1	Hormone Pathway	Potential	Sex - specific SNPs
TOX3	Hormone Pathway	Potential	Sex - specific SNPs
FGFR2	Hormone Pathway	Potential	Sex - specific SNPs

Figure 3. Overview of genes implicated in male breast cancer (MBC) [17].

In a recent study of 413 Italian MBCs, single nucleotide polymorphisms (SNPs) in low-penetrance genes such ESR1, TOX3, and FGFR2 were found to affect breast cancer risk [29,30]. Lecarpentier et al. [31] found that some SNPs and BC have a sex-specific correlation. In particular, SNPs rs9371545 and rs11571833 are linked to ER-negative MBC, whereas other SNPs (rs11249433, rs34005590, and rs2981578), which are known to be connected with ER-positive FBC predisposition, are not. These sex-specific variations may be attributed to either the influence of various endogenous factors on the expression of SNPs or to the activity of various target genes of SNPs during the development of male vs. female BC [31].

Recent findings indicate that epigenetic modulation of the estrogen receptor (ER) pathway may exhibit sex-specific characteristics. In a cohort study involving 56 patients with a family history of breast cancer (comprising 27 males and 29 females) Pinto el al. [32] observed that ER expression was absent in male cases, unlike in females, despite an increased methylation level and decreased expression of *RASSF1A*, a gene implicated in ER-alpha repression. Remarkably, the combination of RAD51B and XRCC3 in the tissue methylation panel allowed for precise differentiation between MBC and gynecomastia [32]. Intriguingly, RAD51B and XRCC3 promoter methylation were shown in normal breast tissues at lower levels than in BC, suggesting a cancerization field effect [32].

From a clinical perspective, germline testing in men with breast cancer provides critical information for risk stratification, early detection strategies, and therapeutic decision-making [17]. Identifying BRCA1/2 or PALB2 pathogenic variants may inform eligibility for targeted therapies such as PARP inhibitors, while also influencing choices regarding surgical options (e.g., consideration of contralateral prophylactic mastectomy) and radiation planning. Furthermore, genetic findings have implications for cascade testing in at-risk family members, enabling personalized surveillance and preventive strategies [20].

Despite its growing clinical relevance, several barriers continue to limit the implementation of genetic testing in MBC. Many healthcare providers and patients are not fully aware of its importance, partly due to the historical underrepresentation of men in genetic cancer studies. Access to multigene panel testing remains uneven across healthcare systems, and concerns about reimbursement and insurance coverage may further hinder its widespread adoption [21].

While direct cost-effectiveness data on germline testing in MBC are limited, evidence extrapolated from studies in female breast cancer and high-risk populations indicates that such testing can be economically advantageous [15]. By enabling early detection, informing risk-reducing strategies, and guiding treatment selection, genetic testing contributes to improved patient outcomes and more efficient healthcare resource utilization. Integrating genetic counseling and standardized referral protocols into routine MBC care could therefore enhance both clinical management and health system sustainability [15–17].

2.4. Clinical-Features

The most common clinical presentation of MBC is a painless retroareolar mass, more frequently occurring in the left breast than the right, with pain reported in only approximately 5% of cases [33]. Due to the limited volume of male breast tissue, nipple involvement is often an early finding. Clinical signs may include nipple retraction (observed in 9% of patients), discharge (6%), or ulceration (6%), as the rudimentary breast ducts are located directly beneath the nipple [34]. Furthermore, as highlighted in a recent study by the International MBC Program (IMBCP) [34], axillary lymph node involvement at diagnosis is more common in men than in women, significantly influencing prognosis.

2.5. Radiological-Assessment

Data on appropriateness of radiological tests in men with breast disease are still limited. According to the American College of Radiology (ACR) guidelines, ultrasonography is recommended as the initial imaging modality for patients under 25 years of age. In contrast, for patients over 25, mammography should be the first-line imaging technique, with ultrasonography employed if mammographic findings are inconclusive or suggestive of malignancy [35]. Mammography has sensitivity of 92–100% and a specificity of 90% in identification of malignant breast tumors in men [36]. The surrounding tissue and eccentric positioning of MBC masses facilitate their identification, often characterized by spiculated margins and irregular edges. Moreover, compared to FBC, MBCs are less commonly associated with microcalcifications [34]. In cases of abnormal or benign mammographic findings, further evaluation with targeted ultrasound should be performed [36]. As part of the ultrasound evaluation for a suspicious breast mass, the ipsilateral axillary lymph nodes should also be assessed, as axillary lymphadenopathy is present in approximately 50% of MBC patients [34]. No reliable data seem to be available on the sensitivity and specificity of ultrasonography in breast disease in men. Hypoechoic mass with irregular or hazy edges, posterior shadowing or posterior acoustic enhancement, architectural distortion with loss of the typical fat-parenchymal interface are all ultrasonography markers of MBC [36].

Compared to female breast cancer (FBC), male breast cancer (MBC) exhibits some distinct imaging characteristics. On mammography, MBC masses are typically eccentrically located relative to the nipple, often presenting as high-density, irregular, or spiculated lesions with less frequent associated microcalcifications. In contrast, microcalcifications are more commonly observed in FBC, especially in ductal carcinoma in situ (DCIS), and their distribution may provide important diagnostic clues in women [36]. Ultrasound findings also differ slightly between the sexes. In MBC, hypoechoic solid masses are often observed with irregular margins and posterior acoustic shadowing, but architectural distortion is generally easier to detect due to the reduced volume of surrounding glandular tissue. In FBC, similar features may be present but can be masked by dense fibroglandular parenchyma, especially in premenopausal women. The lack of substantial breast tissue in men may lead to more conspicuous lesion margins and earlier clinical detection, yet also increases the risk of underdiagnosing smaller or subareolar tumors [37]. These anatomical and radiologic differences highlight the importance of sex-specific interpretation strategies in breast imaging.

The evaluation of the male patient with breast symptoms does not currently have a single accepted standard diagnostic work-up algorithm, but Chau et al. [37] propose one that is based on physical examination findings and, if necessary, adjunctive imaging evaluation with mammography and ultrasound (Figure 4).

The algorithm begins with clinical assessment through physical examination. Patients presenting with normal or benign findings are managed clinically without imaging. In cases with indeterminate or suspicious findings, bilateral mammography is recommended. If imaging results are benign, clinical management continues. For all other findings, further evaluation with specialized mammographic views or ultrasound is conducted. Based on this, indeterminate or suspicious findings warrant biopsy, while benign findings are followed by clinical management.

2.6. Histopathology-and-Proteomic-Markers

Most histopathological variants of BC observed in women are also present in men, albeit with varying incidences. The most common histological subtype of MBC is invasive ductal carcinoma, which accounts for more than 90% of new diagnoses. Ductal carcinoma in situ is diagnosed in only 9–10% of cases [34]. Due to anatomical differences, with male breasts consisting primarily of ducts lacking terminal lobules, the prevalence of invasive lobular carcinoma is considerably lower in men (1–2%) compared to women (15%). In men, invasive lobular carcinoma is often associated with Klinefelter syndrome [2]. Other histotypes, although infrequent, are: Adenocarcinoma not otherwise specified (NOS), invasive papillary carcinoma, carcinoma NOS, medullary carcinoma mucinous carcinoma, inflammatory carcinoma, phyllodes tumor, leiomyosarcoma and Paget's disease [36].

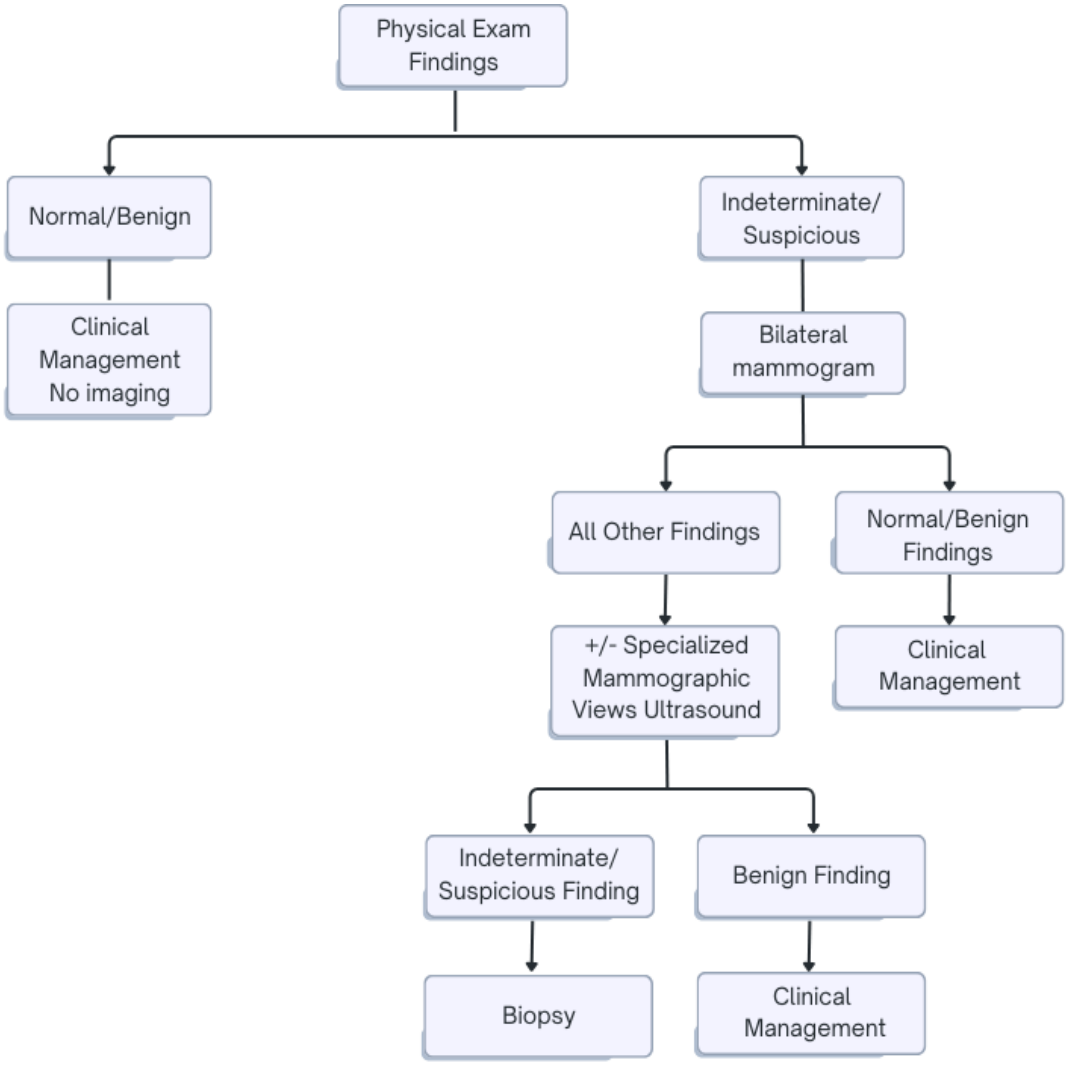

Figure 4. Proposed diagnostic algorithm for the evaluation of male breast symptoms, adapted from Chau et al.

The standard-of-care for treating breast cancer is presently defined by the three proteome markers: ER, progesterone receptor (PR), and human epidermal growth factor receptor (HER2), which have been investigated as both clinical and biomarkers [29]. Similar to females, in males the most common bio-histologic subtype is the luminal A with ER and PR positive and HER2 negative [2]. Clinically this subtype is low-grade, slow-growing, and tends to have a positive outlook. MBC is more frequently receptor positive hormone compared to FBC (ER 96% vs 84%), while the amplification of HER-2 instead is rarer in MBC regarding FBC (0,4% vs. 6%) [38]. The estrogen receptor exists in two isoforms, ER-alpha and ER-beta, which differ both in tissue distribution and biological function. Reproductive organs like ovaries and the endometrium contain ER-alpha receptors, whereas ER-beta receptors are found in non-reproductive tissues like the kidney, brain, bones, and the prostate [2]. In FBC there is a prevalence of ER-alpha receptors, while on the other hand ER-beta fraction is most frequently found in MBC. This could suggest that MBC and FBC exhibit different molecular biological activities, which might require a different strategy for anti-estrogen therapy [2]. The triple-negative (TN) subtype makes up 10–15% of FBC and is extremely uncommon in MBC, accounting for less than 5% of all BC diagnoses.

Androgen receptor (AR) consistently co-express with ER, just like in FBC, and this is associated with an improved overall survival and disease-free survival [29].

MBC exhibits distinct immunophenotypic characteristics compared to FBC, indicating a potentially different pathophysiological mechanism in its development and progression. These differences necessitate the use of treatment strategies tailored specifically for MBC, which may be crucial for therapeutic management.

Figure 5 shows the distribution of molecular subtypes in male and female breast cancer, highlighting the differences and similarities between the two groups [38]. Luminal A is the predominant subtype in both sexes, accounting for 57% of cases in males and 71% in females. These findings emphasize sex-based differences in

molecular subtype prevalence, with male breast cancer showing a higher proportion of Luminal B and a lower prevalence of TNBC and HER2-positive subtypes.

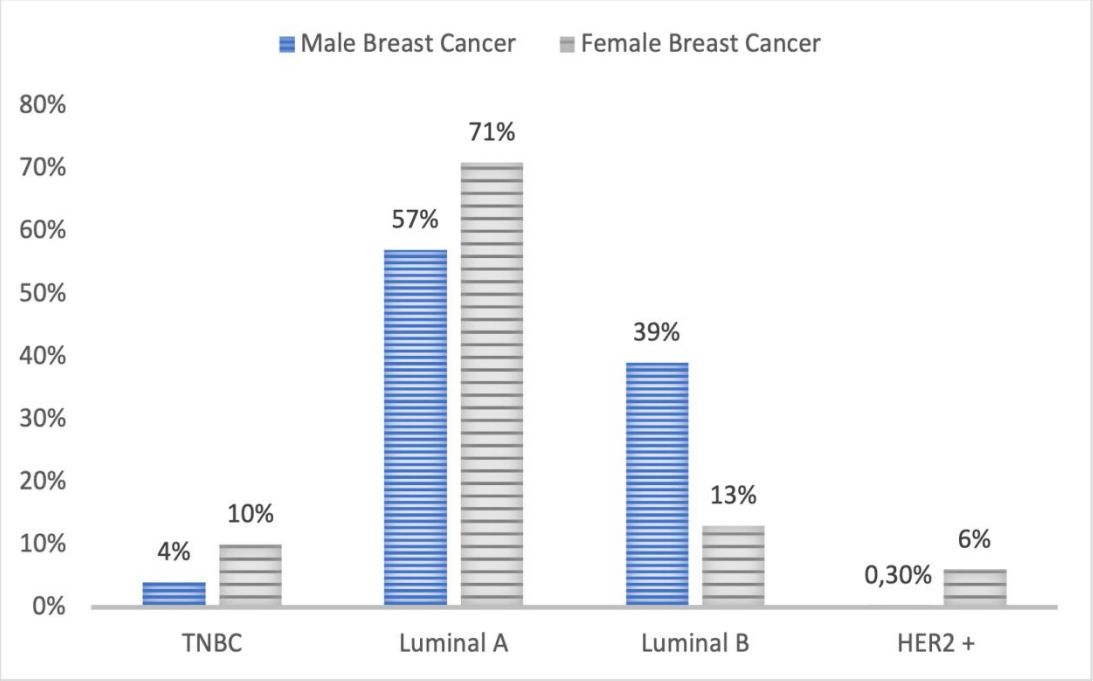

Figure 5. Distribution of molecular subtypes in male and female breast cancer [38].

2.7. Diagnostic-Delay-and-Survival

The disparity in survival rates between MBC and FBC patients is not unexpected, given the absence of screening programs and the less personalized care for males. However, this gap has widened since the introduction of screening programs for FBC in the 1990s [17]. For patients diagnosed during the same period, 7-year OS rates were 77.9% for men and 89.8% for women ($p < 0.05$), highlighting a significant survival disadvantage for MBC [37]. Men often receive suboptimal or inappropriate clinical care, contributing to delays in the detection of breast cancer until more advanced stages. On average, the delay between symptom onset and diagnosis exceeds 10 months [39]. Consequently, more than 40% of MBC are diagnosed at advanced stages, often with high T stage, lymph node involvement, and metastases to the lungs and bones. These factors, along with a high histological grade, are frequently associated with a poor prognosis [40].

Men generally avoid or postpone seeking clinical care compared to women; therefore, sex is an independent risk factor for early mortality.

Due to a lack of awareness and understanding of MBC, men with the condition often seek medical attention only after significant delays following symptom onset. A 2010 interview study [40] revealed that nearly 80% of men with a family history of BC were unaware that men could develop the disease. Furthermore, 40% expressed concerns that a BC diagnosis would be seen as emasculating, and none reported having ever discussed MBC with a healthcare provider. These findings underscore the critical need to raise awareness about MBC among the male population, alongside implementing strategies for earlier diagnosis.

To support a clearer understanding of these differences and to emphasize why MBC requires distinct clinical attention, Figure 6 summarizes the key pathological, diagnostic, and therapeutic distinctions between male and female breast cancer. Comparative overview of male versus female breast cancer, illustrating differences in epidemiology, tumor biology, imaging features, hormone receptor status, and therapeutic management. The figure underscores the necessity for sex-specific clinical pathways and research priorities.

2.8. Screening Program

Mammography screening plays a key role in reducing FBC mortality. While current guidelines do not support routine screening in men due to the disease's rarity, the implementation of screening programs for high-risk male populations is being evaluated.

Marino et al. [41] conducted a study investigating the utility of mammography for BC screening in a cohort of men at higher risk, defined by a personal and/or familial history of BC and/or a known germline pathogenic

variant (PV) in BRCA. The study revealed a cancer detection rate of 4.9 per 1000 in this high-risk group, which was comparable to the 5.4 per 1000 detection rate for screening mammography in women. Based on these findings, the authors concluded that screening mammography is valuable and should be considered for men at elevated risk for BC. Men with gynecomastia can start annual mammographic screening at age 50. In those with a family history of breast cancer, screening is advisable beginning a decade earlier than the age at which the youngest affected relative was diagnosed [42].

PARAMETER	MALE BREAST CANCER	FEMALE BREAST CANCER
INCIDENCE	<1% of all breast cancer cases	99% of all breast cancer cases
MEDIAN AGE AT DIAGNOSIS	67-71 years	60-65 years
MAIN GENETIC FACTORS	BRCA2> BRCA1, PALB2, CHEK2	BRCA1> BRCA2; PALB2, ATM
MOLECULAR SUBTYPES	Predominantly Luminal A; AR + in 90% of cases; triple-negative rare	More heterogeneous; Luminal A/B; HER2 +, triple-negative all frequent
RECEPTORS EXPRESSION	High positivity for ER, PR and especially AR	Variable; ER + common, but broader receptor distribution
CLINICAL PRESENTATION	Retro areolar mass, often palpable; diagnostic delay is frequent	Greater variability; often detected earlier due to higher awareness
STAGE AT DIAGNOSIS	More advanced disease	Often diagnosed at early stage
SYSTEMIC THERAPY	Primarily based on treatment regimens developed for FBC; endocrine therapy (e.g., tamoxifen) is commonly used due to high ER/AR positivity	Well-established, evidence-based treatment approaches

Figure 6. Key Clinical and pathological differences between male and female breast cancer.

There is still no consensus on the optimal follow-up strategy for men with BRCA1/2 mutations. Therefore we reported the main recommendations of the selected guidelines from NCCN (National Comprehensive Cancer Network (Plymouth Meeting, PA, USA)), ASCO (American Society of Clinical Oncology (Alexandria, VA, USA)), SEOM (Spanish Society of Medical Oncology (Madrid, Spain)), ESMO (European Society for Medical Oncology (Lugano, Switzerland)) and ICR (Institute of Cancer Research (London, UK)) on the surveillance of male carriers of BRCA1 and BRCA2 PVs.

2.9. Early-MBC-Treatment

Similar to FBC, surgery is a crucial component in the treatment of early-stage MBC. However, unlike FBC, where two-thirds of patients undergo breast-conserving surgery (BCS) and one-third opt for mastectomy, the majority of men with MBC undergo mastectomy, with only a small percentage (10–24%) being treated with BCS [43]. Only 18% of men with T1N0 disease underwent BCS. This low rate of breast conservation may be due to the frequent location of the tumor in a central area of the breast and close to the nipple-areolar region. In addition, some men may prefer mastectomy to BCS to avoid postoperative radiotherapy [44]. Regarding prognosis, some retrospective studies have shown no significant difference in OS between mastectomy and BCS. When the tumor is quite large or there is lymph node involvement then neoadjuvant therapy (either endocrine-based or chemotherapy) can be administered as an attempt to shrink the tumor and potentially allow for a conservative surgical approach. However, such cases are relatively rare. Axillary lymph node dissection is still widely practiced in MBC, even though it is associated with significant complications including lymphedema, infections, and sensory deficits in the axilla.

Sentinel lymph node biopsy (SLNB) is also poorly used in MBC patients compared to FBC patients, although several studies have shown similar accuracy in axillary lymph node prediction [45,46].

In FBC, adjuvant radiotherapy is indicated in patients with four or more involved lymph nodes, any involvement of internal or supraclavicular mammary nodes, involvement of the chest wall after mastectomy, and for those undergoing BCS. In patients with T1–T2 tumors and 1–3 lymph-node involvement, clinical decision-

making requires a more individualized approach due to lack of prospective radiotherapy data for MBC. As a result, current recommendations generally reflect those that have been introduced for FBC. Recent evidence, however, highlights the potential survival benefit of postmastectomy radiotherapy (PMRT) with overall survival of 83% compared to 54% in those patients not receiving PMRT ($p < 0.001$). Subgroup analysis in the same study revealed improved outcomes both in patients with 1–3 positive nodes (79% vs. 72%, $p < 0.05$) and those with four or more involved nodes (73% vs. 53%, $p < 0.001$). Even though these results are positive, PMRT is still not used regularly in men with breast cancer and its use varies between different data sources. Radiotherapy following BCS is also not universally applied, with only 35–42% of patients receiving postoperative radiation [47–49]. However, Yadav et al. demonstrate a gradual increase in the adoption of both PMRT (from 50% in 2004 to 52% in 2014) and radiotherapy after BCS (from 66% in 2004 to 74.6% in 2014). Developments in delivery of radiotherapy, such as hypofractionated regimens and CT-based regional-planning protocols, are being investigated to improve accuracy and minimize treatment-related toxicity [43].

Adjuvant chemotherapy, including regimens based on anthracyclines, anthracycline-taxane combinations, and cyclophosphamide, methotrexate, and 5-fluorouracil (CMF), has been shown to improve OS in stage II and III disease. Specifically, a phase 2 clinical study of CMF in 31 men with MBC and lymph node involvement demonstrated an OS improvement, with survival rates of 80% at 5 years and 42% at 20 years, compared to historical data. Another retrospective study revealed a reduced risk of recurrence and improved OS in MBC patients treated with anthracycline-based chemotherapy regimens. Currently, adjuvant chemotherapy is typically recommended for MBC patients based on factors such as tumor size, lymph node involvement, ER/PR negativity, and younger age at diagnosis [49–51]. Given that 90% of MBC cases are hormone receptor-positive, endocrine therapy (ET) plays a critical role in treatment. Tamoxifen remains the most widely used therapy in both FBC and MBC. However, ongoing prospective studies are evaluating its effectiveness specifically in MBC.

Several retrospective studies have shown that tamoxifen improves overall survival (OS) in early-stage MBC, especially in patients with lymph node positive status. However one study [43] found that 65% of men were still taking tamoxifen after one year, but this had decreased to 46% at two years, 29% at three, 26% at four, and 18% at five years. The decline in adherence is likely linked to tamoxifen's side effects, including hot flashes, reduced libido, sexual dysfunction, mood changes, and an increased risk of venous thromboembolism. Another class of endocrine therapy (ET) used is aromatase inhibitors (AIs), which are mainly prescribed for postmenopausal women. In men, about 80% of estrogen is produced by the conversion of androgens through the action of the enzyme aromatase in peripheral tissues, while the remaining 20% comes directly from the testes. AIs function by inhibiting this peripheral conversion. However, AIs alone may not be fully effective in men with breast cancer. When estrogen levels drop, the body compensates for that loss in estrogen with a negative feedback loop, where the hypothalamus pumps out more luteinizing hormone (LH) and follicle-stimulating hormone (FSH), potentially leading the testes to produce more testosterone and consequently more estrogen. Research indicates that in healthy men taking anastrozole, estradiol levels can reach around 14.1 pg/mL, while postmenopausal women usually have levels that drop below 1 pg/mL. For men to achieve complete estrogen suppression, aromatase inhibitors (AIs) might need to be paired with either surgical or chemical castration to stop the body from producing compensatory testosterone [43–45].

A gonadotropin releasing hormone (GnRH) analogue can be added to therapy with AI to block FSH and LH secretion in patients who do not tolerate tamoxifen. This has been recommended by several guidelines, including NCCN, and the American Society of Clinical Oncology (ASCO). Nonetheless, current evidence suggests only limited clinical benefit when combining GnRH analogues with AI compared to AI alone. A retrospective study showed a difference of 1.6 months versus 6 months in PFS and 29,7 months vs. 22 months in OS; $p = 0.05$). In the male trial, 56 MBC patients positive to hormone receptors were randomized to receive tamoxifen, tamoxifen with GnRH and AI with GnRH. The study showed a steady decrease in estradiol levels in the two combined arms, but no survival data were reported. In conclusion, despite both retrospective and prospective results suggesting effective estradiol reduction with combined therapy, the superiority of the combination of GNRH plus AI over monotherapy with AI still has to be assessed in future studies, obviously taking into account the side effects. Finally, in the rare subset of MBC patients who exhibit HER2 overexpression, treatment approaches resemble those used in female breast cancer, using HER2-targeted agents despite the lack of prospective studies specifically assessing their effectiveness male populations [52,53].

This flowchart (Figure 7) outlines the therapeutic approach for early-stage male breast cancer, based on nodal involvement and tumor subtype. Node-negative patients undergo mastectomy or breast-conserving therapy (BCT) with sentinel lymph node biopsy (SLNB), while node-positive cases require axillary lymph node dissection (ALND). Adjuvant systemic therapy is then guided by tumor subtype: hormone receptor-positive (HR+) / HER2-negative tumors receive tamoxifen or chemotherapy based on risk, triple-negative breast cancer (TNBC) is treated

with chemotherapy, and HER2-positive cases receive chemotherapy plus HER2-targeted therapy following female breast cancer (FBC) guidelines.

SLNB: Sentinel Lymph Biopsy; ALND: Axillary Lymph Node Dissection; BCT: Breast-Conserving Therapy; TNBC: Triple-Negative Breast Cancer.

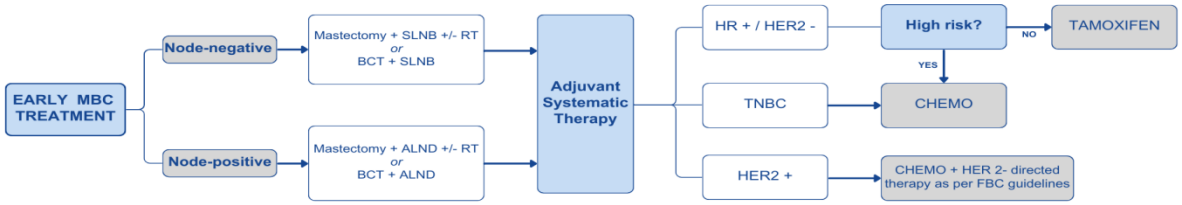

Figure 7. Treatment algorithm for early male breast cancer.

2.10. Advanced-MBC-Treatment

Similar to FBC treatment, ET is the first-line approach for hormone receptor-positive MBC. Tamoxifen is the preferred first-line agent for this condition. In patients experiencing disease progression, it's recommended to use a combination of an aromatase inhibitor (AI) and a gonadotropin-releasing hormone (GnRH) analogue instead of just AI on its own, as previously discussed. Retrospective data reveals that among those who received the AI and GnRH combination, 36.8% achieved a partial response, and another 36.8% kept their disease stable. The median progression-free survival (PFS) and overall survival (OS) were found to be 12.5 months and 35.8 months, respectively [52]. In case of both tamoxifen and AI refractory disease with GnRH analogue, fulvestrant stands out as a potential treatment option, although its use in MBC hasn't been thoroughly explored, largely due to limited study populations. In a pooled analysis of 23 patients with metastatic MBC, 40% received AI and GnRH as first or second line treatment. The results were encouraging, with 26.1% achieving partial responses and 47.8% maintaining stable disease [53]. These findings highlight a possible role for fulvestrant in the management of metastatic MBC. Furthermore, the combination of cyclin-dependent kinase (CDK) 4/6 inhibitors with endocrine therapy has shown a notable improvement in PFS among patients with HR+/HER2− metastatic BC, compared to endocrine therapy alone. This strong evidence has contributed to the approval of treatments like palbociclib for use in metastatic cases [53].

Evidence suggests that combining everolimus with an aromatase inhibitor (AI) can significantly improve progression-free survival (PFS) compared to using AI therapy alone. For patients with advanced HR+/HER2− female breast cancer, the median PFS is 6.9 months, compared to just 2.8 months ($p < 0.001$) [53]. However, it's worth noting that this treatment strategy hasn't been explored in prospective studies specifically for male breast cancer (MBC) patients. In advanced MBC cases, chemotherapy remains a treatment option mainly for those with hormone receptor-negative tumors, for patients whose disease has stopped responding to endocrine therapy, or in situations where immediate disease control is necessary due to visceral crisis [52].

A retrospective study evaluated 50 metastatic MBC patients who were refractory to ET, comparing an anthracycline-based regimen with an anthracycline-free regimen. The study found no significant difference in PFS or OS. In patients with FBC, it was concluded that mono-chemotherapy offers similar efficacy to multi-agent chemotherapy, with the added benefit of lower toxicity. The use of erythbulin as monotherapy has shown promising clinical responses, although the number of cases recruited was limited. Additionally, some clinical studies investigating anti-androgenic therapies, including two retrospective studies and one case report, have assessed the CYP17A1 inhibitor cyproterone acetate with or without GnRH analogs, reporting an overall 53% response rate.

Two recent clinical trials found no significant improvement in progression-free survival (PFS) in metastatic HR+/HER2− FBC patients with the addition of enzalutamide to ET. Recently, there has been growing interest in androgen receptor (AR) agonist therapy, particularly following a large-scale study by Hickey et al., which demonstrated that AR may function as a tumor suppressor rather than a driver in ER+ breast cancer, by opposing ER transcriptional activity [54,55]. In a recent phase 2 randomized trial, researchers explored the effects of Enobosarm, a nonsteroidal, tissue-selective androgen receptor (AR) modulator, on patients with heavily pretreated metastatic ER-positive female breast cancer. The study found a clinical benefit rate at 24 weeks and an objective response rate of roughly 30% in both the 9 mg and 18 mg treatment arms. Plus, Enobosarm showed a good tolerability profile [55].

Given the frequency of BRCA alterations in MBC, poly-ADP-ribose polymerase (PARP) inhibitors have become a potential treatment option. Its use has been studied in two phase III studies: OLYMPIAD and EMBRACA.

In the OLYMPIAD trial [55], a total of 295 patients were enrolled, including 7 men diagnosed with metastatic HER2-negative BC who also had BRCA mutations. These participants were randomly assigned to either receive a PARP-inhibitor known as Olaparib or physician's choice of single-agent chemotherapy. Although there wasn't a specific subgroup analysis for the MBC group, the results showed that Olaparib led to a significantly longer progression-free survival (PFS) compared to chemotherapy (7.0 months versus 4.2 months; $p < 0.001$). Additionally, Olaparib had a higher response rate (59.9% compared to 28.8%; $p < 0.001$) and a more manageable side effect profile [55]. Similarly, the EMBRACA trial included 431 patients, with 9 men with metastatic HER2-negative BC and germline BRCA mutations. They were randomized to receive either Talazoparib or single-agent chemotherapy. Talazoparib significantly improved PFS compared to chemotherapy, with 8.6 months versus 5.6 months ($p < 0.001$), and it also provided better outcomes reported by patients [56].

Given that, as in any treatment, the therapeutic decisions should be taken on a case-by-case basis, balancing the expected benefit with known toxicities, a gradual and sequential scheme of action should be implemented. Finally, immunotherapy and other medical therapies of oncological interest do not have an absolute frame of reference yet, giving the best outcomes when they are chosen specifically for each patient on a case-by-case basis by a multidisciplinary and multi-skills team [56,57].

3. Conclusions

Available data indicate that MBC exhibits distinct molecular and clinicopathological characteristics, which may necessitate different clinical approaches compared to FBC. As summarized in Figure 8, current evidence supports a multidisciplinary, individualized management approach encompassing screening, genetic testing, diagnosis, surgery, radiotherapy, and systemic therapy. This figure provides a visual summary of current clinical recommendations for male breast cancer, structured by clinical domain: screening indications for high-risk individuals, genetic testing and counseling, diagnostic imaging pathways, surgical principles, radiotherapy guidance, and systemic treatment options. It highlights areas where male-specific considerations differ from female protocols and emphasizes individualized, risk-adapted approaches based on current evidence.

Several novel therapeutics, including PARP inhibitors and anti-androgen therapies, currently under investigation for FBC, may also prove beneficial for MBC. A growing trend of clinical trials now includes MBC patients, providing an evidence base that will help shape future treatment strategies for MBC. Hopefully, a collective multinational effort will also facilitate the conduction of prospective trials focused exclusively on MBC in the near future.

An uncommon disease requires an uncommon approach, and thus, further studies and more evidence-based guidelines are essential. Understanding the various risk factors and the hereditary role in MBC development is a step forward. However, additional progress is still needed, particularly in the area of early diagnosis, as MBC is often diagnosed at later stages compared to FBC, frequently with lymph node involvement, which results in a worse prognosis.

The role of hereditary mutations, particularly in the BRCA1 and BRCA2 genes, has been extensively investigated, and a screening program for high-risk men is under consideration. Currently mammography and ultrasound are regarded as the most effective diagnostic tools. Once diagnosed, the optimal treatment for MBC requires a multidisciplinary approach with individualized therapy tailored to histologic subtype, disease stage, biomolecular gene expression, and other patient-specific factors.

Future Directions

Despite significant progress in understanding and managing MBC, several challenges persist, particularly in the development of targeted therapies and treatment guidelines specifically tailored to male patients. Given the biological and clinical differences between MBC and FBC, future research must prioritize prospective, sex-specific clinical trials to refine diagnostic tools, therapeutic strategies, and risk-adapted management protocols.

One of the most pressing areas of investigation in MBC is the comprehensive molecular and genomic profiling of tumors, which remains underdeveloped compared to FBC. Recent studies suggest that MBC may comprise distinct molecular subtypes characterized by differences in hormone receptor status, gene expression patterns, and somatic mutations (e.g., PIK3CA, GATA3, or ESR1 variants). A deeper understanding of these subtypes through next-generation sequencing, transcriptomic, and epigenetic analyses could enable precision oncology approaches and the development of male-specific therapeutic algorithms, rather than relying on

paradigms derived from female populations. Given that over 90% of MBCs express the androgen receptor (AR), one major research priority is to determine the clinical utility of AR-targeted therapies in this setting. Although preclinical and early-phase studies in FBC have demonstrated some efficacy of agents such as enzalutamide, bicalutamide, and abiraterone, MBC-specific data remain extremely limited [15]. Future trials should evaluate AR expression quantitatively and functionally in MBC cohorts, define predictive biomarkers of AR-dependence, and assess combination strategies with endocrine or targeted therapies.

DOMAIN	CLINICAL RECCOMENDATION
Screening	Mammography and ultrasound are considered the most effective diagnostic tools in high-risk men (e.g., BRCA carriers). Regular breast self-examination and clinical breast exam from age 35 are advised in mutation carriers.
Genetic testing	Recommended in all men with breast cancer, especially those with family history. Testing should include BRCA1, BRCA2, and PALB2, with consideration of CHEK2 and other relevant genes. Cascade testing in relatives is encouraged.
Diagnosis	Mammography is preferred in men >25 years; ultrasound is recommended in younger patients or when mammography is inconclusive. Axillary ultrasound should accompany breast imaging in suspicious cases.
Surgery	Mastectomy is the most common surgical approach; breast-conserving surgery may be considered in selected early-stage cases. Sentinel lymph node biopsy is feasible and accurate.
Radiotherapy	Post-mastectomy radiotherapy is recommended in node-positive or high-risk disease and has been associated with improved survival.
Systemic therapy	Endocrine therapy (e.g., tamoxifen) is standard in HR+ MBC.C hemotherapy, HER2-targeted therapies, and PARP inhibitors are considered based on tumour subtype and mutation status.
Future directions	Anti-androgen therapies and immunotherapy are promising investigational options but require further MBC-specific evidence.

Figure 8. Key clinical recommendations in male breast cancer management [41,42].

Another promising avenue is the application of PARP inhibitors in MBC patients harboring germline BRCA1/2 or PALB2 mutations. While olaparib and talazoparib have demonstrated survival benefit in BRCA-mutated FBC, their specific efficacy and toxicity profile in MBC require validation through dedicated studies, especially considering sex-related pharmacodynamics and comorbidity patterns [55,56]. Immunotherapy, a rapidly expanding frontier in oncology, has received little attention in MBC research. Yet, emerging data indicate that a subset of MBCs exhibit PD-L1 expression, tumor-infiltrating lymphocytes (TILs), and high tumor mutational burden (TMB), features associated with immune responsiveness in other cancers [29]. Investigating the tumor immune microenvironment of MBC through multiplex immunohistochemistry, single-cell RNA sequencing, or spatial transcriptomics could identify patients most likely to benefit from immune checkpoint inhibitors or combinatorial immunotherapies. Early-phase clinical trials should be designed to test immunotherapy in biomarker-enriched MBC populations, particularly those with triple-negative or BRCA-mutated tumors.

Early detection is another critical aspect that requires further research. Given that MBC is often diagnosed at more advanced stages, investigating the feasibility of implementing screening programs for high-risk individuals (such as BRCA mutation carriers) could significantly improve early diagnosis rates. Current evidence suggests that mammography and ultrasound may be effective tools in this setting, but further studies are needed to determine optimal screening protocols and their impact on prognosis.

To drive progress in the field, it is essential to foster multinational collaborative efforts that facilitate the inclusion of MBC patients in existing breast cancer trials while also promoting the establishment of dedicated global registries. By generating robust data through these initiatives, researchers and clinicians can develop more precise, evidence-based guidelines that address the unique needs of male patients. As awareness of MBC continues to grow, a multidisciplinary and patient-centered approach remains the cornerstone of effective treatment.

In parallel, clarifying the molecular underpinnings of MBC through dedicated profiling efforts will be essential to develop sex-specific treatment strategies. Particular emphasis should be placed on evaluating the role of androgen receptor-targeted agents and immunotherapies, which hold considerable promise but remain largely untested in this population. Advancing these research areas will be crucial to establish a more personalized and biologically informed therapeutic framework for male breast cancer.

Abbreviations

BC	breast cancer
FBC	female breast cancer
MBC	male breast cancer
HBCO	hereditary breast and ovarian cancer
RR	relative risk
PTEN	phosphatase and tensin homolog
HBOC	Hereditary Breast and Ovarian cancer syndrome
PALB2	partner and localizer of BRCA2
TN	triple negative
HER-2	human epidermal growth factor receptor 2
ACR	american college of Radiology
MLO	breast medial lateral oblique
NOS	not otherwise specified
ER	estrogen receptor
PR	progesterone receptor
TNBC	triple negative basal like
NCCN	national comprehensive cancer network
BCS	breast conserving surgery
OS	overall survival
ALND	axillary lymph node dissection
SLNB	sentinel lymph node biopsy
PMRT	post-mastectomy radiotherapy
CMF	cyclophosphamide, methotrexate and 5-fluorouracil
AI	aromatase inhibitor
LH	luteinizing hormone
FSH	follicle-stimulating hormone
GnRH	gonadotropin releasing hormone
ASCO	american Society of Clinical Oncology
PFS	progression-free survival
SD	stable disease
CDK	cyclin dependent kinase
ET	endocrine therapy
AR	androgen receptor
PARP	poly-ADP-ribose polymerase
SEER	Surveillance, Epidemiology and End Results

Author Contributions

Each author has made substantial contributions to the work. Specifically: S.V.: conceptualization, methodology, formal analysis, writing—reviewing and editing; A. Magnarini: visualization, data presentation; A. Mammarella: software, data curation, investigation; G.X., U.M., V.A.: writing—original draft preparation, investigation; R.G., A.P., R.B.: supervision, validation. All authors have read and agreed to the published version of the manuscript. Each author agrees to be personally accountable for their own contributions and for ensuring that questions related to the accuracy or integrity of any part of the work, even those in which the author was not personally involved, are appropriately investigated, resolved, and documented in the literature. Contributor roles are defined according to the CRediT (Contributor Roles Taxonomy).

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Conflicts of Interest

The authors declare no conflict of interest. Given the role as Editor-in-Chief, Rossana Berardi had no involvement in the peer review of this paper and had no access to information regarding its peer-review process. Full responsibility for the editorial process of this paper was delegated to another editor of the journal.

Use of AI and AI-Assisted Technologies

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