

Male Breast Cancer: Evaluating the Current Landscape of Diagnosis and Treatment

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Abstract: Male breast cancer (MBC) is a rare condition, comprising less than 1% of all breast cancer cases. This review examines the epidemiology, risk factors, clinical presentation, diagnostic approaches, and treatment strategies for MBC in both early and advanced stages. Early diagnosis of MBC poses a significant challenge, as men typically present with more advanced disease than women with breast cancer, likely due to limited awareness and delayed medical care. Data guiding treatment strategies remain limited, as most clinical trials have historically excluded male participants. This review provides a comprehensive analysis of recent advances in MBC, critically examines current diagnostic and therapeutic gaps, and outlines emerging research priorities. By emphasizing the limitations of existing evidence and the urgent need for male-specific clinical trials, this manuscript presents a forward-looking perspective aimed at fostering more inclusive research to develop tailored, evidence-based strategies for male patients.

Keywords: male breast cancer, diagnostic approaches, treatment strategies

Introduction

Male breast cancer is a rare malignancy, accounting for 0.5–1% of all breast cancer cases worldwide, with approximately 2,500 new cases diagnosed annually in the United States.¹ Clinical presentation most often involves a painless breast mass, and approximately half of patients have lymph node involvement at diagnosis.² Diagnostic evaluation relies on mammography and ultrasonography when a breast mass is suspected, since routine screening is not recommended for asymptomatic men.^{3,4} Pathologic confirmation is essential, and genetic counseling and testing are recommended for all men with breast cancer due to the high prevalence of hereditary mutations.^{5,6} Treatment strategies for MBC are largely extrapolated from female breast cancer (FBC) due to the paucity of prospective, male-specific trials.^{2,5} According to Corrigan et al, male patients accounted for only 0.087% of participants across 131 breast cancer clinical trials.⁷ Mastectomy remains the most common surgical approach, though breast-conserving surgery with sentinel lymph node biopsy is a safe alternative in selected cases.^{4,6,8} Adjuvant endocrine therapy, primarily tamoxifen for 5–10 years, is the mainstay for hormone receptor–positive disease, while an aromatase inhibitor (AI) should only be used in combination with a gonadotropin-releasing hormone analog if tamoxifen is contraindicated.^{5,8,9} The role of chemotherapy and targeted therapies is determined by standard indications, with gene expression assays such as Oncotype DX increasingly used to guide adjuvant therapy decisions.^{4,5,10} This comprehensive narrative review synthesizes the latest research on MBC using literature searches of current best practices and aims to provide an up-to-date summary of diagnostic and therapeutic approaches, highlight knowledge gaps, and underscore the need for increased inclusion of men in breast cancer research and clinical trials.

Epidemiology of MBC

MBC is a rare malignancy, globally accounting for approximately 0.6–1% of all breast cancer cases and about 0.3% of all cancers in men.⁵ Incidence rates for MBC have increased modestly over recent decades, with age-adjusted rates rising from 0.85 per 100,000 in 1975 to 1.19 per 100,000 in 2015 in the United States.¹¹ MBC patients are diagnosed at an older age than FBC patients (mean age 67 vs 62 years) and often present with more advanced disease.⁵ Comorbidities are more

prevalent in MBC due to the older age at diagnosis, and these comorbid conditions may contribute to the observed differences in overall survival between men and women.¹² In addition, men with breast cancer have an increased risk of second primary malignancies, including melanoma, prostate, and gastrointestinal cancers, which further complicates management and impacts long-term outcomes.¹² Mortality rates for MBC are also higher than for FBC; large registry-based studies demonstrate that men have a 1.3- to 1.5-fold increased risk of death compared to women, even after adjustment for age, stage, and treatment.^{11,13} A population-based cohort study of patients from the United Kingdom diagnosed with breast cancer demonstrated the survival probability for females one, five, and ten years after diagnosis was 95.1%, 80.2%, and 68.4%, and for males 92.9%, 69.0%, and 51.3%.¹⁴ Despite propensity score matching for age, stage, and treatment, some studies report that the survival gap between MBC and FBC narrows, but does not disappear, signaling that comorbidities and other non-cancer-related factors are contributors to excess mortality in men.^{12,13,15,16} These findings underscore the need for tailored approaches to diagnosis and management in MBC, with particular attention to comorbidity assessment and optimization.

Risk Factors for MBC

Several risk factors have been identified for the development of MBC, including genetic mutations, hormonal imbalances, Black ethnicity, exposure to radiation, and family history.⁵ The most well-known genetic risk factors for MBC are *BRCA2* and *BRCA1* mutations, which are inherited in an autosomal dominant manner. Genetic predisposition to breast cancer is broadly similar between men and women, but there are important sex-specific features. *BRCA2* is the predominant high-penetrance gene in MBC, while *BRCA1* is more prominent in FBC.¹⁷ Recent large-scale analyses have affirmed that *BRCA2* pathogenic variants confer a substantially higher risk of MBC than *BRCA1*, with relative risks of 44.0 for *BRCA2* and 4.3 for *BRCA1*.¹⁸ Both *BRCA1* and *BRCA2* are associated with increased risks of pancreatic and stomach cancers, with *BRCA2* further linked to elevated prostate cancer risk.¹⁸ A large Italian case-control study demonstrated that pathogenic variants in genes other than *BRCA1/2*, particularly moderate-penetrance genes such as *PALB2* and *ATM*, are also associated with a significantly increased risk of MBC.¹⁹ *PALB2* variants conferred a sevenfold increased risk (OR: 7.28), and *ATM* variants a fivefold increased risk (OR: 4.79).¹⁹ Carriers of these variants were more likely to have a personal or family history of cancer, supporting the use of multigene panel testing in MBC patients to guide risk management and clinical decision-making.¹⁹ Klinefelter syndrome also increases the risk of MBC due to the extra X chromosome, which increases estrogen levels.²⁰ Other etiologies of hyperestrogenism in men that increase the risk of breast cancer include obesity, liver disease, or exogenous hormone exposure.¹ Finally, family history of breast cancer is among the compelling risk factors for MBC, with approximately 15–20% of cases having a family member with the disease, compared with 7% in the general male population.²¹

Clinical Presentation

MBC is typically diagnosed at an older age than FBC, with average ages of 68 and 62 years, respectively.²² MBC is also diagnosed at more advanced stages, with larger tumors and more nodal involvement, and up to 47% of men having axillary nodal involvement at the time of diagnosis.^{22,23} The delayed stage at diagnosis may be due to limited awareness of presenting symptoms, which most commonly include a painless, firm breast lump and may be accompanied by nipple retraction, discharge, bleeding, or skin ulceration.²² Most MBC tumors are hormone-positive and ductal in etiology, reflecting the lower incidence of lobular carcinoma in men.²² For unknown reasons, papillary histology appears to be more frequent in men than in women.¹ Other histological subtypes of breast cancer are rare in men.

Diagnostic Approaches

Mammography and ultrasonography are commonly used in the evaluation of MBC. The American College of Radiology recommends ultrasound for men aged <25 years with an indeterminate palpable mass, and mammography is performed if suspicious or indeterminate features are noted on the ultrasound.²⁴ For men aged ≥25 years with an indeterminate palpable breast mass, a diagnostic mammogram is useful for distinguishing benign from malignant breast masses.²⁴ Carrasco et al demonstrated in a series of 638 patients that ultrasonography had a lower sensitivity of 88.9% compared to 95% for mammography in distinguishing benign from malignant disease but had a similarly high specificity of 95.3%.²⁵

There is no relevant literature regarding the use of breast MRI for the initial evaluation of MBC; therefore, it is not indicated for evaluation of palpable breast masses in men.²⁴ Once a suspicious lesion is detected, a core needle biopsy or fine-needle aspiration is essential to confirm histopathological diagnosis.

Treatment Strategy for Early-Stage Disease

Surgical treatment for early-stage MBC is based on early-stage FBC and has evolved over time. After reports demonstrated that sentinel lymph node sampling was as feasible and accurate in MBC as it was in FBC, it slowly replaced axillary lymph node dissection as the standard of care for staging MBC with a clinically node-negative axilla.^{26,27} Similarly, mastectomy has traditionally been considered the standard surgical approach for male breast cancer, whereas lumpectomy is less commonly performed due to limited breast tissue and the typical proximity of tumors to the nipple–areolar complex. However, a review of The Surveillance, Epidemiology, and End Results (SEER) database of MBC patients from 1983 to 2009 who underwent either mastectomy or lumpectomy demonstrated that lumpectomy was not independently associated with worse breast cancer-specific survival (odds ratio 1.09, 95% confidence interval 0.87–1.37) or overall survival (odds ratio 1.12, 95% confidence interval 0.98–1.27) after controlling for age, race, stage, grade, and administration of radiotherapy.²⁸ In a retrospective analysis of 8,445 MBC patients from the National Cancer Database, breast-conserving therapy (BCT) was associated with improved survival compared to mastectomy.²⁹ Additionally, a prospective multi-institutional cohort study reported low postoperative complication rates with BCT, comparable to those seen in the FBC population.³⁰ While the underlying mechanisms of these associations require further investigation, current evidence suggests that BCT is a safe and feasible treatment option in MBC, offering clinically meaningful survival benefits.

Guidelines for adjuvant radiotherapy in early-stage MBC are limited, and postoperative radiation therapy is frequently underutilized in patients with MBC. Cardoso et al demonstrated that 45% of MBC patients treated with BCT, regardless of nodal status, and 30.7% of patients with lymph node positive tumors treated with mastectomy were not provided adjuvant radiotherapy.³¹ Generally, adjuvant radiation therapy should be provided according to the guidelines developed for FBC as multiple studies have suggested a clinically meaningful benefit for radiation therapy in men with early and locally advanced stages.³² For example, a SEER database analysis of males with stage I–III breast cancer between 2010 and 2015 demonstrated that postoperative radiation therapy was associated with improved survival, especially after breast-conserving surgery, for those with four or more positive lymph nodes or large primary tumors (T3/T4).³³ Similarly, a 2018 meta-analysis of 29 studies involving 10,065 men (23% with T4 tumors, 50% node-positive, and 93% having undergone mastectomy) found that 64% received adjuvant radiation, which was associated with improved locoregional control, overall survival, and distant metastasis-free survival.³⁴ Further investigations are necessary to improve our understanding and wider utilization of adjuvant radiotherapy for MBC.

In recent years, gene expression profile testing has guided adjuvant chemotherapy decisions and estimated the risk of distant recurrence in women with hormone receptor-positive, HER2 negative early-stage breast cancer. The use of Oncotype DX and other genomic assays in MBC is based on extrapolation from FBC data, due to the rarity of MBC and the lack of male-specific clinical trial evidence.¹⁰ A SEER database review of this assay in 322 MBC patients demonstrated a larger proportion of men had an $RS > 31$ and $RS < 10$ compared to women, suggesting differences in tumor biology between men and women; the analysis also reported that increasing RS risk categories ($RS < 18$, 18–30, and ≥ 31) were associated with decreased 5-year breast cancer-specific survival (99%, 96%, and 81%, respectively) and overall survival (93%, 86%, and 70%, respectively).³⁵ Among those with an $RS \geq 31$, 67% of MBC patients and 71% of FBC patients received chemotherapy in the SEER analysis.³⁵ Although these results suggest the prognostic value of genomic assays in MBC, there is a lack of clinical trial data demonstrating the benefits of chemotherapy. Therefore, chemotherapy with or without HER2-targeted therapy should be recommended for males with breast cancer according to the guidelines for females with breast cancer.³⁶

The majority of male breast cancers are hormone receptor-positive, with approximately 99% expressing estrogen receptors (ER) and 81% expressing progesterone receptors (PR).³¹ In early-stage MBC with hormone receptor positive tumors, tamoxifen, a selective estrogen receptor modulator, is the most utilized adjuvant endocrine therapy, and has been demonstrated to reduce recurrence risk and improve overall survival based on observational studies.^{37,38} A meta-analysis

by the Early Breast Cancer Trialists' Collaborative Group showed that tamoxifen significantly reduced the risk of recurrence in patients with MBC, corresponding to its efficacy in FBC. In contrast, retrospective studies have demonstrated worse survival outcomes among patients with MBC treated with an aromatase inhibitor (AI) than among those treated with tamoxifen.³⁹ Thus, AI monotherapy is not preferred in MBC, although men with hormone receptor positive breast cancer who have contraindications to tamoxifen may be offered a gonadotropin-releasing hormone (GnRH) antagonist with an AI, which may help overcome the lack of estradiol suppression with AI monotherapy.¹² Although there are no clinical trials on early-stage MBC to guide the optimal duration of adjuvant endocrine therapy, extrapolation from FBC studies suggests that the duration should be at least five years, with an extended duration of ten years in men with a high risk of recurrence.⁴⁰ Adjuvant cyclin-dependent kinase 4/6 (CDK4/6) inhibitors can also be used in MBC with a high risk of recurrence, as demonstrated in the MonarchE trial, which enrolled 21 male patients (0.7%) in the intent-to-treat population and showed that abemaciclib with endocrine therapy resulted in absolute improvements in 3-year invasive disease-free survival and distant recurrence-free survival rates of 5.4% and 4.2%, respectively.⁴¹

Treatment Strategy for Advanced-Stage Disease

According to NCCN guidelines, the management of advanced breast cancer in men is generally aligned with established approaches used in women. Metastatic hormone receptor positive disease is treated with endocrine therapies such as tamoxifen, a GnRH agonist combined with an AI, or fulvestrant.⁵ Unlike FBC, concurrent administration of a GnRH analog is recommended when an AI is used in MBC.³⁶ A prospective, randomized Phase II study in MBC found that combining an AI with a GnRH agonist led to greater suppression of serum estradiol levels compared to historical controls treated with AI monotherapy.⁹ In addition, population studies have shown improved responses with the combination of an AI and a GnRH analog over AI monotherapy, likely due to the inadequate suppression of testicular estrogen production by AIs alone.⁴² Collectively, these findings support the use of combined AI and GnRH agonist therapy in men. A pooled literature analysis also demonstrated the efficacy of fulvestrant monotherapy, with a median progression-free survival of 5 months, comparable to efficacy in females.⁴³ Finally, evidence supporting the use of CDK4/6 inhibitors in men remains limited, as the pivotal clinical trials evaluating these agents have predominantly included female participants. Kraus et al demonstrated that palbociclib combined with endocrine therapy was associated with a longer median treatment duration and higher real-world response rates compared to endocrine therapy alone, with a safety profile consistent with that observed in women, supporting the use of CDK4/6 inhibitors in metastatic hormone receptor positive MBC.⁴⁴ Another retrospective study of MBC patients treated with either palbociclib (n=16) or ribociclib (n=9), in combination with a GnRH analog and either fulvestrant or an AI, reported a median progression-free survival of 10 months in the second-line setting—comparable to outcomes observed in the MONALEESA-3 and PALOMA-3 trials involving postmenopausal women.^{45–47} Other therapies, such as mTOR inhibitors, PIK3CA inhibitors, or other specific targeted agents, lack specific clinical trial data for MBC, and recommendations regarding these agents are extrapolated from studies of female participants and real-world data. Similarly, recommendations regarding chemotherapy, HER2-targeted agents, immunotherapy, and PARP inhibitors in advanced MBC have been extrapolated from FBC.⁴⁸

Conclusion

In summary, MBC is a rare disease that is typically diagnosed at an older age and more advanced stage than FBC, with distinct risk profiles and unique challenges in diagnosis and management. Current therapeutic strategies for MBC are largely extrapolated from FBC due to the underrepresentation of men in clinical trials and the scarcity of male-specific prospective or randomized data. This review is limited by the current evidence base on MBC, which is largely derived from retrospective and registry-based studies characterized by small sample sizes and substantial heterogeneity across study design and outcome reporting. These methodological limitations reduce the generalizability of findings and hinder the ability to draw definitive conclusions about optimal management strategies in men. Furthermore, important biological and clinical differences between MBC and FBC—such as hormone receptor status, genetic predisposition, and tumor biology—may not be fully captured or addressed by current treatment paradigms that are primarily derived from studies in women. Future research should prioritize inclusion of men in clinical trials, promote multinational data collaboration, and support the development of tailored management strategies that reflect the distinct biology and clinical course of

MBC. Addressing these gaps will be essential to improving outcomes and quality of life for men diagnosed with this disease.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in the drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

Funding

The authors did not receive support from any organization for the submitted work.

Disclosure

The authors report no conflicts of interest in this work.

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