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Review article

Male Breast Cancer Biology, Screening, Treatment, and Follow-Up: A Narrative Review

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Abstract

Male breast cancer (MBC) is a rare type of cancer that affects men, accounting for only 1% of all cancers in men and all breast cancer cases worldwide. Its rarity is due to the differences in male endocrine function and the smaller amount of mammary tissue in males. Due to its infrequency, there is limited knowledge about the disease, and treatment recommendations are often based on extrapolation from clinical trial data involving female breast cancer patients. Men with MBC typically present in their 50s or older and may mistake a suspicious breast mass for a benign condition called gynecomastia. Various known risk factors contribute to breast cancer in men. Currently, there are no international randomized control trials (RCTs) specifically focused on MBC, and management guidelines are primarily derived from studies conducted among female patients. Localized and resectable cases of breast cancer typically require surgical intervention, followed by radiotherapy, chemotherapy, hormonal therapy, or potentially utilizing recent advancements in immune-oncology agents. A comprehensive approach that involves a multidisciplinary team ensures appropriate treatment and can lead to favorable outcomes. However, screening for MBC is limited due to the lack of large-scale international RCTs demonstrating its effectiveness in reducing MBC-related mortality.

Keywords: Gynecomastia; Breast neoplasm; Male breast; Risk of malignancy; Treatment

Introduction

Definition of MBC

Breasts are commonly recognized as symbols of femininity, sexuality, and motherhood in societies (1). Breast cancer is commonly perceived as a women's disease, and many people are unaware that men can also be affected by this condition. From a biological perspective, breasts are present in everyone, making breast cancer a possibility for both genders. Male breast cancer (MBC) is rare disease in men, representing around 1% of all breast cancer cases and resulting in a lifetime risk of about 0.1% (1/1000) (2). Despite its rarity, the incidence of MBC is on the rise, paralleling the increasing incidence of female breast cancer, particularly in urban areas of the western countries. Traditionally, knowledge and treatment

strategies for MBC have been extrapolated from female breast cancer due to the scarcity of MBC-specific research. However, this approach may overlook key differences in the pathophysiology and clinical management between male and female breast cancer patients.

The average lifetime risk of a man being diagnosed with breast cancer is about 1 in 670, compared to 1 in 8 for women. The median age of diagnosis for MBC is typically later than that for female breast cancer, with most men being diagnosed in their sixties and seventies. This difference in age of onset may influence both the biological behavior of the tumor and the response to therapy. Clinically, MBC often presents as a painless palpable mass beneath the nipple or areola, with nipple discharge and skin changes being fewer common presentations. The underlying etiology of MBC is not fully understood, but known risk factors include genetic predispositions, such as mutations in the BRCA2 gene, and environmental factors, such as prior radiation exposure.

Given the unique challenges presented by MBC, including its rarity, later age of onset, and potential differences in tumor biology, a more nuanced understanding of its clinical and molecular characteristics is essential. MBC develops when the cells in the breast tissue grow uncontrollably and form a mass or lump. Various factors can increase the risk of MBC, including personal, environmental, and inherited factors. Similar to women, advancing age is a risk factor for MBC. Other risk factors consist of chest radiation, external estrogen exposure, testicular disorders, liver disease, obesity, and conditions linked to high estrogen levels like Klinefelter's syndrome. Additionally, inherited mutations such as BRCA2, BRCA1, CHEK2, and PALB2 mutations play a significant role as risk factors. There is a paucity of biomarker investigations focusing on male breast cancer, despite a growing interest in this area over the last decade. Extensive collaborative research endeavors such as the International Male Breast Cancer Program have primarily emphasized ERα, progesterone receptor (PR), and HER2 breast cancers, which are already well-incorporated into clinical protocols (3). However, due to its rarity, there is still a lack of awareness and research regarding male breast cancer. This will enable the development of tailored treatment strategies and improve outcomes for men with breast cancer.

This review aimed to shed light on the current landscape of MBC, discussing its epidemiology, risk factors, pathophysiology, and treatment options, with a focus on emerging trends and evidence-based practices (Table 1).

Table 1: General characteristics of male breast cancer (MBC)

Variable	*Characteristics*
Prevalence	MBC accounts for about 1% of all breast cancer cases.
Incidence Rate	100 times less common in men than in women.
Average Age at Diagnosis	67 yr old.
Symptoms	- Lump or swelling in the breast- Redness or flaky skin in the breast area- Irritation or dimpling of breast skin- Nipple discharge- Pain in the nipple area
Risk Factors	- Genetic mutations (e.g., BRCA2)- Family history of breast cancer- Radiation exposure- Hormonal imbalances
Diagnosis	Clinical examination, mammography, biopsy.
Treatment	Surgery, radiation therapy, chemotherapy, hormone therapy.

Statistics and prevalence

MBC is a relatively rare disease, approximately 0.6%-1% of all breast cancers and roughly 0.3% of all cancers diagnosed in men are attributed to it (4). In Iran, the most prevalent cancers in men are stomach, prostate, and colorectal cancers (5). Although rare, MBC is estimated to represent at

least 0.8% of all breast cancer cases in the country (6).

Just like the incidence of breast cancer in women, MBC is also on the rise. In the last 25 years, there has been a 26% increase in MBC. In 2019, statistics show that 25,143 men were affected worldwide, with a mortality rate of 48.1% (7). Although MBC can occur at any age, it is most commonly diagnosed in men between the ages of 60 and 70. A large retrospective cohort study consisting of 19,795 MBC patients found that the median age of diagnosis was 65 yr, and 15% of patients received their diagnosis before the age of 50 (8). Men who have a family history of breast cancer or a genetic mutation in the BRCA1 or BRCA2 genes are at a higher risk of developing the disease (9).

Risk Factors

There are various risk factors that can elevate the likelihood of breast cancer development in men. These risk factors encompass:

1. Age: MBC is more commonly diagnosed in older men, particularly those over the age of 60 (8).
2. Family history: Men who have a family history of breast cancer, particularly in a first-degree relative like a mother or sister, face an increased risk of developing the disease (10).
3. BRCA gene mutations: Men who had mutations in the BRCA1 or BRCA2 genes have an elevated risk of developing breast cancer. Typically, these genes produce proteins that play an important role in inhibiting the growth of cancer cells (11).
4. Exposure to radiation: Men who have experienced significant exposure to radiation, particularly in the chest area, face an increased risk of developing breast cancer (12).
5. Hormonal imbalances: Certain hormonal imbalances, such as those caused by conditions like Klinefelter syndrome or cirrhosis of the liver, can increase a man's risk of developing breast cancer (13). In the context of male breast cancer, the relationship between fatty liver disease and cancer risk is complex. Cirrhosis, a form of liver scarring that can result from NAFLD, may alter hormone levels in men, potentially influencing the risk of breast cancer. Specifically, cirrhosis can lower androgen levels and raise estrogen levels, which has been linked to an increased risk of breast cancer in men. Additionally, obesity, which is a common risk factor for NAFLD, is also associated with a higher risk of MBC (14).

Symptoms

The symptoms of MBC can include:

A. Lump in the breast or underarm

A lump in the breast or underarm is one of the most common symptoms of male breast cancer. The lump may be painless or tender to the touch, and it may feel hard or firm. The lump may be located in one breast or in both breasts, and it may be accompanied by other symptoms such as changes in the nipple or skin of the breast (15).

B. Pain or tenderness in the breast

Pain or tenderness in the breast is not a common symptom of male breast cancer, but it can occur in some cases. The pain may be mild or severe and can occur in one or both breasts (16).

C. Changes in the nipple

Changes in the nipple can be a symptom of male breast cancer. The nipple may become inverted, meaning it is pulled inward instead of pointing outward. It may also become swollen, red, or scaly. In some cases, a discharge may be present from the nipple (17).

D. Swelling in the breast

A prevalent symptom of MBC is breast swelling, which can be localized or affect the entire breast. This swelling may be accompanied by other symptoms including the presence of a lump, alterations in the nipple or skin, or enlargement of the lymph nodes beneath the arm (18).

Diagnosis

The diagnosis of MBC typically involves several steps, including a clinical breast exam, imaging

tests, and a biopsy (19). The following are some common diagnostic procedures used in the diagnosis of male breast cancer:

A. Clinical breast exam

A clinical breast exam (CBE) is a physical exam of the breast tissue and lymph nodes by a healthcare provider. During a CBE, healthcare provider should examine both breasts and the lymph nodes under the arm and around the collarbone for any lumps, swelling, or other abnormalities. They may also examine the nipple and areola for any changes (20).

B. Imaging tests

Imaging tests are an important component in the diagnosis and management of male breast cancer. The same imaging modalities used for female BC are also used for MBC (21).

Mammography is the most commonly used imaging test for the detection of breast cancer. It is a type of X-ray that produces images of the breast tissue. Mammography is recommended for all men with symptoms of breast cancer or those at high risk of developing the disease (15). However, it may not be as sensitive in detecting breast cancer in men as it is in women because men have less breast tissue (21).

MRI (magnetic resonance imaging) is another imaging test that may be used to evaluate breast tissue in men. MRI uses a powerful magnet and radio waves to produce detailed images of the breast tissue. It may be more sensitive than mammography or ultrasound in detecting breast cancer, but it is also more expensive and may not be as readily available (21).

C. Biopsy

Biopsy is the definitive way to diagnose male breast cancer. A biopsy is a procedure in which a small sample of tissue is removed from the breast and examined under a microscope to determine if cancer cells are present (22).

There are several types of biopsies that may be used to diagnose male breast cancer, including:

1. Fine-needle aspiration biopsy (FNAB): A small, thin needle is inserted into the breast to remove a small sample of cells for examination (23).
2. Core needle biopsy (CNB): a larger needle is employed to extract a small sample of tissue from the breast. This procedure allows for a more substantial tissue sample compared to a standard needle biopsy, providing greater accuracy in diagnosing and analyzing breast abnormalities (24).
3. Surgical biopsy: A small incision is made in the breast to remove a larger sample of tissue for examination (19).
4. Excisional biopsy: The entire tumor or a portion of it is removed for examination (19).

The choice of biopsy method depends on various factors, including the tumor's size, location, the patient's overall health, and personal preferences. It is crucial to recognize that biopsies serve not only as a diagnostic tool but also aid in determining the stage of cancer and influencing treatment decisions.

D. Genetic testing

Genetic testing plays a vital role in assessing and managing male breast cancer. It enables the identification of inherited genetic mutations that can elevate the risk of developing the disease in men. By undergoing genetic testing, patients can gain valuable insights into their genetic profile and understand their susceptibility to breast cancer. This information is essential for guiding appropriate screening, prevention, and treatment strategies (25).

The BRCA1 and BRCA2 genes are widely recognized as significant genetic mutations linked to breast cancer. These mutations are associated with an elevated risk of developing breast cancer in both women and men. Men who carry a BRCA1 or BRCA2 mutation face a higher risk of developing breast cancer compared to the general population. It is important for individuals with these mutations to be aware of their increased risk and to take appropriate measures for screening, prevention, and early detection (26).

In addition to the BRCA1 and BRCA2 genes, several other genes have been associated with an increased risk of breast cancer in men. These genes include PALB2, CHEK2, ATM, and PTEN. Mutations in these genes can contribute to a higher susceptibility to developing breast cancer in males (27).

It's important to note that genetic testing is not recommended for everyone. The decision to undergo genetic testing should be made in consultation with a qualified healthcare provider who can help weigh the benefits and risks of testing and provide guidance on how to interpret the results (27).

Treatment

A. Surgery

As the primary treatment for male breast cancer, surgery plays a vital role in removing the cancerous tissue from the breast. The specific type of surgery recommended is determined by several factors, including the tumor's size, location, the patient's overall health, and their personal preferences. The primary objective of surgery is the complete removal of the cancerous tissue, enabling optimal cancer management and potentially reducing the risk of recurrence (18). The selection of the most appropriate surgical approach is a collaborative decision made between the patient and their healthcare team.

There are two main types of surgery for male breast cancer:

1. Lumpectomy: A lumpectomy is a surgical procedure that involves the removal of the tumor along with a small amount of surrounding breast tissue. This particular surgical approach is often recommended for smaller tumors that have not spread to other areas of the breast. By removing the tumor and a margin of healthy tissue, a lumpectomy aims to achieve complete tumor removal while preserving the majority of the breast. This approach is frequently combined with other treatments, such as radiation therapy, to enhance the chances of successful cancer management. The decision to undergo a lumpectomy will be based on factors such as tumor size, location, and individual patient considerations (28).
2. Mastectomy: A mastectomy is a surgical procedure that entails the complete removal of the breast. This type of surgery is commonly recommended for larger tumors or instances where the cancer has spread to other areas within the breast. By removing the entire breast, including the breast tissue, nipple, and areola, a mastectomy aims to eliminate the cancerous cells and reduce the risk of recurrence. The decision to undergo a mastectomy is based on various factors, including tumor size, stage, location, the presence of multiple tumors, and individual patient preferences. In some cases, reconstructive surgery may be performed to restore the appearance of the breast following a mastectomy (28).

In certain instances, during surgery, a procedure known as lymph node dissection may be performed to evaluate whether the cancer has spread to other areas of the body, specifically the lymph nodes in the armpit. This involves the removal and examination of the lymph nodes to determine if they contain any cancer cells. Lymph node dissection provides valuable information about the extent of cancer spread and helps guide further treatment decisions. The decision to perform a lymph node dissection is based on factors such as the size and characteristics of the tumor, as well as individual patient considerations.

After surgery, the tissue that was removed will be examined under a microscope to determine if all of the cancer has been removed. If cancer cells are found at the edges of the removed tissue, further surgery or additional treatment may be recommended to ensure that all of the cancer has been removed (18).

B. Radiotherapy

The primary objective of radiation therapy is to eradicate any residual cancer cells that may be present after surgery and diminish the risk of cancer recurrence. This therapy utilizes high-

energy X-rays or other forms of radiation to precisely target and destroy cancer cells. By delivering radiation to the affected area, radiation therapy aims to eradicate any remaining cancer cells and minimize the likelihood of cancer regrowth. The duration and schedule of radiation therapy will be determined based on individual factors, such as the stage of the cancer, surgical outcome, and overall treatment strategy (29).

Radiation therapy for MBC is typically well-tolerated; however, it may give rise to certain side effects. Common side effects may encompass temporary skin redness, irritation, or itching in the treated region, as well as fatigue and breast swelling. These side effects are generally transient and tend to subside once the treatment is concluded (30).

In rare cases, radiation therapy may cause long-term side effects such as heart or lung damage, although these risks are generally low (31). Your healthcare team can provide more information on the potential risks and benefits of radiation therapy for your specific situation (29)

C. Chemotherapy

In cases where MBC has spread to the lymph nodes or other areas of the body, or if the cancer is hormone receptor-negative, chemotherapy may be recommended as part of the treatment plan. Chemotherapy involves the use of potent medications designed to destroy cancer cells and inhibit their growth and division. By administering these powerful drugs, chemotherapy aims to target and eliminate cancer cells that may be present in other parts of the body. The decision to undergo chemotherapy is based on various factors, including the stage of the cancer, the individual's overall health, and the characteristics of the tumor (32).

The selection of chemotherapy drugs for MBC is tailored to the individual's specific cancer characteristics and treatment requirements. Typically, chemotherapy is administered in cycles spanning several months. The drugs are often administered intravenously (IV) through an IV line, although certain chemotherapy medications can also be taken orally (33).

Chemotherapy may lead to side effects, which can include fatigue, hair loss, nausea and vomiting, loss of appetite, and an increased susceptibility to infections. However, significant advancements in chemotherapy have been made to mitigate the severity of these side effects.

D. Hormone therapy

In cases where the cancer cells in MBC have receptors for estrogen or progesterone hormones, hormone therapy, also referred to as endocrine therapy, may be suggested as part of the treatment plan. The aim of hormone therapy is to hinder the effects of these hormones, effectively slowing down or halting the growth of cancer cells. By blocking the hormone receptors, hormone therapy helps to disrupt the signals that promote the growth and division of cancer cells. The specific medications used in hormone therapy may vary, and the treatment duration and frequency will be determined by the healthcare team based on the individual's specific condition and treatment goals. Regular monitoring and follow-up appointments will be scheduled to assess the effectiveness of hormone therapy and address any potential side effects or concerns (34).

The specific hormone therapy drugs used for MBC may vary depending on the individual's cancer, and the treatment may be taken orally as a pill or tablet. Hormone therapy may be used alone or in combination with other treatments such as surgery or chemotherapy (15).

Hormone therapy can cause side effects, which may include hot flashes, decreased libido, mood changes, and joint pain. However, these side effects are usually mild and go away after treatment is complete.

E. Targeted therapy

Targeted therapy is an advanced approach to cancer treatment that employs drugs or substances to specifically target certain molecules or proteins responsible for the growth and spread of cancer cells. Unlike chemotherapy, which affects rapidly dividing cells indiscriminately, targeted therapy is intended to be more precise and selective. By focusing solely on cancer cells, targeted

therapy aims to spare healthy cells from unnecessary harm. This tailored treatment strategy allows for a more targeted attack on the underlying mechanisms driving cancer growth, potentially leading to enhanced efficacy and reduced side effects compared to traditional chemotherapy. The selection of targeted therapy drugs is determined by the individual's specific cancer type and the molecular characteristics of the tumor (Table 2). Regular monitoring and follow-up assessments will be conducted to assess the treatment's effectiveness and manage any potential side effects (35).

Table 2: Major types of Male breast cancer

Type of Breast Cancer	*Description*
Invasive Ductal Carcinoma	This is the most prevalent type, where cancer cells start in the ducts and then invade other parts of the breast tissue. These cells can also spread to other parts of the body[1].
Ductal Carcinoma in Situ (DCIS)	In DCIS, cancer cells are confined to the ducts' lining and haven't spread to other breast tissues. It may lead to invasive breast cancer.
Lobular Carcinoma	Although rare in men due to fewer lobules, this cancer develops in the lobules and accounts for about 1% of male breast cancers.

For MBC cases where cancer cells show elevated levels of a protein called HER2 (human epidermal growth factor receptor 2), targeted therapy becomes a viable option. HER2-positive breast cancers are known to exhibit accelerated growth rates and a higher likelihood of metastasis. In such instances, targeted therapy drugs like Trastuzumab and Pertuzumab can effectively hinder the effects of HER2 and impede the proliferation of cancer cells. By specifically targeting the HER2 protein, these drugs aim to disrupt the signaling pathways that promote the growth and spread of HER2-positive breast cancer cells. The utilization of targeted therapy in HER2-positive MBC contributes to improved treatment outcomes and a more personalized approach to combating the disease. The specific targeted therapy regimen will be determined based on individual patient factors and in consultation with the healthcare team. Regular monitoring and follow-up assessments will be conducted to evaluate the treatment's efficacy and manage any potential side effects (36).

Targeted therapy drugs are typically given through an I.V. line and may be used alone or in combination with other treatments such as chemotherapy or hormone therapy. Targeted therapy can cause side effects, which may include fatigue, nausea, diarrhea, and increased risk of infection. However, these side effects are usually mild and go away after treatment is complete (35, 37).

Prognosis and Follow-up

The prognosis for MBC is influenced by several key factors, such as the stage of the cancer, tumor size, metastasis, and the overall health of the individual. Early detection and timely treatment play a crucial role in determining the prognosis. When the cancer is diagnosed at an early stage and has not spread to distant sites, the prognosis is generally more favorable (32, 38).

Regular follow-up care is essential after treatment for MBC to closely monitor for any signs of cancer recurrence or treatment-related side effects. This ongoing care typically involves regular physical exams, blood tests, imaging tests (such as mammograms, chest X-rays, or CT scans), and other tests as needed (38).

Advancements in diagnostic techniques, treatment options, and personalized medicine have contributed to improved prognosis and survival rates for male breast cancer. The collaboration between healthcare professionals and patients is

essential in developing an effective treatment plan tailored to the specific needs and characteristics of the individual (15).

It's also important to continue to practice healthy habits after treatment, such as maintaining a healthy diet, staying physically active, and avoiding tobacco and excessive alcohol use. These lifestyle factors can help to reduce the risk of cancer recurrence and improve overall health and well-being (39).

A. Survival rates

Survival rates for MBC depend on various factors, including the stage of the cancer, the size of the tumor, whether the cancer has spread to other parts of the body, and the individual's overall health. Survival rates can also vary based on the type of treatment received (40).

Based on data from the American Cancer Society, the five-year relative survival rate for MBC is approximately 83%. Around 83% of men diagnosed with MBC are projected to survive for at least five years following their diagnosis. However, it is essential to recognize that survival rates are calculated based on population averages and may not accurately reflect the prognosis of every individual case. Various factors, including cancer stage, treatment response, overall health, and individual characteristics, can influence an individual's specific prognosis (32, 41).

Factors that may affect survival rates include the stage of the cancer at diagnosis, the size and location of the tumor, the presence of hormone receptors or HER2 protein, the individual's age and overall health, and the type of treatment received (26, 40).

B. Monitoring and follow-up care

Monitoring and follow-up care are important aspects of the ongoing management of male breast cancer. After completing initial treatment, your healthcare team will recommend a schedule for follow-up visits and tests to monitor for any signs of cancer recurrence or side effects from treatment (38).

Follow-up care may include regular physical exams, blood tests, imaging tests (such as mammograms, chest X-rays, or CT scans), and other tests as needed. The frequency of follow-up visits and tests may vary depending on the individual's cancer and treatment history (15, 18, 32).

In addition to medical follow-up, it is important to continue to practice healthy habits after treatment, such as maintaining a healthy diet, staying physically active, and avoiding tobacco and excessive alcohol use. These lifestyle factors can help to reduce the risk of cancer recurrence and improve overall health and wellbeing.

In male breast cancer, which is a rare but similar disease to its female counterpart, STAT5's role is particularly interesting. STAT5 is activated in macrophages by factors derived from breast cancer cells, influencing macrophage function within the tumor microenvironment. This activation of STAT5 in macrophages drives the expression of inflammatory factors and is suggested to protect against tumor progression by promoting immune stimulatory genes(42).

Furthermore, the deletion of STAT5 in myeloid cells has been associated with enhanced metastasis, indicating that the presence of STAT5 in tumor-associated macrophages may have a protective effect against the spread of the disease (43). Understanding the mechanisms by which STAT5 influences macrophage function and tumor progression in MBC could lead to new therapeutic approaches that suppress tumor-promoting functions while enhancing anti-tumor responses.

Immunotherapy, a groundbreaking approach that harnesses the body's immune system to combat cancer, is an active area of research in breast cancer treatment. While its application in MBC treatment is not yet widespread, ongoing studies are exploring its effectiveness in this specific population. Immunotherapy holds significant potential for enhancing the body's ability to recognize and eliminate cancer cells, leading to improved treatment outcomes. Continued research aims to elucidate the efficacy and safety of immunotherapy in male breast cancer, paving the way for future advancements in this field (44).

Advancements in genetic testing and precision medicine also offer hope for the future of MBC treatment. By identifying specific genetic muta-

tions and tailoring treatment to an individual's unique genetic profile, we may be able to improve treatment outcomes and reduce side effects (45).

In addition to research on new treatments, efforts are also being made to improve early detection and screening for male breast cancer. Improved screening methods, such as breast MRI and genetic testing, may help to identify men who are at high risk for developing breast cancer and detect the disease at an earlier stage (46).

Conclusion

Overall, there is reason for hope that ongoing research will lead to new and more effective treatments for male breast cancer. As our understanding of the disease improves, we may be able to develop more targeted and personalized approaches to treatment, ultimately improving outcomes for men with breast cancer.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of Interest

No potential conflict of interest was reported by the authors.

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