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Overview of male breast cancer

Joseph Daniels [1,*], Abena Yeboah Aduse-Poku [2] and Phylicia Gawu [3]

[1] *National Centre for Radiotherapy, Oncology and Nuclear Medicine, Korle Bu Teaching Hospital, Accra, Ghana.*
[2] *Oncology Directorate, Komfo Anokye Teaching Hospital, Kumasi, Ghana.*
[3] *Department of Radiation Oncology, Mayo Clinic Comprehensive Cancer Center, Phoenix, Arizona, USA.*

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Abstract

Breast cancer (BC) is an epithelial neoplastic disease that usually begins in the ducts or lobules of the breast with the potential to spread to other parts of the body. BC is primarily a disease that affects females but can also occur in men due to the presence of (limited) male breast tissue. Nevertheless, male breast cancer (MBC) should not be seen as just the occurrence of female breast cancer (FBC) in males. Males share common risk factors with postmenopausal women including age, family history, breast cancer gene (BRCA) mutations, and exposure to therapeutic radiation as well as hormonal factors. MBC is uncommon partly because of the masculine endocrine landscape and the relatively limited volume of mammary tissue in males. There is a general lack of awareness of the occurrence of BC in men due to the extremely high incidence of FBC vis- a-vis the rare incidence of MBC. Some men may easily mistake a suspicious breast mass for gynecomastia, a far more common benign occurrence among males. There are currently no international randomized control trials (RCTs) on MBC. Management guidelines in use today are based predominantly on the results of trials conducted among FBC patients. The most effective therapy for MBC is surgery followed by radiotherapy, chemotherapy, and hormonal therapy. Screening for MBC is limited partly due to the absence of large international RCTs demonstrating its usefulness in decreasing MBC-related mortality.

Keywords: Male breast; Breast cancer; Male breast cancer; BRCA ½; Cancers in men; Estrogen receptor; Androgen receptor; Gynecomastia; Klinefelter syndrome; Targeted therapy

1. Introduction

Breast cancer (BC) is an epithelial neoplastic disease that usually begins in the ducts or lobules of the breast with the potential to spread to other parts of the body. Cancer can also originate in the connective tissue (sarcoma) or lymphoid tissue (lymphoma) of the breast, however, these entities are not considered BC and hence are beyond the scope of this review. BC is primarily a disease of females but can also occur in men due to the presence of (limited) male breast tissue [1]. Male breast cancer (MBC) is uncommon partly because of the masculine endocrine landscape and relatively limited mammary tissue. Even though estrogen is considered a female sex hormone, it is also present in males, albeit in smaller amounts. Hyperestrogenism is an important risk factor for the development of breast cancer in the male population. Unlike female breast cancer (FBC), the majority of MBC cases are estrogen receptor-alpha positive (ERα+) which indicates the involvement of estrogen in the pathobiology of MBC [2]. John of Arderne (1307-1392), a prominent English surgeon of his time, was the first to describe MBC in the western hemisphere [3]. One of the earliest reports of MBC in the 20th century that got a lot of attention was a publication in April 1938 about a 50-year-old Indian male with a huge non-metastatic primary breast tumor for whom there were no viable treatment options [4]. Notably, MBC was a rare occurrence then and remains so, close to a century later but same cannot be said about FBC. MBC has not been extensively researched like FBC therefore a lot still remains unknown about this disease entity. There are thousands more publications on FBC than MBC for good reason. Unlike FBC which is currently the most frequently diagnosed

* Corresponding author: Joseph Daniels; Email:josefdaniels@gmail.com

cancer among both men and women the world over, MBC accounts for a very small percentage of cancers in men, (< 0.5% in the US). Multiple studies have reported MBC incidence rates of < 1% of all breast cancer diagnoses [5, 6]. Genetic predisposition plays a key role in the development of BC in both males and females. The ratio of men with BRCA2 mutations who develop MBC may be as high as 1:10. Klinefelter syndrome confers a risk of BC that approaches that of females. MBC should not be seen as just the occurrence of FBC in males. Even though FBC and MBC share common epigenetic characteristics, they also have differences that set them apart from each other both epigenetically and mutationally [7]. MBC differs remarkably from FBC not just in terms of patients' gender and related physiological characteristics but also tumor biology as well as epidemiology, prognosis and fatality [8]. MBC, although rare, can have a devastating effect on the victims of the disease. The limited volume of normal male breast tissue presents the advantage of early and easy detection of abnormal breast lumps and the disadvantage of easy spread of even small-sized cancers to the underlying chest wall muscles, overlying skin, nipple areolar complex and/or draining lymph nodes. In comparison with FBC, MBC is associated with older age at diagnosis, late presentation and significantly worse prognosis. There is a general lack of awareness of the occurrence of breast cancer in men due to the extremely high incidence of FBC vis-a-vis the rare incidence of MBC. Some men may easily mistake a suspicious breast mass for gynecomastia, a far more common benign occurrence among males.

There are currently no international randomized control trials on MBC. Current management guidelines are based predominantly on results of trials conducted among FBC patients. Mastectomy with or without post-mastectomy radiotherapy (PMRT) is the standard of care for MBC. Hormonal therapy with ERα blockade is key in the adjuvant management of MBC. Tamoxifen (TMX) is the gold standard for endocrine therapy in the adjuvant setting for hormone receptor-positive (HR+) MBC and also plays a pivotal role in the metastatic setting. The use of aromatase inhibitors (AIs) may result in poorer outcomes compared with TMX in men with BC. The use of novel agents such as Cyclin-Dependent Kinase 4/6 (CDK4/6) inhibitors (Palbociclib, Abemaciclib, Ribociclib), mammalian target of rapamycin (mTOR) inhibitors (Everolimus, Rapamycin) and phosphatidylinositol-4,5-bisphosphate 3-kinase (PIK3CA) inhibitors in combination with TMX or AIs or fulvestrant can be extrapolated from data on FBC patients. There are a few clinical trials that also support their use in advanced HR+ MBC. The Androgen receptor (AR) is also expressed in MBC and constitutes a viable target for treatment. This review describes the clinical epidemiology, risk factors, diagnostic workup and principles of management of MBC as well as possible treatment outcomes of MBC.

1.1. Anatomy

The lymphatic drainage of the mammary glands is similar in both males and females. The thickness and composition of the chest wall are the same among both sexes. Naturally, the female mammary gland has more adipose tissue than that of males. Additionally, female mammary glands have a lot of lobes and lobules which are associated with the production of breast milk. By anatomical design, the male mammary gland is deficient in lobes and lobules in view of its lack of lactatory function. Due to the limited amount of adipose tissue, the nipple-areolar complex is in close proximity to the chest wall in males. This has negative implications for the natural history of the disease.

1.2. Epidemiology

The global incidence of MBC remains very low, ≤ 1% of all diagnosed breast cancers. However, the incidence is reported to be on a gradual rise even as female breast cancer also rises in incidence [9, 10]. Between 2004 and 2014, the incidence of MBC in the United States of America (USA) increased from 7.2% to 10.3% [11]. According to Surveillance, Epidemiology, and End Results (SEER) data, there was an overall increase of 40% in incidence from 1975 to 2015 for MBC. The incidence of BC is reported to be about 70 times more common among black women than black men in USA [12]. BC represents < 0.5% of cancer diagnoses in men and 1% of all breast cancer cases in USA. In the United States, it is estimated that 1 in 1000 males develops BC whereas 1 in 8 females develops the disease [6]. Yearly, MBC affects about 400 men compared to 50,000 women in the United Kingdom. In the USA, 2,700 males are diagnosed with BC annually whereas 1 in 1,000 develops the disease at some point in their lives [13]. There is a disparity in the global incidence of MBC with relatively more cases reported in Africa, Europe and America in descending order of frequency. High MBC rates of 15%, 6% and 5% have been reported in Zambia, Central Africa and Uganda respectively [14]. Hyperestrogenism is considered a key driving factor behind these high rates [15]. Asian men have the lowest incidence [16] whereas Israeli men have the highest incidence rates of 0.08 per 100,000 population [17]. A meta-analysis of MBC in Africa published in 2007 showed that North and sub-Saharan African countries have male to female ratios of 0.027 and 0.049 respectively with an overall average ratio of 0.042 across the continent, which is much higher than reported ratios in developed nations [18]. Increased life expectancy is assumed to be one of the main reasons for the observed rise in incidence since MBC is essentially a disease of older males. In Africa, MBC patients tend to be about 7 years older than patients with FBC. The average age at diagnosis for MBC in Africa was reported as 54.6 years meanwhile other studies have reported a unimodal age distribution of MBC with a peak age of 71years [18].

1.3. Etiology

MBC is a very rare diagnosis among individuals with breast neoplasia, consequently relatively few studies have explored its etiology. This observation is partly ascribed to the limited tumor sizes of MBC (< 5cm in 66% of cases) which is usually barely sufficient for histopathological analysis leaving very little or no residual tissue for molecular and genetic investigations [19]. The exact etiology of MBC is not well understood but various risk factors and predisposing conditions have been elucidated.

1.4. Risk factors

Males share common risk factors with postmenopausal women including age, family history, BRCA mutations, and exposure to therapeutic radiation as well as hormonal factors. Most patients nevertheless present without overt risk factors. Exogenous hormone therapy such as for the management of prostate cancer does not confer increased risk of MBC. Several genetic and environmental risk factors for MBC have been identified.

1.4.1. Age

BC can develop in males of any age; however, it is frequently diagnosed in older men > 60 years. Patients diagnosed with MBC are generally older than those diagnosed with FBC. The average age at diagnosis for BC has been reported to be at least 7 years earlier for African women than in African men [20, 21]. An average age of 67.7 years at diagnosis among 25 cases of MBC has been reported in Morocco which is >10years older than the average age of patients with FBC [1].

1.4.2. Klinefelter syndrome

Klinefelter syndrome which is associated with hypoandrogenism and hyperestrogenism increases the risk of BC by 20 – 30% and is by far the strongest risk factor for MBC [22]. This syndrome is an acquired genetic condition characterized by an extra copy of the X chromosome (47, XXY) resulting in 47 chromosomes instead of 46. Affected individuals have stereotypical masculine features & genitalia and often develop smaller testicles as well as enlarged breasts.

1.4.3. Genetic predisposition

Family history of MBC diagnosis as well as heritable genetic mutations contribute significantly to the risk of developing MBC. Approximately 30% of MBC cases have a positive family history. It has also been reported in a meta-analysis of case control studies of MBC that as much as 20% of all MBC patients have at least one first degree relative with BC with 4 – 40% of all MBC cases being familial [23]. MBC is more associated with BRCA 2 (4-16%) than BRCA 1 (≤ 4%) mutations [9]. This is consistent with the results of the Consortium of Investigators of Modifiers of BRCA 1/2 that reviewed data from 3184 BRCA1 and 2157 BRCA2 families. They demonstrated an increased risk of MBC linked with BRCA1 (relative risk (RR) 4.30), and BRCA2 (RR = 44.0) [24]. Other recent studies have demonstrated an 80-fold increased risk of MBC among men with BRCA2 mutations as compared to men in the general population. BRCA1 mutations are associated with a much lower median age at diagnosis (52 years) compared to BRCA2 patients and those without these mutations. BRCA2 associated MBC is considered to be more aggressive than sporadic cases. Cowden syndrome, caused by PTEN gene mutations has also been implicated in susceptibility to MBC [25]. Patients with CHEK2 and CYP17 mutations also have an increased risk of MBC [15, 26].

1.4.4. Occupational/ Environmental exposure

Working in hot environments (a risk factor for testicular failure) has been associated with increased risk of MBC in several studies involving blast furnace, rolling mills and steel factory workers as well as truck drivers and employees of soap and perfume industries [15]. Occupational exposure to carcinogens such as polycyclic aromatic hydrocarbons (PAH) in petrol exhaust emissions for at least 3 months have been associated with a 2.5 fold increase in risk for MBC [27]. Exposure to carcinogenic organic substances such as benzene and compounds of the ethylene family (trichloroethylene, dichloroethylene or perchloroethylene) are also associated with increased risk of MBC [27-29].

1.4.5. Hyperestrogenism

High estrogen levels are associated with BC in both males and females. BC has been documented among transsexual (male to female) individuals 5-10 years after initiating estrogen therapy. It has been shown that these individuals (transgender women and transfeminine people) have a higher risk of BC than other males (cisgender men) [30]. Hyperestrogenism can occur as a result of Klinefelter-associated gonadal dysfunction, obesity or excess alcohol consumption, all of which are associated with increased risk of BC. Exposure to estrogen or suppression of androgens results in increased estrogenic activity which translates into substantially increased risk of MBC among males. Even

though cases of MBC have been reported among men treated for prostate cancer with androgen deprivation therapy (ADT), no studies have demonstrated ADT as a risk factor for MBC. Orchidectomy and undescended testes increase risk of MBC, up to 12-fold by the former [31]. Obesity has been demonstrated to increase the risk of MBC in several studies [32, 33]. Some authors have also suggested that testosterone use, finasteride as well as orchitis and epididymitis may be associated with increased MBC risk [34, 35], [26, 32, 33, 36].

1.4.6. Radiation

An 8-fold increase in MBC risk per sievert has been reported among atomic bomb survivors [37]. The use of radiotherapy for the treatment of unilateral gynecomastia and thymoma have been shown to increase the risk of MBC by as much as 1.6 to 1.9 fold . There is a high relative risk of 7.2 associated with therapeutic use of radiation (Figure 1). Chest irradiation in the treatment of lymphoma or Wilm's tumor in children is more likely to increase the risk of BC as a secondary malignancy than irradiation to the brain or extremities. However diagnostic use of radiation for chest imaging has not been shown to increase susceptibility to MBC (RR=1). Although minimal total doses < 25Gy are currently used in the management of ADT induced gynecomastia in men with prostate cancer, no long-term studies have established the risk of MBC from this radiation exposure [38].

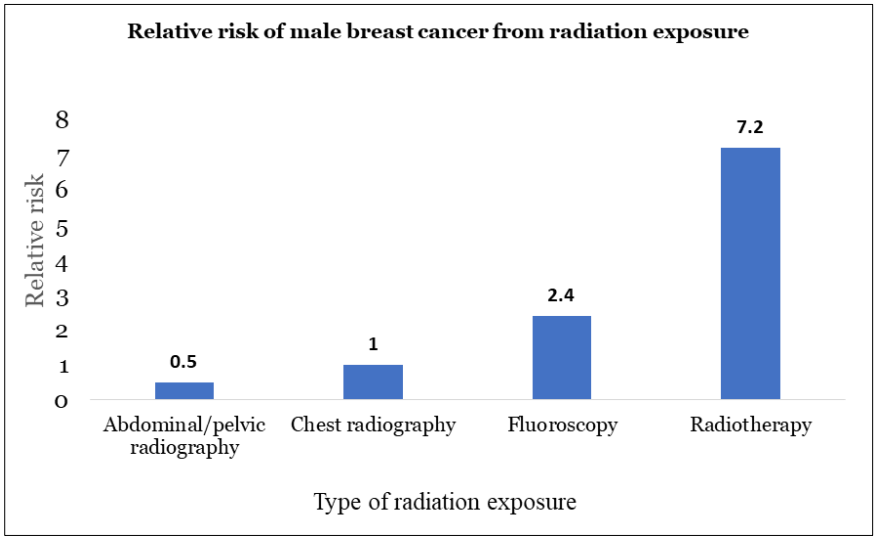

Figure 1 Relative risk of MBC due to exposure to different kinds of radiation [15, 37, 39]

1.4.7. Smoking

Smoking has also been shown to increase the risk of breast cancer [15]. Current female smokers with history of ≥ 10 years of tobacco use are believed to have a 10% higher risk of BC than never smokers whereas those who have smoked for < 10 years have not been associated with increased risk [40, 41]. These findings have however not been confirmed among male BC patients.

1.4.8. Gynecomastia

Gynecomastia occurs more frequently than MBC and is the most common male breast abnormality. It is especially common among adolescent boys and older men due to hormonal imbalance. It could also occur secondary to some endocrine tumors. It can also be due to Klinefelter syndrome which is an established risk factor for MBC. Even though cases of carcinoma in situ have been reported among males with gynecomastia there is no conclusive evidence directly linking it to MBC [3].

1.4.9. Prolactin

Prolactin is a hormone of the anterior pituitary with the main role of maintaining lactation. Multiple authors have reported no association between circulating prolactin and MBC but others have also reported cases of bilateral MBC in males with hyperprolactinemia due to pituitary adenomas [42].

1.4.10. Other risk factors

Some authors have reported an increased risk of MBC associated with lack of exercise, birth order – likely higher risk in first borns, bone fracture after age 45, marital status (higher risk among the never married), previous breast pathology and history of testicular pathology [26, 39, 43]. Hepatic insufficiency also leads to increased levels of estrogen which increases the risk of MBC.

1.4.11. Pathobiology

Male breast tissue has a lot of ducts but very few lobules, consequently lobular carcinomas are extremely rare in MBC (< 2%) compared to FBC (15%) mainly because of the absence of acini and lobules in normal male breast tissue [44]. The most common subtype of MBC is invasive ductal carcinoma (90%)[45, 46] . Ductal carcinoma in situ (DCIS) is another subtype that may occur in males with BC. The EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program represents the first and largest study to characterize male breast cancer. In the first part of the analysis of this study, it was demonstrated that DCIS is the most frequently observed precursor lesion and its presence seemed to be associated with a better clinical outcome. In this study, a significant proportion of patients with Invasive MBC also had adjacent DCIS [47] . Currently, there is no available data correlating the presence of DCIS and clinical outcomes in MBC but interestingly this study demonstrated that for MBC Luminal Her2+, particularly the Luminal B Her2+ patients with adjacent DCIS component, there was an improved overall survival (OS) compared to those without a ductal carcinoma in situ component. This suggests that the coexistence of DCIS May portend a biologically less aggressive disease though this assertion is yet to be proven by standardized methods or protocols. Majority of MBC patients present with moderately differentiated (WHO grade 2) disease. Lymph node positive disease is detected in about 50% of diagnosed cases of MBC [7]. MBCs are also more prone to bone and lung metastasis than FBC [48]. There are several special histological types of breast cancer that very rarely occur in males. These include adenoid cystic, medullary, metaplastic, micropapillary, mixed, mucinous, papillary, and tubular carcinomas.

1.5. Immunohistochemistry

MBC cases are most often than not, hormone receptor positive and HER2/neu negative which is reflective of the so-called luminal A phenotype. Among females, this molecular subtype is associated with the best survival outcome and represents a subgroup of patients who are most likely to benefit from hormonal therapy as well as chemotherapy. Several biomarkers have been investigated for potential significance in the clinical setting including estrogen receptors (ERα, ERβ1, ERβ2, ERβ5), progesterone receptor (PR), androgen receptor (AR), Bcl-2, HER2, p53, E-cadherin, Ki67, survivin, prolactin and FOXA1. Survivin and Bcl2 have been shown to have no effect on survival whereas p53 and HER2 are associated with poor survival. AR has promising potential as a target for therapeutic intervention in the management of MBC [7].

1.6. Clinical presentation

MBC can be unilateral, usually left sided (left to right ratio = 1.07:1) or bilateral. Most patients with MBC typically present with an abnormal breast mass or axillary lymphadenopathy. A painless breast lump is the most common complaint patients have at presentation (Figure 2). Occult male breast cancer is a very rare presentation where there is axillary lymphadenopathy in the absence of a detectible breast lump [15]. Unexplained increase in size of the male breast can be easily mistaken for gynecomastia. Oftentimes patients present late with locally advanced disease [44]. About 40% have stage III or stage IV disease at the time of diagnosis [15, 49]. Late presentation could be associated with stigma attached with cancer diagnosis and a lack of awareness about the potential occurrence BC among adult males. Less frequently occurring symptoms include nipple retraction, nipple discharge and skin ulceration. These are late symptoms indicative of advanced stage BC. About 75% of patients with a palpable breast mass have a hard and fixed nodule involving the subareolar complex. Due to the limited amount of breast tissue in males, involvement of the nipple occurs more easily and frequently than in females [50]. Figure 2 illustrates the percentage frequencies of the most common presenting symptoms of MBC. Very rarely, MBC presents with Paget's disease. A study reported that male patients with breast cancer tend to be older, present with advanced clinical stage, have high histological grade, mostly hormone receptor positive (80%) , HER2 negative as compared to female patients [48]. About 15% overexpress human epidermal growth factor receptor 2 (HER2) whereas 4% are triple negative (estrogen receptor, progesterone receptor, and HER2 negative)[51].

The distribution of primary sites of breast cancer in males and females is similar with most tumors localized to the upper-outer quadrant, 17% and 33% respectively. The least frequently involved site is the axillary tail (< 1%) followed by the lower-inner quadrant of the breast (Figure 3).

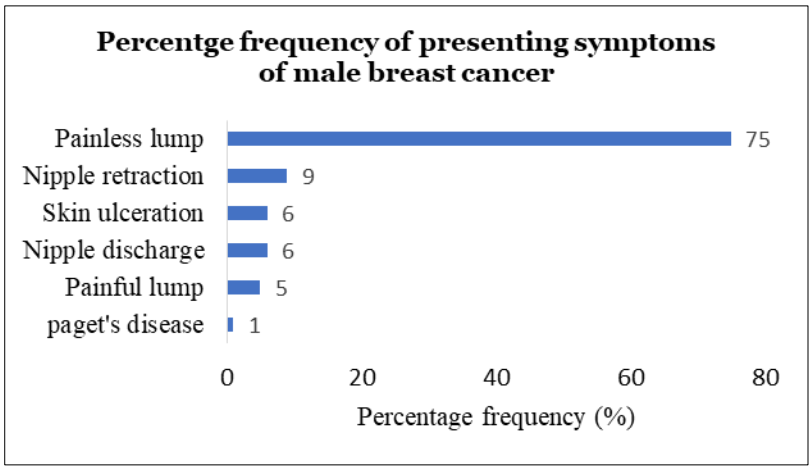

Figure 2 Percentage frequency of typical presenting symptoms of male breast cancer [52]

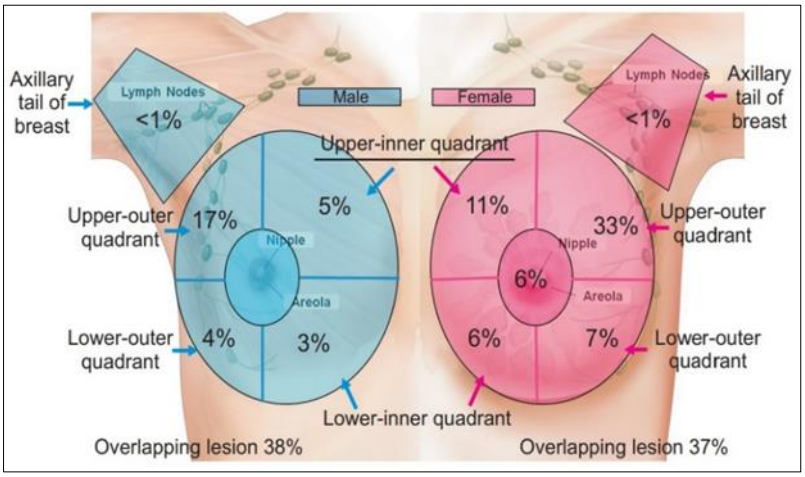

Figure 3 Comparison of distribution of primary sites of FBC and MBC [53]

1.7. Diagnostic workup

Breast ultrasound (USG) is usually complementary to a mammogram for the purpose of further evaluation of abnormal mammographic changes and for the evaluation of lymph nodes. USG is also employed in image guided biopsies of suspicious breast or axillary lesions. Compared to tomosynthesis, USG is affordable, readily available and carries no risk of diagnostic radiation exposure. A diagnostic mammogram (bilateral) has a higher predictive value in men than women basically due to limited male breast tissue. Breast mammography in males with BC is highly sensitive (92%), and specific (90%) with a high negative predictive value [54]. Microcalcifications are rarer in MBC than FBC. Annual screening mammograms are the backbone of post -treatment surveillance for the detection of locoregional disease recurrence. Computer tomography (CT) scans of the chest and/or abdomen are used as part of metastatic workup or for image guided biopsies of suspicious lesions. CT in planning position and virtual CT simulation are required for advanced forms of radiotherapy delivery such as 3-dimensional conformal radiotherapy (3DCRT) or intensity modulated radiotherapy (IMRT). Magnetic resonance imaging (MRI) is especially useful in the detection of mammographically occult breast lesions. It presents the advantage of higher soft tissue resolution compared with CT. It is also spares patients from exposure to diagnostic irradiation and can be done with contrast material that is not nephrotoxic. Bone scintigraphy is a nuclear medicine modality that is extremely useful for the detection of osteoblastic metastatic lesions. It is however not widely available and also not capable of detecting osteolytic lesions. Normal organs such as the bladder and kidneys typically show increased uptake of the radionuclide material (usually Technetium-99). Bone scans cannot distinguish between inflammatory conditions and tumor metastasis in bone tissue leading to a potentially high false positive rates among patients with inflammatory bone conditions. Positron emission tomography (PET) has a far greater ability to detect malignant breast tissue than either MRI or CT. This ability is dependent on the histology and size of the tumor. Even though high sensitivities of 68% and 92% have been reported for small (≤ 2cm) and large (> 2cm) tumors respectively, the accuracy for detection of premalignant (in situ carcinomas) can be as low as 2% [55]. There are

currently no image-based BC screening recommendations for asymptomatic men. The extremely low incidence of MBC among men makes screening of the population at risk ineffective and without significant benefit unlike screening for FBC. Genetic counseling and testing are recommended for high-risk populations such as patients with a positive family history of any of the cancers that are driven by BRCA mutations such as breast, ovarian, pancreatic or prostate cancer. All suspicious breast or axillary lesions must be biopsied to confirm histological diagnosis prior to commencement of any form of therapy for BC. Fine-needle aspiration is an effective way to biopsy BC tissue [56].

1.8. Differential diagnosis

The male breast just like that of females can also be the site of distant spread of other cancers especially in patients with disseminated carcinoma of the prostate gland receiving hormonal therapy [48]. Rarely, the male breast can be a site of distant metastatic spread for melanoma, non-small cell lung cancer, leukemia and lymphoma as well as renal adenocarcinoma [57].

1.9. Principles of management

In view of the rarity of MBC, there are not much data or randomized control trials specifically guiding its management. Current treatment recommendations are mostly based on studies conducted among female BC patients [58]. Thus, the principles of management of MBC are similar to FBC with only a few exceptions. The most effective therapy for MBC is surgery followed by radiation, chemotherapy and hormonal therapy [11]. A study involving 539 patients with stage IV MBC demonstrated that among ER positive cases, trimodality treatment with surgery, radiotherapy and systemic therapy conferred a significant survival benefit compared with surgery plus systemic therapy alone. Five-year overall survival rates with trimodality therapy and surgery plus systemic therapy were 40% and 27% respectively ($p < 0.002$) [59].

1.9.1. Surgery

The procedure of choice for T1 and T2 tumors is usually modified radical mastectomy with axillary dissection. Breast conservation surgery (BCS) is a feasible alternative in carefully selected patients and may offer good cosmesis and self-image with acceptable tumor control rates [60]. Patients with T3 or T4 tumors typically receive neoadjuvant chemotherapy prior to surgical resection. A SEER database analysis showed that out of 5,425 males treated between 1983 and 2009 for BC, 4,707 (87%) underwent mastectomy whereas 718 (13%) had lumpectomy, with a growing percentage of patients having lumpectomy in the latter years of the study. The 10-year breast cancer specific survival (BCSS) was 83% after lumpectomy and 77% following mastectomy [61]. In a stage – specific analysis of 4,276 patients diagnosed with MBC between 1973 and 2008 reported use of BCS in only 10% of cases but with similar cancer-specific survival in men treated with lumpectomy plus radiotherapy compared with mastectomy alone [62]. Mastectomies are often accompanied by axillary nodal clearance since up to a third of MBC cases present with stage III disease. For early-stage or lymph node negative MBC, the use of sentinel lymph node biopsy is increasingly popular and now recommended as standard therapy in these clinical settings. Locoregional failure following surgery is intricately linked with status of resection margins, number of positive lymph nodes and the size of the primary tumor.

1.9.2. Radiation therapy

Although indications for radiation therapy are the same in males and females with BC, some authors have reported underutilization of radiotherapy in MBC [63]. Analysis of 13,000 males from the National Cancer Database demonstrated that men were more likely to have total mastectomies but less likely to have radiotherapy [64]. Indications for adjuvant radiotherapy include T3 or T4 tumors, ≥ 4 positive lymph nodes and positive resection margins. High-risk features for local recurrence such as gross multifocality, high histological grade or peritumoral vascular involvement should be considered in the planning of radiation therapy. Irradiation involves tangential parallel opposing beams of high energy photons or electrons directed to encompass the chest wall to include the mastectomy scar, skin and pectoralis muscles. A typical conventional dose regimen of 50Gy in 25 fractions over 5 weeks is recommended [65]. However, hypo-fractionated regimen such as 40Gy in 15 fractions or 43.5 Gy in15 fractions have been offered with acceptable control rates as evidenced from the UK Start B trial and more recently by Wang and her colleagues from Beijing. These regimens are gradually becoming popular especially in the pandemic and post pandemic era [66].

1.9.3. Chemotherapy

Systemic therapy with chemotherapeutic agents remains a cardinal feature in the management of MBC. Chemotherapy can be used in both neoadjuvant or adjuvant settings with or without Her2 targeted therapy as recommended in guidelines for FBC. The efficacy of neoadjuvant chemotherapy in males versus females has been compared using data from the National Cancer Database (Leone et al). This study demonstrated that men receiving neoadjuvant chemo

achieved lower proportions of pathological complete response rates than women and had significantly worse overall survival. Neoadjuvant chemotherapy downstages the breast tumor and also offers prognostic information. Pathological complete response rates have now become an important prognostic tool and surrogate marker of OS.

1.9.4. Hormonal therapy

Principles of hormonal manipulation differs slightly among male and female BC patients. Per the American Society of Clinical Oncology (ASCO) guidelines Tamoxifen (TMX) is the recommended endocrine adjuvant therapy for hormone receptor positive patients. Based on the results of the ATLAS trial that highlighted the benefit of extended hormonal therapy, patients should have adjuvant TMX for at least 5 years with the possibility of extension to 10 years in carefully selected patients [67, 68]. For patients in whom tamoxifen is contraindicated, a Gonadotrophin releasing hormone (GnRH) analogue plus an AI is preferred.

In males, about 80% of circulating estrogen is derived from peripheral aromatization of testicular and adrenal androgens, while the remaining 20% is produced directly from the testes. Even though aromatase inhibitors (AIs) have been shown to cause significant reduction in estrogen levels in MBC patients, they are not able to completely inhibit the testicular production of estrogen. Therefore, there are often residual detectable levels of estrogen in males unlike postmenopausal females on AIs. Another postulated reason for the possible failure of AIs as monotherapy in MBC has been linked to the feedback loop hypothesis. Non-steroidal AIs such as letrozole and anastrozole have been found to cause an increase in FSH and LH levels which can lead to an increase in androgen production resulting in the increase in substrate for aromatization. Maura et al in the study of estrogen suppression in males while utilizing anastrozole noted a ~50% reduction in estradiol levels with attendant parallel increase in serum testosterone levels. The Suboptimal reduction in estradiol levels due to the above factors thereby restricts the use of AIs alone in the absence of castration. Consequently, in men, the use of single agent adjuvant treatment with aromatase inhibitor has been associated with inferior outcomes compared to tamoxifen alone. Among BC patients, TMX is associated with a similar 5-year OS of 89.2% and 85.1% (P = 0.972) in males and females respectively. However, the 5-year OS of patients on AI therapy was shown to be significantly greater in females than males (85.0% versus 73.3%; P = 0.028) [69, 70].

In HR+ advanced disease, systemic endocrine therapy still plays an important role. Available data supports the use of single agent Fulvestrant with similar efficacy as in FBC. Chemotherapy, HER-2 targeted therapy and PARP inhibitors are options for managing advanced BC in both males and females. In non-HR+ advanced male breast cancer, indications and recommendations regarding the use of chemotherapy, HER2 targeted therapy, immunotherapy and PARP inhibitors are similar to those for advanced FBC. Hormonal therapy is the main treatment for metastatic disease, but chemotherapy can also provide palliation [15]. Systemic endocrine therapy for the management of BC is not without adverse effects. Tamoxifen has a number of side effects including hot flushes, weight gain, decreased libido and malaise. Less common side effects include alteration of hepatic function, thromboembolic effects (lung embolism, strokes, etc), erectile dysfunction, rash and diarrhea. Aromatase inhibitors on the other hand are known for toxicities such as arthralgia, hot flushes, leg swellings and mood disturbances.

1.9.5. Targeted therapy

Targeted therapeutic options for the management of HER2-positive BC include monoclonal antibodies (Trastuzumab, Pertuzumab, Margetuximab), antibody-drug conjugates (Ado-trastuzumab emtansine (Kadcyla or TDM-1) and Fam-trastuzumab deruxtecan (Enhertu)) as well as kinase inhibitors (lapatinib, Neratinib, Tucatinib). The main adverse effects of these drugs are cardiotoxicity, severe diarrhea, hand-foot-syndrome, hepatotoxicity as well as pulmonary toxicity. Patients being managed with such agents should be monitored for the early detection and management of these side effects [65]. Targeted therapeutic options for the management of HR+ BC include CDK4/6 inhibitors (Abemaciclib (Verzenio), Palbociclib (Ibrance) and mTOR inhibitors (Everolimus (Afinitor). Pooled analyses of multiple clinical trials suggest that fulvestrant can be used in MBC with similar efficacy as in FBC with comparable toxicity profile [71]. PARP inhibitors Olaparib (Lynparza) and Talazoparib (Talzenna) are indicated for use in patients with BRCA mutations. These drugs work by blocking the PARP proteins leading to the death of cancer cells as a result of impaired DNA repair. There are reports of patients treated with PARP inhibitors developing hematological malignancies such as myelodysplastic syndrome or acute myeloid leukemia (AML). Antibody-drug conjugates (ADC) such as Sacituzumab govitecan (Trodelvy) can be used in the setting of TNBC. ADC is a monoclonal antibody joined to a chemotherapy drug and can be used as a single agent in the management of advanced TNBC, following the trial of ≥ 2 other chemotherapeutic regimens.

1.9.6. Prognosis

In comparison to FBC, MBC is associated with significantly worse overall prognosis primarily because of the advanced extent of disease at the time of diagnosis. However, there is no difference between the long- term survival of FBC and

MBC patients when compared age for age or stage for stage[72]. Independent prognostic factors include age at diagnosis, tumor size, tumor grade, hormone receptor status, distant metastatic site and the socioeconomic characteristics of patients. Late age at onset of disease, advanced tumor stage at diagnosis, high histological grade and positive hormone receptor status portend for poor prognosis [48] . MBC is associated with a higher mortality rate than FBC [12]. Seven-year overall survival rates of 77.9% compared to 89.8% have been reported among male and female breast cancer patients respectively. The 5-year overall survival rate of patients with male breast cancer is about 60%. Five and 10-year overall survival rates of 55% and 43.9% respectively have been reported in eastern Europe much lower than 71.4% and 70.3% respectively previously recorded in Germany [73]. The risk of developing secondary primary cancers is higher among MBC patients than women with BC [74-76]. The presence of BRCA2 mutations also portend for poorer prognosis: 5-year OS of 28% versus 71% in patients without BRCA2 mutation. Clinical stage of the disease at the time of diagnosis and lymphadenopathy are very important prognostic factors. Five year overall survival for stages I, II and III are estimated to be about 75-100%, 50-80% and 30-60% respectively [45]. Other studies have demonstrated AR and Forkhead box protein A1 (FOXA1) to be positively prognostic of disease-free survival (DFS). Age > 67 years at the time of diagnosis has been reported by some authors to be the strongest predictor of OS and DFS [7] . Although AR expression is associated with better outcome in MBC in terms of DFS, it has not been found to improve OS in multivariate analysis [77]. A Brazilian study involving 75 MBC patients that demonstrated distant metastasis at the time of diagnosis, older age ≥65 years, tumor stage ≥IIb and positive smoking status to be negative independent factors associated with an increased mortality risk [78]. Another study conducted in the USA among 2,475 men, aged >65 years identified tumor size & grade as well as involvement of lymph nodes and androgen receptor status as independent prognostic factors for MBC survival [79].

1.10. Follow-up

Males with unilateral BC have a relatively high risk of developing BC in the contralateral breast. Breast cancer recurrence, whether locoregional or distant, can occur even after 15 years of initial diagnosis of the primary tumor. This observation provides anecdotal evidence for the long term follow up of MBC patients who go into remission after primary treatment. Younger men < 50 years at the time of diagnosis have the highest risk of tumor recurrence. Screening for MBC is limited partly due to the absence of large international randomized trials demonstrating its usefulness in decreasing MBC related mortality [65].

2. Conclusion

The incidence rate of MBC is on the rise but still remains very rare among cancers affecting men. In spite of the fact that the most important risk factors are Klinefelter syndrome, BRCA 1 or 2 gene mutations and a positive family history for BC, most patients present with no clearly identifiable risk factor. Gynecomastia is the most common breast disorder among men and an important differential diagnosis for a painless breast swelling which is the commonest symptom of patients with MBC. Generally, there is delayed presentation and diagnosis of MBC which translates into poorer overall survival outcomes and increased levels of comorbidities due to the relatively older average age of patients at presentation. The most important prognostic indicators are stage at diagnosis and lymph node status. Adoption of effective screening strategies among high-risk populations is required to reverse the trend of late presentation with locally advanced or metastatic disease. AR is expressed in all molecular subtypes of BC and has the potential to become a critical target for therapy in both MBC and FBC.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest.

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