Male Breast Cancer

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ABSTRACT

Male breast cancer (MBC) is a rare disease, accounting for less than 1% of all breast cancer diagnoses worldwide. Although breast carcinomas share certain characteristics in both genders, there are notable differences. Most studies on men with breast cancer are very small. Thus, most data on male breast cancer are derived from studies on females. However, when a number of these small studies are grouped together, we can learn more from them. This review emphasizes the incidence, etiology, clinical features, diagnosis, treatment, pathology, survival, and prognostic factors related to MBC.

Keywords: Breast cancer, male gender, review

Introduction

Over the past two decades, major improvements have been achieved in the understanding of breast cancer, and cure can be offered if the disease is diagnosed at an early stage. However, the disease is more often diagnosed at more advanced stages (3 or 4) in men, in contrast to women. Its rarity among men as well as lack of awareness leads to its detection at later stages. Randomized studies cannot be carried on due to the low incidence of breast cancer in males, with only a few published prospective therapeutic studies in the literature. While the information on male breast cancer (MBC) was obtained from retrospective studies, the recommendations for treatment were derived from studies conducted on female breast cancer (1). This review presents the frequency, etiology, clinical-pathological characteristics and treatment approaches for the rare MBC.

Epidemiology-Etiology

Male breast cancer is rare and constitutes 0.5-1% of all patients with breast cancer. The reason of the low incidence rate in men is the relatively low amount of breast tissue along with the difference in their hormonal environment. Even though breast tissue is less in men as compared to women, the factors that influence malignant changes are similar. The Surveillance, Epidemiology and End Result (SEER) Program reported that the incidence of breast cancer was highest at ages 52-71 during 1973-2000, whereas the peak incidence in males was 71 years (2). In fact, some authors state that MBC imitate the behavioral pattern of post-menopausal female breast cancer. The incidence of breast cancer in males and females has increased in the past 25 years. International Association of Cancer Registries (IACR) emphasized this increase and stated that the incidence of female breast cancer increased by 20%, while breast cancer-related deaths increased by 14%. The SEER data also showed that the rate that was 1.1 for 100.000 men in the mid-1970s and raised to 1.44 for 100.000 men by 2010 (3). In USA, 2240 men were diagnosed with breast cancer within the year 2013. The lifetime rate of diagnosis with male breast cancer is 1 in 1000. According to the IACR Turkey data, 0.37% of all cancer types among males are breast cancer (4, 5). IACR has published its new cancer estimates for the year 2012. The most recent cancer estimates for 28 cancer types in 184 countries, which record cancer data, have been made available for users on the GLOBOCAN 2012 website (6).

The rate of presentation with advanced stage breast cancer has been decreasing in men. As a matter of fact, a study conducted in 1995 reported the rate of Stage 1-2 disease on diagnosis as 70%, whereas it was reported as 67% in 2010 and 82% in 2015 (7-9). MBC constitutes less than 1% of male cancers and it has a varying rate of incidence across different geographies and ethnic groups (10, 11). Its annual prevalence in Europe is 1 in 10.000 men and these cases constitute less than 1% of all patients with breast cancer (4). However, this rate is above 6% in Central African countries (12). This relatively higher rate is attributed to liver damage and to endemic

infectious diseases that lead to high levels of estrogen. In Japan, the annual MBC incidence is below five in a million (13). The only race where MBC incidence is above the average is the Jewish men and this characteristic is independent from living in the USA or Israel (14, 15). Based on our current knowledge, there is no convincing evidence that gynecomasty is associated with MBC; however, it is considered that it may be associated with shared hormonal risk factors (10). Breast cancer may be incidentally found in the specimens of cases operated on for gynecomasty, whereas gynecomasty may be found in the specimens of cases operated on for breast cancer (at a rate of 9% to 40%) (16, 17). It is reported that 6% to 38% of patients with breast cancer have clinical gynecomasty. These rates are not different from those of the normal population (18). A positive family history increases the relative risk 2.5 times, and 20% of men with breast cancer have a first degree relative with the same disease (4, 19). While the relative risk for a first second male breast cancers 30 times higher, this rate is only around 2-4 times for women. The risk for breast cancer on the contra lateral side is the highest for those at or below the age of 50, as in women (20, 21).

The known risk factors for male breast cancer are listed in Table 1. The incidence is directly proportional to age. While the age difference between men and women at the time of diagnosis is higher in the USA, this difference is not that high in the Middle East and Southern Asia (22, 23). The risk factor of genetic predisposition in men is similar to that of women. Klinefelter syndrome is the strongest risk factor for MBC and it is seen in approximately one out of every 1000 men (10, 24, 25). Family history of breast cancer brings about a 2.5 times relative risk for men. Nearly 20% of men with breast cancer have a positive family history. BRCA mutations increase the risk for male breast cancer (26). The best-known genetic linkage to MBC is the BRCA2 mutation (27). BRCA1 mutation, however, has a more limited role in MBC. The presence of BRCA2 mutation in sporadic MBC is rare. MBC in patients with the mutation tends to present at a younger age. Similarly, breast cancer in men with Klinefelter Syndrome is detected in the young ages (18). The other genetic factors include androgen receptor (AR) gene, CYp17, PTEN tumor suppressor gene and CHEK2 mutation (28). Nearly 3% to 7.5% of MBC cases have Klinefelter syndrome (28-30). In addition to BRCA1 and BRCA2, CHEK2 is a kinase effective in DNA repair. There is some evidence indicating that CHEK2 creates predisposition to male breast cancer (31).

Several risk factors such as early menarche, late menopause, age at first live birth are still valid for female breast cancer, and are not applicable to men. Several studies evaluating risk factors for male breast cancer have been conducted. The prospective National Institute of Health (NIH)-AARP Diet and Health Study ultimately identified 121 men who developed breast cancer (5). In this analysis, a negative correlation with physical activity was established and having history of a first-degree relative with male breast cancer (relative risk, RR, 1.92; 95%CI 1.24–3.91) and increased body mass index (>30 vs. <25; RR 1.79, 95%CI 1.10–2.91) were found to correlate with increased breast cancer. The factors that influence the ratio of estrogen to androgen, external administration of estrogen or testosterone (32), obesity (29, 33–35), orchitis/epididymitis (29), presence of a history of prostate cancer treated with estrogen (36) and Klinefelter Syndrome (25, 29) increase the risk of male breast cancer. Another study that analyzed the USA Veterans Affairs database detected 642 MBCs (29). The risk factors were found to be the presence of diabetes (RR 1.30, 95%CI 1.05–1.60), orchitis/epididymitis (RR 1.84, 95%CI 1.10–3.08),

Table 1. Risk factors for male breast cancer (3, 4, 9, 19, 24-29,32-35, 42-47)

- Age
- Genetic factors
  - o Proven
    - Family history
    - BRCA2>BRCA1
  - o Potential
    - PALB2
    - Androgen receptor
    - CYP17
    - CHEK2
    - Conditions related to abnormal estrogen-androgen ratio
  - o External use of estrogen and testosterone
  - o Obesity
  - o Orchitis, epididymitis
  - o Finasteride
    - Lifestyle
  - o Inadequate exercise
    - Exposure
  - o Proven
    - Radiation
  - o Potential
    - Electromagnetic field
    - Heat
    - Volatile organic compounds (such as tetrachloroethylene, p-chloro-ethylene, trichloroethylene, dichloroethylene, etc.), chemicals
- Other potential risk factors
  - o At birth (Potentially a higher risk in first deliveries)
  - o Bone fractures after the age of 45

Klinefelter syndrome (RR 29.64, 95%CI 12.26–71.68) and gynecomasty (RR 5.86, 95%CI 3.74–9.17). Interestingly, gallbladder stone was also detected as an important risk factor for Afro-American MBC cases (RR 3.45, 95%CI 1.59–7.47). A very strong association between MBC and Klinefelter was observed in the Veteran study and in several other similar studies. For example, the Swedish Registry study reported a 50-times higher rate of breast cancer in those with Klinefelter Syndrome (25). History of liver disease, past breast and testicular pathologies are other risk factors that have been described (4).

More interestingly, the male breast cancer is stated to be a preliminary finding for other malignant processes. A review focusing on 69 male breast cancer cases identified simultaneous prostate cancer in 12 patients (17% of the cases examined) (37). Actually, there is a theoretical association; the aromatase inhibitor used in MBC treatment increases

serum testosterone levels and enables the growth and proliferation of prostate cancer clones (38). Apart from prostate cancer, there are studies that support the association of MBC with leukemia, pancreas, small intestine and rectum malignancies (39-41). Various epidemiologic studies have been performed (42), professional exposure to certain chemicals such as polycyclic aromatic hydrocarbons (43-45) and electromagnetic field (46, 47) were detected as potential factors in the development of male breast cancer (4, 48, 49).

Symptoms, Clinical Signs and Manifestations
The most common presentations are painless palpable mass, skin ulceration, and nipple retraction or discharge in approximately 75% of the cases, similar to women (7, 50-53). Since the breast tissue in men is undersized, the nipple is mostly involved at early stages. The incidence of retraction is 9%, discharge 6% and ulceration is 6% (10). The mass is frequently localized to the subareolar region. It is seen less frequently in the upper outer quadrant (54, 55). The left breast is involved more frequently than the right; 1% of the cases are bilateral.

Male patients are frequently at a higher age than female breast cancer (FBC) at diagnosis (5-10 years older) and at a higher stage (27, 56-59).

The staging of the disease during presentation is as follows on the basis of the Tumor-Node-Metastasis (TNM) system presented by the largest case series in the literature: Stage 1: 37%, stage II: 21%, stage III: 33%, stage IV: 9% (51, 52, 60, 61). While the period between disease onset and diagnosis was 29 months in the past (62), this period has been reduced to 6 months in the newer series (63). It is evident that the disease is diagnosed at more advanced stages in men as compared to women. In fact, more than 40% of the patients are already at stage 3 or 4 when they present to the clinic. The lesser amount of breast tissue in men also results in the involvement of chest wall at an early stage. For that reason, it has also been stated that the TNM may not be appropriate for men (64).

Diagnostic Imaging Methods and Differential Diagnosis
The majority of lesions in the male breast are benign and gynecomasty constitutes most of these lesions. Within these, less than 1% is primary breast cancer. Even though male breast is relatively small, mammography (MG) is technically feasible and adds useful information to clinical examination (65). In the presence of a clinically suspicious lesion, MG should be preferred over ultrasonography (USG). Sensitivity and specificity of mammography are reported as 92% and 90%, respectively (66). A normal male breast is essentially composed of fat tissue and contains only a few secretory canals. It does not have Cooper ligaments, and has none or very little ductal and interlobular connective tissue. For that reason, it has a radiolucent appearance on mammography (67). The tumor is visualized on MG as a hyperdense, well defined, lobulated mass with spiculated margins or as a structural distortion. Microcalcification is observed less as compared to FBC; its tendency of clustering is low, and generally appears as wide, round and dispersed calcifications.

Doyle et al. (68) emphasized the radiologic and pathologic differences between male and female breast cancer in their review:

1) The incidence of invasive lobular cancer and in-situ disease are lower in men as compared to women.
2) Male breast cancer more frequently manifests itself as a locally advanced disease (skin and/or nipple involvement).
3) MBCs are more often localized in the subareolar area, whereas FBCs are localized in the upper outer quadrant.

4) Malignant calcifications in MBC are less frequent as compared to women.
5) Since neoplastic papillary lesions appear as complex cystic lesions and simple cysts are rare in men, cystic lesions should be evaluated in detail.

Invasive cancers typically appear as solid lesions on USG. When suspicious changes are found in USG or MG, further evaluation is required for definitive diagnosis (69, 70). In patients with nipple discharge, an examination with smear may be needed. The extent of the disease should be evaluated via laboratory examination, pulmonary X-ray, bone scintigraphy and dominal computed tomography (CT) (71). Positron emission tomography - computed tomography (PET-CT) is better than PET or computed tomography (CT) alone for assessing the extent of the disease, and especially for accurately identifying small metastases and lymph node metastases as well as the response to chemotherapy (72).

A differential diagnosis should be made between gynecomasty and cancer in masses of the male breast. The most frequent benign mass of the breast, which may be unilateral or bilateral, is gynecomasty (73). It may be generally recognized through physical examination. Gynecomasty is characteristically symmetrical, bilateral and has a discoid shape under the nipple and areola. As for carcinoma, it develops a painless hard mass at an eccentric location. Besides breast cancer, the reasons that cause a mass in the male breast include gynecomasty, abscess, hematoma, lipoma, fat necrosis, ductal ectasia, intraductal papilloma, cyst, and metastatic tumors (74). Metastasis to the breast is generally 5-6 times more often in women as compared to men (approximately 0.5% to 6.6% of breast malignancies), which is accounted for by differences in hormonal and endothelial cell adhesion molecules, as well as in breast size and vascularity (75). The most frequent primary tumors in men, which metastasize to the breast include melanoma, lymphoma, prostate, lung and colon tumors (76).

Treatment

Treatment of early-stage disease
The standard treatment for early stage male breast cancer is surgery followed by adjuvant endocrine treatment, chemotherapy (CT) or radiotherapy (RT) depending on prognostic factors, which is the same as in women.

Surgical treatment approach and axillary lymph node dissection
Up until the 1970s, the main surgical method was radical mastectomy as in women. Considering the lesion size, this approach was replaced by less invasive procedures such as modified radical mastectomy over time (77-79). Currently, modified radical mastectomy and axillary lymph dissection or sentinel lymph node biopsy (SLNB) is recommended if the tumor is not fixed to the pectoral muscle (80). Actually, American Society of Clinical Oncology guidelines state that SLNB is appropriate for men (7). Radical mastectomy is performed if there is extensive involvement of the chest wall and Rotter ganglions (78). Breast-conserving surgery (lumpectomy) may be performed in elderly patients, with a serious concomitant disease, who has gynecomasty along with a small tumor since the male breast is small and most tumors have a subareolar location, but this procedure is rarely preferred (81). Adjuvant RT is also added to the treatment of such patients. Surgeries that are more radical do not contribute to survival. In cases with high tumor burden, preoperative CT may be useful. Patients with a metastatic disease or a poor overall condition may receive a combined treatment with simple mastectomy or local tumor excision with postoperative RT (82).

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Radiotherapy (RT)

Radiotherapy is mandatory if breast-conserving surgery is performed (83). However, the data about RT indications following mastectomy are limited. RT is generally applied in case of involvement of the nipple and skin (84). Adjuvant loco-regional RT is performed more often in MBC than in women because of the more advanced stages and the more aggressive progress in males. Post-mastectomy RT decreases local recurrence by 2/3 in women and has a positive effect on long-term survival (85). On the other hand, it is suggested that post-mastectomy RT does not improve local recurrence and survival rates in MBC and that it enables local tumor control but does not influence overall survival (86, 87). However, there is no evidence showing that RT indications need to be different for men than those for women. In summary, RT is recommended in the presence of a positive lymph node, a tumor larger than 5 cm and margin positivity in MBC (71).

Chemotherapy (CT)

Excluding non-neoplastic reasons, primary and adjuvant chemotherapies have significantly increased the survival rates for 5-10 years (7-9). A limited number of prospective, randomized clinical studies exist, which indicate the benefit of adjuvant systemic therapy for MBC (88). On the other hand, decreased recurrence and mortality rates have been reported with adjuvant CT in retrospective studies (53, 89). Furthermore, the prognosis and response rates to therapy in with metastatic MBC are similar to those of women. For that reason, it is considered that early stage MBC patients would benefit from adjuvant therapy (77). There is not enough information about the poor prognostic factors according to which a decision for adjuvant CT could be taken. Usually, the prognostic factors that are used in women are applied to men. There is an indication for CT in those with positive lymph nodes, in tumors larger than 1 cm, and negative for hormone receptors (90, 55). Triple negativity (hormone receptors and HER2/neu negativity) is a sign of aggressiveness, this suggests a high-risk patient and is accepted as an indication for CT. HER2/neu and p53 expression are indicators for poor prognosis, and these patients may require a more aggressive systemic treatment. For node negative patients, anthracycline-based CT is preferred whereas anthracycline and taxane are used for those with positive lymph nodes. Based on the data from treatments in women, trastuzumab must be administered in case of HER2/neu positivity, in node-positive or high-risk node negative disease (10).

Adjuvant Endocrine Therapy

Adjuvant endocrine therapy alone or in combination with CT is recommended for MBC patients, based on the positive results in clinical studies on early-stage FBC patients. However, there are only a few retrospective studies on this issue with no randomized clinical trials. These studies also demonstrated decreased recurrence and mortality rates (77, 91). Most male patients are hormone-receptor (HR) positive, and either tamoxifen or another hormone therapy for 5 years is recommended to those with positive estrogen receptor according to their prognostic factors, similar to women (90). There are also studies defending that hormonal therapy should be the primary treatment method since MBC is rich in hormone receptors and is a cancer that is more sensitive to hormones, while other adjuvant therapies need to be administered in large tumors and positive axillary lymph nodes (92). Tamoxifen is the generally accepted medication for hormonal therapy. The role of aromatase inhibitors in adjuvant therapy is limited.

Treatment of locally advanced disease

The treatment of male patients with T3/T4 or inflammatory breast cancer is initiated with neo-adjuvant CT and surgery is performed on those whose tumor becomes amenable to operation. Subsequently, adjuvant tamoxifen is recommended for HR positive cases. It should also be kept in mind that adjuvant hormonal therapy may be an alternative to CT in most cases (93).

Treatment for advanced disease

Approach to metastatic breast cancer is based on the same principles in both men and women. Metastasis is identified at diagnosis in approximately 5-15% of MBC cases. Di Lauro et al. (94) reported that the most frequent location for metastasis visceral in 76% (lung, liver), bones in 20% and soft tissue (skin) in 4% of the cases in their series of 50 male breast cancer cases. For treating metastatic diseases orchiectomy, adrenalectomy and hypophysectomy have been performed in the past. Since the response rate of the more frequent HR-positive tumors to hormone therapy is 25% to 58%, tamoxifen is currently used as first-choice therapy in such tumors. CT is recommended if the tumor is unresponsive to hormonal therapy (95). Progestins, androgens and luteinizing hormone-releasing hormone agonists may be used in hormone therapy, albeit at a lower rate (55). The value of aromatase inhibitors such as anastrozole and letrozole in metastatic breast cancers has not been fully established. Systemic CT is used in male HR-negative patients with a rapidly progressing and life-threatening visceral disease. Although it is thought that trastuzumab may be useful in HER-2/neu positive disease, the data available on this issue is insufficient.
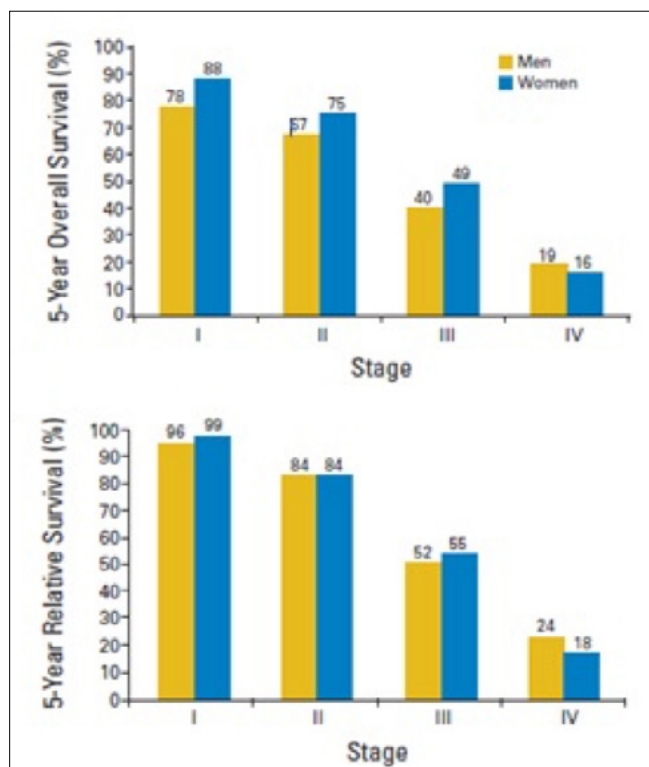
Pathology

Male breast cancer is different from female breast cancers with respect to clinical-pathologic characteristics. Despite that, the diagnosis and treatment approaches are based on the results obtained in female breast cancers, since the data regarding MBC are mainly composed of retrospective, single-center case series rather than randomized clinical trials (56, 96, 97). Previous studies have demonstrated that the rate of HR positivity in MBC is higher and most patients are more sensitive to anti-hormonal treatment (27). Almost all histologic types pertaining to FBC have also been reported for MBC, with varying rates. According to the SEER data, 93.7% of MBC is ductal or unclassified, and only 1.5% is of the lobular sub-type (96). This rate is in contrast with those in women (12-15%) (54). This is due to the fact that the male breast tissue remains rudimentary. It is generally exposed to increased estrogen concentrations, is not differentiated and does not result in lobular formation. The tumor grade was detected as 12–20% Grade I, 54–58% Grade II and 17-33% Grade III tumors (43). The other histological types are papillary (2.6%) and mucinous (1.8%) tumors (54). MBC shows a higher estrogen and progesterone receptor expression as compared to women (90% ER, 81% PR in males vs. 60-70% ER or PR in females) (96). As for HER-2/neu expression, it is lower in men in comparison to women (55). The molecular subtypes of breast cancer in women have been widely studied in terms of immunohistochemistry and its importance has been proven (98-100). Accordingly, normal breast-like, basal-like, luminal A, luminal B, and HER2-enriched subtypes have been identified. There is no consensus on molecular subtyping of male breast cancer, and the few studies with small group of patients yielded inconsistent results. In a study of 134 cases from multiple centers, Kornegoor et al. observed luminal type A as being the most frequent type with a rate of 75% (101). While luminal type B was the second most frequent type with 21%, the incidence rate of other types was only 4%. Tumors in luminal B subtype tend to have a higher nuclear degree (93). In another study conducted on 960 patients, the patient distribution was as follows: 84.9% HR-positive/HER2-negative, 11.5% HR- negative/HER2-positive, 0.6% HR-positive/HER2-positive and 2.9% Triple negative (102).

Prognosis, Survival and Prognostic Factors

Despite the decrease in mortality rate in female breast cancers, the mortality rate in MBC remained unchanged since 1975 (103). The most important prognostic indicator is the stage at diagnosis and lymph node involvement (Figure 1). The overall 5-year survival rate is around 40-65% (7, 52, 77, 104). However, when evaluated according to stage at diagnosis; the 5-year survival rate is 75-100% for stage 1, 50-80% for stage 2, and is decreased to 30-60% for stage 3 (52). Although several studies have stated that the prognosis was worse in MBC than in females, it was determined that there were no differences in the prognosis of the two genders when paired according to age and stage (105). A large study with more than 335 male patients found that if nodal status is used to compare MBC and FBC, then the prognosis was similar (106). The less favorable results in male patients are due to the more advanced stage at presentation as well as a higher mean age at presentation leading to more co-morbidity (52, 107). While estrogen-receptor (ER) positive tumors have a better prognosis, no such association has been shown for progesterone (68). HER2 positivity is a poor prognostic characteristic (108). It is reported that survival is shorter and prognosis is poor in basal-like and HER2+/ER- subtypes in comparison to other groups (109). A secondary cancer may develop in 9-12% of MBC cases during follow-up (74, 110). The incidence rate of bilateral breast cancer in men is low (111). In the presence of metastatic disease (bone, lung, liver, brain, etc.), the median survival is reported as 26.5 months (88).

Conclusion

Breast cancer is a rare disease among men and the number of cases included in studies is small. It may be confounded with benign diseases, and both patients and physicians may underestimate its signs. Since its detection is delayed, the disease is usually at advanced stages at the time of diagnosis. Breast cancer behaves differently in males. There is a need for multi-center studies with more patients that focus on the treatment, prognosis, tumor biology and parameters influencing survival.

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Figure 1. (A) Overall (B) Relative survival in male and female breast cancer: Surveillance, Epidemiology- and End Results registry, 1973 to 1998 (n=2.537)

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