

Review Article

Male Breast Cancer: Current Essentials & Review

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Background: Breast cancer in male is a very rare condition but some of the reported case series had shown that its incidence is increasing over the last 25 years. The etiology of breast cancer in males differs from that of females in many ways. The literature lacks the prospective randomized evidences supporting the treatment of male breast cancer. Only retrospective evidences are available and all guidelines are extrapolated from the best available data of treatment of female breast cancer. Therefore, we have reviewed, compiled and tried to present the best available literature which highlights the treatment of male breast cancer. The reported incidence of breast cancer in men is around 1.2%-2% of all cancers in males and less than 1% of all breast cancers in both sexes. If it involves both breasts then it becomes an extremely uncommon condition which accounts for only 1% of all male breast cancer. Elderly males are most commonly diagnosed with breast cancer and they are approximately 5 to 10 years older than the women. The most common reason of breast cancer in males is excess of estrogen in the body and all conditions which leads to hyperestrogenism are responsible for increasing the risk of cancer.

Keywords: Male breast cancer; Hyperestrogenism; Radiation therapy; Chemotherapy; Mastectomy

Background

Breast cancer in male is a very rare condition [1,2]. Its incidence is also very rare. The reported incidence is around 1.2%-2% of all cancers in males and less than 1% of all breast cancers in both sexes [3]. Bilateral breast cancer in males is an extremely uncommon condition with accountability of only 1% of all male breast cancer [4]. Elderly males are more commonly diagnosed with breast cancer and the age difference is approximately 5-10 years older in comparison to women with breast cancer [5]. One report had suggested that the incidence of male breast cancer is rising and it has increased to 26% over the last 25 years [6]. The clinical course and presentation of male breast cancer is similar as with female breast cancer however there are some important differences [7,8]. As compared with female breast cancer, male breast cancer does not have supporting literature of prospective randomized trials. There is a limited literature regarding treatment of male breast cancer and only retrospective evidences are available [9]. Therefore, we have reviewed, compiled and tried to present the best available literature which highlights the treatment of male breast cancer.

Geographical Distribution

The incidence of male breast cancer differs worldwide however at most of the places it is less than 1%. In United states (US) and United Kingdom (UK), yearly about 0.5 to 1% of cases of male breast cancer are diagnosed. In US it accounts for less than 0.5% of all cancer diagnoses in men [10]. In Tanzania and some of the areas of central Africa, it accounts for up to 6 % of all breast cancers [11]. The probable reason behind this may be due to hyperestrogenism resulting from hepatic infectious diseases [12].

Common Etiology

The most common reason of breast cancer in males is excess of

estrogen in the body. All conditions which lead to hyperestrogenism are responsible for increasing the risk of cancer. The syndromic association of this cancer has been found with an inherited Klinefelter syndrome which results from inheritance of an additional X chromosome [13]. There are some primary testicular conditions which has shown an increased risk of this cancer in males which includes undescended testes (cryptorchidism), testicular injury and orchitis [14]. These conditions may be associated with lower androgen production, resulting in a higher than normal estrogen to androgen ratio. Other conditions associated with excessive estrogen production are few hormonal therapies which may contain estrogen or testosterone, hepatic dysfunction, obesity, marijuana use and thyroid disease.

Genetic Factors

The risk for male breast cancer increases with inherited BRCA 2 rather than BRCA 1 mutations [15]. Men who inherit germline BRCA 2 mutations have an estimated 6% lifetime absolute risk of breast cancer and this accounts a 100-fold higher risk than in the general male population [16]. A BRCA 1 mutation occurs very rarely, except in individuals of Ashkenazi Jewish ethnicity. One study found that 4.5% of Ashkenazi Jewish men presenting with breast cancer have a BRCA 1 mutation [17]. It indicates that there is a need for genetic counseling and testing of BRCA mutations. The other genes with mutations which appears to increase the risk of breast cancer in males are mutations in the Phosphatase and Tensin Homolog (PTEN), tumor suppressor gene (Cowden syndrome), tumor protein p53 (TP53; Li-Fraumeni syndrome), partner and localizer of BRCA 2 (PALB2) and mismatch repair genes (Lynch syndrome) [18-20]. However the absolute risk of male breast cancer is very low as compared with female breast cancer with these genetic alterations.

Clinico-Pathological Presentation

There is absence of routine screening examination procedures

and awareness about this cancer due to its rare presentation. This may be the reason that this cancer is diagnosed at a more advanced stage as compared to female breast cancer [21]. In about 40-50 % of cases, the clinical presentation of this cancer is with presence of lump which may be painless, firm, usually located at sub areolar region with involvement of nipple areola complex [22].

The most common histological subtype in male breast cancer is invasive ductal carcinoma as same in female breast cancer and it accounts approximately 85 to 90 percent of breast cancers in men [23]. Acini and lobules are absent in male breast hence lobular histological subtype is rarely found in male breast with its accountability around 0.5-1.5% [24]. The other subtypes like Paget disease and inflammatory breast cancer have rarely been described in men [25,26]. The presentation of Ductal Carcinoma *In Situ* (DCIS) in males differs from females. It tends to present more commonly with low grade variety, at a later age with intraductal papillary form [27]. Immunohistochemical evaluation shows that most of the male breast cancers are hormone receptor positive with detection of equal percentage of luminal -A, luminal -B with lower percentage of Human Epidermal Growth Factor Receptor 2 (HER2) Positivity and very rarely with triple negative presentation [28].

Diagnostic Modalities

Mammography

The common differential diagnosis of male breast cancer is gynecomastia and mammogram clearly differentiates cancer from benign conditions. The reported sensitivity and specificity rates of mammography are 92 and 90%, respectively [29]. Mammographic features suggestive of malignancy include eccentricity to the nipple, speculated margins and micro calcifications. By contrast, gynecomastia typically appears as a round or triangular area of increased density positioned symmetrically in the retroareolar region.

Tissue diagnosis

Any suspicious breast lesion requires tissue diagnosis to confirm the disease. The available options are Fine Needle Aspiration Cytology (FNAC) and core needle biopsy. Compared with FNAC, core needle biopsy offers a more definitive histologic diagnosis, avoids inadequate samples, and usually distinguishes between invasive versus *in situ* cancer [30]. If inadequate tissue is obtained with core biopsy, an open biopsy should be performed.

Differential Diagnosis

Male breast lesion should be differentiated from the following conditions [31].

Gynecomastia

It typically presents as bilateral, symmetric breast enlargement with poorly defined borders. There will be absence of axillary lymphadenopathy or skin changes or fixity to underlying chest wall muscles.

Pseudogynecomastia

It represents an increase in breast fat rather than glandular tissue. Clinical examination differentiates it from cancer.

Fibromatosis

Fibromatoses (or desmoid tumors) are locally aggressive tumors.

The diagnosis requires histologic examination.

Infections

It may be associated with systemic presentation with fever and malaise. Clinically it presents as breast abscess or skin infections which are commonly manifests as painful inflammation.

Pseudoangiomatous stromal hyperplasia

It is characterized as a benign, stromal proliferation. On imaging it presents as a solid, well-defined, noncalcified mass.

Lipoma

These are asymptomatic breast masses comprised of fat.

Other rare tumors that occur in men includes schwannoma, myofibroblastoma, and hemangiomas.

Staging Evaluation

The male breast cancer should be evaluated as similar with female breast cancer as per the available guidelines. It is classified as similar to female breast cancer as per Tumor, Node, Metastasis (TNM) staging system developed by the American Joint Committee on Cancer (AJCC) and endorsed by the Union for International Cancer Control (UICC) [32].

Surgical Management

Early stage disease

Men with T 1 to T2, N0 to N1 early stage breast cancer should undergo simple mastectomy rather than a mastectomy with pectoral muscle removal. Some of the retrospective data had shown that mastectomy with pectoral muscle removal does not add any benefit and there is equivalent local recurrence and survival for the both procedures [33]. There is lack of literature over breast conserving surgery in male breast as there is a small volume of breast tissue. Most common location of this cancer in males is sub areolar with nipple involvement. Hence, other surgeries like Nipple- and skin-sparing mastectomy have not been explored in male breast cancer which is cornerstones of female breast cancer.

Management of regional lymph nodes

It is a crucial part of a breast cancer in both male and female. The management is similar in males as in females except clinically node negative male breast cancer as there is lack of literature support. The role of Sentinel Lymph Node Biopsy (SLNB) in female breast cancer is accepted and established procedure but in male breast cancer still there is lacunae in the randomized trials due to rarity of this tumor. American Society of Clinical Oncology (ASCO) guidelines recommends sentinel lymph node biopsy in early-stage breast cancer [34]. But its role is unproven in male breast cancer. Some of the small reports had suggested that it is feasible and accurate in male breast [35]. The next question which is still unanswered is if SLNB comes positive, should we go for Radiation Therapy to axilla or completion axillary dissection. In near future, we may be able to find the answer.

Locally advanced disease

Locally advanced male breast cancer (T3N0 or stage III disease) or inflammatory breast cancer are treated in a similar manner as locally advanced female breast cancer. The standard approach is neo adjuvant chemotherapy followed by surgery which is accepted and

proven fact in female breast cancer.

Adjuvant Treatment

Radiation Therapy (RT)

Indications for RT in male breast cancer are extrapolated from the available data of female breast cancer. Only retrospective case studies are available favouring adjuvant RT in male breast cancer.

Indications for RT in male breast cancer are:

- Patients who underwent breast-conserving surgery are treated with whole-breast radiation and may also receive a boost to the tumor bed and, if axillary nodes are involved, axillary radiation.
- Patients who underwent a mastectomy for T4 or T3 disease. There is limited literature supporting post mastectomy RT and the available evidence is retrospective which had shown that post mastectomy RT appears to reduce locoregional recurrence but the influence on survival is not clear [36].

Systemic chemotherapy

Prospective trials evaluating the benefits of adjuvant chemotherapy in male breast cancer have not been performed. Therefore, the same guidelines for adjuvant systemic therapy in women are generally followed for men with breast cancer [37].

Endocrine therapy

It is recommended in men with hormone receptor-positive breast cancer following surgery rather than observation. Available evidences are retrospective and rest is extrapolated from the trials enrolling women with hormone receptor-positive breast cancer. Though an Aromatase Inhibitor (AI) with Gonadotropin-Releasing Hormone Agonists (GnRHa) is an acceptable alternative, tamoxifen is the preferred agent recommended by the guidelines from ASCO [38]. Patients with contraindication to tamoxifen should be offered with AI + GnRHa. Retrospective studies suggest that there is an improvement in overall survival for men with hormone receptor-positive breast cancer treated with adjuvant tamoxifen [39]. The reason behind use of AI is that testicular production of estrogen is not inhibited by an AI. Use of GnRHa may suppress this production and improve outcomes when used with AIs in men. The Male-GBG54 trial [40] is a 50-patient prospective randomized phase II study evaluating tamoxifen with or without GnRHa versus an AI with GnRHa in male breast cancer patients. Their preliminary results are out and suggest that AI plus GnRHa therapy was associated with a 64 percent suppression in estradiol levels. Although there was no AI-alone arm in this study, it does provide some support for the use of GnRHa, if AI is going to be used in this setting.

Bisphosphonates

Men with early-stage disease should not be treated with bone-modifying agents to prevent recurrence, but could still receive these agents to prevent or treat osteoporosis, according to ASCO guidelines [38].

Prognosis

Surveillance, Epidemiology, and End Results Program (SEER) has analyzed database of male breast cancer patients which were diagnosed between 2005 and 2009. They found that patients had

experienced a worse prognosis compared with women, with a risk of death 41% higher than females. The 5- and 10-year survival rates of male patients were 85 and 73%, respectively and which was lower than female patients, 90 and 85%, respectively [41].

Surveillance

There is very limited data suggesting the increased risk of contralateral breast cancer but the absolute risk appears to be low [42]. ASCO screening guidelines are as follows:

- Ipsilateral annual mammogram should be offered to men with a history of breast cancer treated with lumpectomy, regardless of genetic predisposition.
- Contralateral annual mammogram to men with a history of breast cancer and a genetic predisposing mutation.
- Breast magnetic resonance imaging is not recommended routinely.

Metastatic Disease

Men with metastatic or advanced breast cancer are approached similarly as that of female breast cancer. The various endocrine modalities available are AIs with GnRHa, CDK 4/6 inhibitors (palbociclib), PI3K inhibitor (alpelisib), mTOR inhibitors (everolimus), second line agents (aminoglutethimide, megestrol acetate, antiandrogens, corticosteroids, cyproterone acetate).

Conclusion

Breast cancer in males is a very rare entity and uncommonly diagnosed cancer. It is diagnosed most frequently in advanced stage and advanced age. Early detection is the only way to plan for curative intent. There is a need of prospective randomised trials to define the guidelines for its management, till that time multidisciplinary team approach is the only cornerstone for its treatment.

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