Male Breast Cancer

Edward Yu, MD PhD, FRCPC.
Department of Oncology, Western University, London, Ontario, Canada

Epidemiology

Male breast cancer (MBC) is a rare disease worldwide. MBC accounts for approximately 1% of all breast cancer and less than 0.5% of all male cancer deaths in the United States.(1).

Incidence:

The best estimate of incidence rate for MBC in all population where data are available is one per 100,000. , but seems to be increasing (2).
Worldwide, the highest incident of MBC reported was 3.4 cases per 100,000 in Recife ,Brazil,the lowest incidence rates of 0.1 cases per 100,000have been reported in parts of Columbia, Singapore, Hungary, and Japan.

Risk Factors:

The risk of developing MBC was positively associated with the following charactistics: never married, Jewish Decent, previous benign breast disease, gynecomastia, history of testicular pathology, prior live disease, and first – degree relative with breast cancer. Prior exposure to radiation may also increase the risk of MBC.

Clinical Features

Most breast tissue in male is located in the subareolar area. Therefore , MBC typically presents as a painless, firm subareolar mass and the nipple areola soon becomes retracted. Because of the scantiness of breast tissue in men, lesions are close to the skin, tumor fixation to the pectoralis major and skin are often observed.

Diagnosis

In patients aged over 50 years, breast cancer must be differentiated from various forms of senile breast hypertrophy that may be associated with concomitant conditions or, more often, pharmacological treatments that interfere with hormonal metabolism. As in women, careful physical examination of the breast and the regional (axillary and supraclavicular) lymph nodes is essential in men presenting with breast enlargement or a node. Because of late diagnosis, even small male breast cancers have a marked tendency to spread to the axillary lymph nodes.

In addition to mammography, with either core needle biopsy or fine-needle aspiration (FNA) for pathologic confirmation should be confirmed to obtain the

diagnosis. .Although the efficacy of FNA in diagnosis of MBC is difficult to establish due to limited case series reported in the literature, adequate tissue sampling is critical for establishing the diagnosis and performing estrogen receptor (ER), progesterone receptor (PR), and HER2 receptor analysis.

Pathology

Invasive ductal carcinoma is the most common histopathologic subtype of MBC, accounting for 85% of all cases. The remaining 15% of the cases are ductal carcinoma in situ (DCIS) and papillary carcinoma. Lobular carcinoma and lobular carcinoma in situ (LCIS) can occur as isolated example and case reports, the rarity of lobular carcinoma and LCIS in males is thought to be owing to the lack of acini and lobules in normal male breast tissue.

Staging and Prognostic Factors

Staging of male breast cancer:
Male and female breast cancers are staged according to the American Joint Committee on Cancer (AJCC) Staging system

Breast cancer staging.

Primary tumor (T)
T0 no evidence of primary tumor.
Tcis carcinoma in situ.
T1 tumor 2 cm or less.
T2 tumor more than 2cm but not more than 5 cm.
T3 tumor more than 5 cm.
T4 tumor with direct extension to chest wall or skin.

Pathologic regional lymph node(pN).
pN0 no regional lymph node mets; i- neg IHC.

pN1 i+ pos IHC cluster less than 0.2mm; mi micromets greater than 0.2mm but less than 2mm; mets in 1-3 lymph nodes.

pN2 mets in 4-9 lymph nodes.

pN3 mets in 10 or more lymph nodes.

Distant metastasis (M)
M1 distant metastasis.

Stage grouping

Stage 0	Tcis
Stage I	T1N0M0
StageIIA	T0-2N0-1M0
StageIIB	T2-3N0-1M0
StageIIIA	T0-3N1-2M0
StageIIIB	T4NN0-2M0
StageIIIC	anyTN3M0
StageIV	anyT, anyN M1

Prognostic Factors
MBC, similar to female, stage, tumor size, and axillary lymph node status appear to be the most important factors influencing outcome.

The prognosis in men is the same as in stage- matched female patients. Men tend to fare less well overall because of late presentation and more advanced disease.

Treatment:

Surgical Management
For localized breast in men the current operative procedure of choice is total mastectomy with sentinel node (SLN) biopsy. Although breast conservation therapy with lumpectomy followed by breast irradiation has been shown to have equivalent outcomes as mastectomy in women with early stage breast cancer, breast conservation therapy is generally not considered as an option for men because the tumor is almost always in the central quadrant, for oncological reasons necessitates removal of the nipple areola, and the lack of adequate surrounding breast tissue in men.

Adjuvant Systemic Therapy
Because of the low incidence of MBC, recommendations for adjuvant chemotherapy, adjuvant endocrine therapy, or both after surgical resection of the tumor are based primarily on the benefits derived from clinical trials for women with early-stage breast cancer.

Adjuvant Chemotherapy
In an NCI study of initial report of 24 MBC patients with node positive stage II treated with adjuvant cyclophosphamide, methotrexate, and 5-fluorouracil (CMF),

5 years survival was 80% and median survival of 98 months (3).This was significant better than survival from historical controls. A study from MD Anderson Cancer Center with node positive MBC treated with CMF, with 20 years follow up showed that overall survival at 5, 10, and 20 years was 85%,65%,and 42% respectively (4).

Although available data supports the benefit for adjuvant chemotherapy in men ,it is the current recommendation that adjuvant therapy in MBC should be adopted from those for women with early breast cancer. In view of the toxicity of chemotherapy and the fact that over 30% of MBC patients are age d over 70years (5) adjuvant chemotherapy should only be considered in men with receptor-negative disease and with substantial risk of recurrence.

Adjuvant Endocrine Therapy

MBC are often positive for estrogen and progesterone receptors, previous data indicate the improvements in disease-free and overall survival in patients give hormone treatments such as diethylstilbestrol, medroxyprogesterone, Luteinizing hormone- releasing hormone (LHRH) agonist and orchiectomy, in comparison with historical controls. Tamoxifen is, at the present, the main drug used as adjuvant treatment for MBC and is often recommended for 5 years. In one study (6) reported 5-year actuarial survival (61% vs 44%)and disease free surviva (55%vs 28%)l in 39 patients who received tamoxifen compared with historical control group(7). Tamoxifen is generally tolerated in men. The common side effects of tamoxifen in men were reported including decreased libido, weight gain, hot flashes, mood alteration and depression.

Data in the adjuvant setting on the use of aromatase inhibitors or fulvestrant in MBC is not available at the present time.

Adjuvant Radiation Therapy

There is no prospective randomized clinical trial available that evaluates the role of adjuvant radiation therapy in MBC. Although the technical aspects of radiation therapy varied over time and between series making assessment of the clinical impact of postmastectomy radiation therapy (PMRT) difficult, there are several series (8-13) reported the benefit of PMRT. It reduced locoregional recurrence for MBC, but has had no apparent impact in overall survival .In one recent study (13) of 75 MBC patients treated with PMRT , the local relapse rate reported to be 4% compared with surgery alone of 24% .the locoregional control of disease was greater in high risk (close resection margin, positive node and advance stage) MBC patients. Other studies suggested that the same indications for PMRT that apply to female breast cancer should be used in men. Studies of women with stage II breast cancer who received PMRT showing a survival advantage (14) may be applicable for similar patients with MBC

Treatment of Metastatic Disease

A great majority of breast cancers in men are endocrine responsive, and in fact , orchiectomy used to be the standard of care for treatment of metastatic male breast, together with other aggressive surgical procedures such as hypophysectomy and adrenalectomy as primary treatment modalities.
Orchiectomy was reported to have response rates between 32% and 67%, with a median survival of 56 months in responding patients compared to 38 months in nonresponding patients (15). Castration also increased the probability of response to second-line ablative treatment, and some patients who failed orchietctomy responded to adrenalectomy or other endocrine treatment such as tamoxifen (16).

Aggressive surgical interventions are rarely used today, and hormonal therapy is an attractive alternative as it avoids surgical morbidity and mortality, is reversible and is psychologically more acceptable to most men.

Tamoxifen is considered to be the first line treatment for metastatic male breast cancer at the present time, with overall response rate of 49% reported (17). However, there is no prospective randomized trials have evaluated the real response rates and toxicity of tamoxifen in men.

The new selective aromatase inhibitors (anastrozole, letrozole, and exemestane) are also very active agents for treatment of advanced disease in postmenpausal women with hormone receptor-positive breast cancer. Experience of the use of these selective aromatase in male breast cancer is very limited.

Fulvestrant, a 7 –alkylamide derivative of estradiol, is an estrogen antagonist (18) that competitively binds to and degrade estrogen receptors in human breast cancer tissue. The drug been demonstrated to be effective in postmenopausal women with metastatic breast cancer.
For metastatic male breast cancer, only anecdotal data are available on the efficacy of fulvestrant (19)

Systemic chemotherapy is usually considered a second- line therapy in metastatic male breast cancer. Chemotherapy can provide significant palliation after hormonal therapy has failed, or in those with receptor- negative disease, and in those with life-threatening visceral disease. The overall response rate for all chemotherapy regimens in men has been estimated at 40% (20).

Data for other chemotherapy agents such as taxanes, capecitabine,vinorebine or gemcitabine in men is limited. Similarly, there is no information currently available on the benefits of trastuzumab in the rare male breast cancer cases with HER2-positive tumor.

Management Summary

In man a suspicious breast mass should be evaluated by tissue sampling. Needle is the preferred method of diagnosis.

Total mastectomy and sentinel node biopsy is the treatment of choice for most MBC.

Chest wall and regional lymph node irradiation should be given using the criteria developed for use in women.

Adjuvant systemic therapy recommendations are similar to those for women with the same disease stage. For patients with tumors positive for hormone recetors, adjuvant tamoxifen with or without chemotherapy should be recommended. For patients with hormone receptor-negative disease, chemotherapy should be recommended. In patients with metastatic disease, chemotherapy should be recommended for hormone receptor-negative , or rapidly progressing disease. Tamoxifen, and perhaps aromatase inhibitors should be considered for patients with indolent hormone receptor-positive disease.

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