REVIEW ARTICLES

BREAST CANCER IN MEN

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Summary

Breast cancer in males is a relatively rare entity. In the sub-region, several reports indicate a higher incidence rate compared to other regions in the world. For many years, management strategies were derived from evidence based protocols established for managing female breast cancer. There are however, differences in the epidemiology, presentation, molecular profiles and response to therapies including chemotherapy, hormonal and targeted therapies. Outcomes even though mirroring female breast cancer may actually exhibit differences dependent on stage, race, prognostic and economic variables. The lack of large randomized trials on this subject has resulted in ad hoc management practices across the globe. With new information from renewed interest in the subject, screening and diagnostic guidelines are being established for high-risk groups and we expect to see improvements in outcomes for patients with male breast cancer. This article attempts to bring to light a summary of the current interest, recommendations and controversies in the management of male breast cancer.

Keywords : male breast cancer, hormone therapy, chemotherapy, surgery, radiotherapy, survival.

Introduction

Breast cancer in men accounts for approximately 1% of all breast cancers diagnosed in the United States each year[1]. In Ghana, it accounts for about 2.9% of all breast cancers seen, consistent with the slightly higher rates reported in other parts of Sub-Saharan Africa with most patients presenting with advanced disease[2]. To date there are no randomized trials or large databases to validate current treatment strategies. Most of the information on breast cancer in men is derived from retrospective studies spanning several decades, and treatment recommendations are extrapolated from results of trials in female patients. Male breast cancer behaves like postmenopausal women with breast cancer. However, compared to all female breast cancers, it has poorer outcomes attributed to advanced stage at diagnosis and less aggressive management practices[3].

Epidemiology and Risk Factors

Male breast cancer usually occurs in the 7th decade, a decade later than occurs in females, with younger male patients more likely to have inherited genetic mutation[4]. Several risk factors are associated with higher incidence. These include Klinefelter syndrome, a family history of breast cancer, increased estrogen levels as occurs in conditions such as testicular disorders (e.g., cryptorchidism, mumps orchitis, and orchiectomy, use of finasteride and other hormonal ablation therapies used to manage prostate cancer , previous radiation exposure , gynecomastia, thyroid diseases, occupational and environmental exposures such as thermal heat, electromagnetic fields, polycyclic aromatic hydrocarbons, and dietary factors)[5-7]. Male breast cancer seems to have a higher male to female ratio in blacks compared to whites[8]. The Surveillance, Epidemiology, and End Results(SEER) database form the united states records on breast cancer from 1976 - 2005 shows that improvement in overall breast cancer cause specific death rates is less pronounced in males compared with females (28% versus 42% respectively)[9].

A meta-analysis of male breast cancer in 27 African countries suggests more late presentation , younger age (54.7years), higher incidence rates compared to developed countries, with Zambia reporting rates as high as 15%[10].Higher incidence rates in the sub region could be attributed to high estrogen levels following endemic infectious and other chronic liver disease processes [6,11]. Cirrhosis of the liver results in hyperestrogenism in men secondary to increased binding of androgens to increased sex tubulins[12]. This has been reported as a causative association and could be a result of gynecomastia predisposing to cancer.

Genetics

BRCA1 and *BRCA2* autosomal dominant genes are the major breast cancer susceptibility genes associated with a significant proportion of heritable breast cancer cases[13]. Mutation of these DNA repair genes in women confer a 40%–70% lifetime risk of breast cancer. There is a greater representation of BRCA2 tumors (41.7% vs 8.3%, p=0.0008) and under representation of BRCA1

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tumors in men compared to women (5.0% vs 14.4%, p=0.0001)[14]. Male patients with *BRCA2* mutations tend to present at a younger age and associated with a poorer survival[14]. Mutations in other genes may be implicated in the etiology of male breast cancer but are yet to be confirmed. BRCA2 is associated with aggressive prostate cancer and few reports indicate a higher incidence of breast cancer in males with this genetic mutation, and therefore it is recommended they undergo screening for both prostate and breast cancer [15].

Androgen suppression therapy for the management of prostate cancer may be associated with increased breast cancer risk secondary to altered androgen to estrogen ratio or may be related to inherited genetic mutations conferring a higher risk[16] . On the other hand transgender males who received androgen suppression therapy so far have not demonstrated an increased risk of breast cancer[17].

Screening for Male Breast Cancer

Current recommendations for screening are based on guidelines developed for females with BRCA mutations. All males with a family or personal history of breast cancer should undergo screening: monthly self breast examination, semi annual clinical breast examination and yearly mammograms for those found to have gynecomastia on the baseline mammogram[18]. The standard of choice remains mammography which has a sensitivity and specificity value of 92 and 90% respectively and a positive and negative predictive value of 99 and 55% respectively[19]. Mammograms are reliable for distinguishing gynecomastia from malignancy; the two could coexist in the same breast. Sonography by itself has a high false positivity rate but is valuable for evaluating complex masses, whereas Magnetic resonance imaging is currently recommended in males who require further evaluation of a highly suspicious mass[20]**.**

Pathology

Data from the SEER cancer registry show that 93.7% of male breast cancers are ductal carcinomas, 2.6% papillary, 1.8% mucinous, and 1.5% are lobular carcinoma[21]. Ductal carcinoma in situ (DCIS) occurs in about 10% of male breast cancers with the most common growth patterns being papillary and cribriform. Lobular carcinoma in situ is very rare because the male breast lacks terminal lobules[21].

Approximately 80-90% of male breast cancers are estrogen receptor positive, and 65-90% are progesterone receptor positive[4]**.** The *her2-neu* proto-oncogene is less likely to be overexpressed in male breast cancer. A large Italian study by Ottini et al identified 382 MBC with *her2- neu* positivity of 2.1%, and triple negative tumors as 3.7 %. Also, BRCA2 mutation was associated with family history, high grade, hormone receptor negative disease and resulted in poorer outcomes[22].

The hormone positivity rate for male breast cancer is expected to be lower in Africa following similar patterns as female breast cancer , therefore receptor testing is highly recommended to individualize treatment[23].

Clinical Features

The most common presenting symptoms in male breast cancer are painless sub-areolar lump, nipple retraction, and bleeding from the nipple[24-26]. Men with a previous history of breast cancer have a greater risk of developing contralateral breast cancer and a few present with *de novo* metastatic disease[27]. Based on the American College of Radiology of Appropriateness criteria, males younger than 25 years with a breast mass have lower chances of harboring a malignancy and therefore should have initial ultrasonography complemented by mammography if suspicious, whereas males older than 25 years should have bilateral mammography with ultrasonography, and biopsy for a breast mass[28]. Mammographic findings are abnormal in up to 90% of male breast malignancy and often depict eccentric masses with irregular spiculated edges[29].

Significant prognostic factors are tumor size and lymph node involvement. Tumors measuring 2–5 cm have a 40% higher risk of death than men with tumors <2 cm in maximum diameter[4]. Similarly, lymph node involvement is associated with a 50% higher risk of death compared to those without lymph node involvement[6]. Other identified prognostic features associated with better survival are ER+/PR+, Androgen Receptor negative, *her 2 neu negative* and ki67/p53 low group (median: 11.5 years; 95%CI: 6.2–16.8 years) and worst in PR- group (median:4.5 years; 95%CI: 1.6–7.8 years)[30].

Management of Early Disease

Generally follows the same management strategies as in females as no prospective randomized trials have been conducted to establish treatment protocols in men[31]. Trucut biopsies are preferable to ensure enough tissue is obtained for further mandatory immunohistochemistry testing.

Even though several small studies have reported the successful use of sentinel node biopsy in males, randomized studies establishing the sensitivity and specificity of sentinel node biopsy in male breast cancer have not been possible[32]. Breast conservation in males may be a challenge due to difficulties in obtaining negative margins resulting in a high rate of upfront radical mastectomies performed[33]. As pertains in females, a minimum of ten axillary lymph nodes should be dissected to obtain adequate prognostic and therapeutic information[34].

The indications for adjuvant radiation therapy in male breast cancer patients' follows same recommendations as in women, which includes breast conservation, T3/T4 tumors and positive axillary nodes. Following mastectomy, lesions greater than 5 cm with persistently positive surgical margins, lymph node positive disease, lympho-vascular space invasion, peri-

neural invasion should be referred for radiation therapy[35]. Predictors of local regional failure included margin status, tumor size, and the number of involved axillary lymph nodes, lympho-vascular and peri-neural invasion[35].

Adjuvant chemotherapy is recommended in all breast cancer patients who have a substantial risk of recurrence. Whereas the data supporting adjuvant chemotherapy in women are strong, there are few studies with low numbers on the effectiveness of adjuvant chemotherapy in men. A prospective study conducted by the National Cancer Institute (NCI) in USA in which 24 male patients with stage II breast cancer were treated with adjuvant CMF (cyclophosphamide, methotrexate, and fluorouracil) showed a projected 5-year survival rate of more than 80%, significantly higher than a similar cohort of historical controls[36]. Retrospective series have suggested adjuvant chemotherapy lowers the risk for recurrence in male patients[37]. Given the established benefit of chemotherapy in women and the suggestive evidence in men, most clinicians use similar guidelines for adjuvant chemotherapy as in female patients.

Tamoxifen is the recommended choice for positive hormone receptor staining in men[37]. Aromatase inhibitors are considered contraindicated because at least 20% of circulating estrogen in males is independent of aromatase and therefore indicated only in circumstances when tamoxifen is contraindicated or fails to control disease[38].

All patients exhibiting Triple negative and *Her 2* positive disease should receive adjuvant chemotherapy, preferably anthracycline and Taxane based chemotherapy with or without Trastuzumab depending on *Her 2 neu* staining[39].

Management of Locally Advanced Disease

Neoadjuvant chemotherapy should be considered for localized unresectable disease to improve resectability followed by radiotherapy to control local symptoms[40]. For patients with persistently unresectable disease, radiation therapy should be offered. Hormonal therapy has a role in receptors- positive disease most often following chemotherapy. Neoadjuvant hormonal therapy may be an option when there are contraindications to chemotherapy. However more than six months of treatment is required to achieve adequate shrinkage of disease and complete responses are rare with tamoxifen even in females[41].

Maximal tumor reduction with systemic therapies should be achieved prior to surgical intervention and this may require administering several cycles of chemotherapy and switching protocols. Positive surgical margins directly correlate with poor outcome and should be avoided[42].

Management of Recurrent Disease

Poorly managed local recurrence may result in early distant disease. A disease free interval of greater than one year has a better prognosis compared with less than 6 months[43]. All patients should be evaluated for metastatic disease including radiological assessment of the lungs and liver. Bone scans and brain imaging are only indicated when there is high suspicion of disease involvement. Plain X-ray of the involved bone is recommended where bone scintigraphy is unavailable. The latter is preferred because bone scintigraphy completely assesses the skeletal system for evidence of osteoblastic bony involvement.

Second line treatment depends on previous therapies received, response achieved and disease extent. Surgery is an option for resectable lesions and clear surgical margins must be achievable. Patients who did not receive prior radiotherapy should be offered chest wall radiation. Anthracycline chemotherapy is associated with cardiotoxicity and lifetime maximal doses should not be exceeded[44]. The role of hormone and *Her2 neu* therapies are dependent on receptor status obtained for new lesions[45].

Management of Metastatic Male Breast Cancer

The general approach to the treatment of metastatic male breast cancer is similar to that in female breast cancer. Hormonal therapy is often the first approach in men with estrogen and/ or progesterone receptor positive tumors in the absence of a visceral crisis. Tamoxifen has established efficacy in the metastatic setting with an approximate 50% response rate and is currently the preferred first-line approach for receptor positive male breast cancer[36]. Surgical ablative therapies such as orchiectomy, adrenalectomy, hypophysectomy and chemical castration using luteinizing hormone–releasing hormone agonists, with or without antiandrogens are reported to be effective in metastatic male breast cancer following tamoxifen failures[46].

Men with hormone receptor negative, hormone-refractory disease or rapidly progressing visceral metastases should be managed with chemotherapy using the same protocols established for women[47]. The tole of Trastuzumab in managing *Her2-neu* overexpressing metastatic male breast cancer is however currently under debate as response rates are considered suboptimal[39].

Survival Patterns for Male Breast Cancer

Several studies have demonstrated similar survival rates for both sexes with breast cancer after correcting for age, stage, molecular subtyping and other prognostic indicators[48].

Male breast cancer patients are less likely to receive post lumpectomy radiation and adjuvant chemotherapy compared to their female counterparts and these poor management practices could account for poorer outcomes[49]. BRCA2 mutations are associated with significantly lower survival compared to normal males ($p=0.04$)[50]

In a series of 137 male patients, adjuvant chemotherapy was beneficial in node positive disease

(HR =0.78), and significant survival benefit for patients with hormone positive disease treated with hormonal therapy (hazard ratio= 0.45,p=0.02)[51]. Several reports indicate worse prognosis in black compared to white patients with breast cancer specific mortality hazard ratio in black males is at least double compared to white[49]. A small study from Nigeria reports a 5 year overall survival for 57 men following adequate surgery to be less than 25% compared to 47.6 % in a study of survival for female breast cancer patients from Ghana (11,53) . This poor outcome may be attributed to general lack of hormone receptor testing for male breast cancer patients in the sub region. A recent publication from the USA comparing outcomes for black versus white male breast cancer patients revealed a worse outcome in younger black males which became non-significant when corrected for covariates such as income and insurance i.e. access to care[53]. In the latter study, there were no differences observed for males older than 65 years and could be explained by improved access to Medicare facilities above age 65 years.

Conclusion

In spite of the rising incidence, male breast cancer is still considered rare. Many present with advanced disease resulting in poor control in spite of better prognostic features compared to female counterparts. Tumors of the male breast are more likely to express estrogen and progesterone receptors and less likely to overexpress *Her 2 neu* compared to women and therefore receptor staining is pivotal in the management of male breast cancer. A multidisciplinary approach is recommended with decisions based broadly on principles established for female breast cancer. Education of patients, families and health providers will increase awareness of male breast cancer, ensuring early presentation, prompt referral for early diagnosis, treatment and improved survival. Large randomized trials in male breast cancer are encouraged to direct evidence based therapies in Africa as conclusions from small studies may be biased.

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