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VOLUME 14

SURGERY

Roshan Lall Gupta's Recent Advances in SURGERY

Editor
Puneet

JAYPEE

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CHAPTER

2

Carcinoma Male Breast

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INTRODUCTION

Male breast cancer (MBC) is an uncommon disease, accounting for less than 1% of all breast cancers diagnosed worldwide. About 2,000 new cases of MBC occur annually in the United States (SEER registry data), and the incidence is slowly increasing, from about 1,500 estimated new cases in 2002 to 1,990 in 2008 to 2,240 in 2013. Deaths due to breast cancer in men for the year 2013, in the United States, are estimated to be 410.

Given the rarity of the disease, most recommendations on diagnosis and treatment have been extrapolated from those laid down for management of breast cancer in women. However, this may not always be applicable; the male hormonal milieu is different, and this may have a unique influence on risk, prognosis and treatment outcome. Specific information on the epidemiology, behavior, management issues and outcome of treatment in MBC is sparse and controlled trials nonexistent because of the infrequency of the problem. From birth till puberty, breasts in both genders are similar. In the male, in the prepubertal phase, the slight increase in estrogen and the marked increase in androgen levels results in transient proliferation of the ducts and stroma followed by atrophy leaving only the subcutaneous fat and a small area of subareolar glandular tissue. The male breast has no Cooper's ligaments. In the female, the presence of estrogen and progesterone leads to lobular development, which is not seen in men.

EPIDEMIOLOGY

Male breast cancer accounts for about 0.2% of all cancers in men. The median age at diagnosis is about 68 years, and the age ranges from 9 years to 94 years. The age-specific incidence rates of MBC increase linearly and steadily with age reaching a peak incidence at about 75 years of age. In contrast, age-specific incidence rates for female breast cancer (FBC) typically follow a bimodal distribution, a first rapid peak at about 50 years of age followed by a second more gradual increase with age—referred to as Clemmensen's hook. In an international population-based study over a 40 year period, Miao et al. (2011),

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noted that the incidence of MBC recorded in four European cancer registries, had remained at a stable low rate (0.4/100,000 person years) whereas, FBC had become increasingly common (51.4/100,000 person years in early 1970s to 80.3/100,000 person years after the year 2000). Incidence of MBC had shown a more steep increase in the Singapore registry although it did not reach statistical significance. In a similar population-based study, data for a period of 15 years (1991–2005) from four Western nations, namely England, Scotland, Canada and Australia, was analyzed by White et al. (2011). In addition to an increase in absolute numbers, age-adjusted incidence of MBC increased in all four nations. The observed global increase in incidence of FBC has been largely explained by the introduction of screening mammography and hormone replacement therapy in the 1980s and changes in lifestyle and reproductive patterns whereas altered lifestyle causing increasing rates of obesity, and alcohol intake are possible contributions to increasing incidence of MBC.

A geographic variability in incidence of MBC has been described in Tanzania and Central Africa where 6% of all breast cancers occur in men. The high incidence in the African population is attributed to prevalence of hepatic dysfunction due to chronic infestations that result in high circulating levels of estrogens. Ethnic variations were reported in a study from the United States. Incidence rates were greatest among African Americans and least in Asians and Central and South Americans. Black men had the highest age-adjusted incidence rates, were younger at presentation and were more likely to present with distant metastases.

RISK FACTORS

Many risk factors for MBC involve imbalance between estrogen and androgens indicating the importance of a hormonal drive in the occurrence of MBC. Family history is an important risk factor for MBC. Positive family history of a first-degree female relative having breast cancer is seen in up to 15–20% of patients. However, the effect of a positive family history of MBC on risk is less easily studied than in women, given the rarity of this event. Guth et al. (2011) reported a cluster of MBC in three male siblings who developed breast cancer over a period of 21 years. All the female relatives remained unaffected. None of the three cases showed the typical known genetic/clinical risk factors for MBC. They suggested a possible X-linked recessive inheritance. In general, studies suggest that a positive family history of either male or female first-degree relative with breast cancer is associated with a twofold to threefold increase in MBC risk. The risk increases if more first-degree relatives are affected particularly if the malignancy occurs at a younger age.

There is a strong association of MBC with Klinefelter's syndrome. This hereditary syndrome occurs in about 1 in 100 men and is usually not recognized until puberty. Affected individuals typically exhibit a eunuchoid

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habitus, gynecomastia and small firm testes. Men with Klinefelter's syndrome have increased secretion of follicle-stimulating hormone but low levels of androsterone and normal to low levels of estrogens. About 3–4% of MBC cases are reported to have Klinefelter's syndrome and males with this condition have a 50 times increased risk of breast cancer. Possible explanations for this association include abnormal hormonal stimulation of cell proliferation in mammary ductal epithelium and treatment with exogenous testosterone, which is converted to estrogen in the peripheral adipose tissue. Among patients with Klinefelter's syndrome, breast cancer mortality rates are similar to those in women.

Other risk factors related to hormonal levels include obesity due to higher circulating levels of estrogen. Risk estimates for men in the highest category of weight or body mass index tend to range between 1.63 and 5.45 compared with those in the lowest category. In obese men, estrogen production, metabolism and bioavailability are enhanced. Conversion of testosterone to estradiol and androstenedione to estrone occurs in peripheral adipose tissue. In men, testosterone levels decline with greater body weight, whereas estrogen levels increase. Also, for any given estrogen level, a greater amount is bioavailable in obese men, due to decreased levels of sex hormone binding globulin.

Exogenous estrogen administered for prostate cancer has been shown to result in moderate acinar and lobular formation of breast tissue that could lead to increased likelihood of developing breast cancer. Transsexuals who have been treated with surgical castration and who are receiving combined progestative and estrogen treatment have also been documented to have increased incidence of breast cancer.

In patients with cirrhosis of the liver, there is excess of estrogen and reduction in androgens. This is secondary to elevated sex steroid binding globulin. As a result, there is a fourfold increase in risk of MBC which was documented in a cohort study by Sørensen et al. (1998). In sub-Saharan Africa, infectious hepatotoxic disease is said to compound genetic risk. Testicular dysfunction resulting in reduced androgen levels such as that seen in cryptorchidism increases risk of MBC. Mumps in adults may result in testicular atrophy, damage to Sertoli and Leydig cells and increased risk for MBC. Testicular trauma, orchiectomy and congenital inguinal hernia all of which may reduce androgen levels may also increase risk of MBC.

The association, if any, between idiopathic gynecomastia or gynecomastia associated with cirrhosis, following estrogen therapy for prostate cancer or as a side effect of other nonhormonal drugs such thiazides and tricyclic antidepressants and MBC is not clear. In a cohort of 445 men with gynecomastia, the authors have documented no case of breast cancer.

Men working in hot environments such as blast furnaces, steel works and rolling mills have increased risk for MBC. High ambient temperatures could result in testicular failure resulting in altered estrogen to androgen ratio.

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Associations have also been described with occupations involving working with soap, perfumes, petrol and exhaust fumes, the responsible carcinogen most likely being polycyclic aromatic hydrocarbons (PAH), found in tobacco smoke and exhaust emissions. PAH-DNA (polycyclic aromatic hydrocarbons-deoxyribonucleic acid) adducts are chemical compounds formed by interactions between PAH compounds and DNA that indicate an increased likelihood of cancer formation in the tissue. Increased levels have been found in tumors and in benign breast tissue of patients with breast cancer. Exposure to electromagnetic fields may affect pineal gland activity leading to reduced production of melatonin, which has been to shown in animal studies to increase breast tumorigenicity. Irradiation to the breast in men and prepubertal women increases the risk of breast cancer to the same extent in both genders. Boys irradiated for thymic hypertrophy, lymphoma, prepubertal gynecomastia or even eczema, may develop the disease after a long latency. Among 45,880 male survivors of an atomic bomb, 9 cases of MBC were diagnosed over a period of 40 years (a crude rate of 1.8/100,000 person years), the risk related to the extent of exposure.

Excessive intake of alcohol has been considered to contribute some risk due to the occurrence of liver cirrhosis with resultant elevated circulating levels of estrogen. However, most studies have not found an association between alcohol intake and MBC. Neither increased risk due to meat consumption nor a protective effect of fruit and vegetables has been consistently demonstrated.

GENETIC FACTORS

It is estimated that approximately 10% of men with breast cancer have a genetic predisposition. Genes implicated in the etiology of MBC include *BRCA2, AR* gene, CYP17, PTEN tumor suppressor gene (Cowden's syndrome) and the *CHEK2* gene.

BRCA1 does not appear to be associated with significantly increased risk for breast cancer in men (1.5 times lifetime risk). BRCA2 mutations, on the other hand, play a particularly prominent role in MBC. Relative risks associated with both mutations are highest for men in their thirties and forties and decreases with increasing age, particularly with BRCA2 mutation carriers. The *BRCA2* gene is located on chromosome 13q12-13. It regulates the intracellular localization and DNA binding ability of RAD51. Loss of these three abilities following inactivation of BRCA2 may be an important event leading to genomic instability and tumorigenesis. Families of men who have breast cancer have a 60–70% possibility of having BRCA2 mutation. The frequency of BRCA2 mutations in men without a strong family history is much lower. A population-based study from California identified only 2 of 54 cases (4%) as having BRCA2 mutations. Another study on 102 Italian men with breast cancer found no BRCA1/2 mutations. In contrast, in a population-based study

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from Iceland, 40% of males with breast cancer were carriers of the founder BRCA2 mutation, namely, 999del5. MBC associated with BRCA2 mutation presents at an earlier stage.

As in women, BRCA-associated breast cancers in men tend to manifest specific genotype-phenotype correlations. The majority of BRCA1 related MBCs are human epidermal growth factor receptor 2 (Her2) negative; grade 3 tumors showing high proliferative activity. In contrast, BRCA2 related MBC present with high-tumor grade, absence of progesterone receptor (PR) and Her2+ status.

Germ line mutations in the *AR* gene have also been suggested to predispose to MBC. It is proposed that AR develops the ability to bind to estrogen response elements and therefore activates estrogen-regulated genes. Alternately, AR mutation may result in reduced androgen levels leading to increased estrogen–androgen ratio and increased susceptibility to MBC. Germ line mutations in other genes namely, *CHEK2*, *PTEN* (Cowden's syndrome) and CYP17 have been linked to increased risk for MBC but data are mixed regarding the relevance due to rarity of MBC.

CLINICAL FEATURES

Published data has shown that men with breast cancer are likely to have more advanced disease and poorer prognosis compared to women because of poor awareness of disease leading to delayed diagnosis by as much as 6–18 months. This is, however, not seen in those male patients who have had breast cancer in their families. Awareness in these families reduces mean delay to only 1 month. This impression of late stage of disease and poor prognosis in males is, however, not supported when the comparison is made after matching for age and stage. In such patients, men have the same or better prognosis than women.

As with women, the most common symptom of breast cancer is a painless lump seen in 75–85% cases. Because most of the breast tissue in men is under the nipple and areola, the lesion is usually subareolar in location. This also causes the nipple areola to become retracted early in the course of the disease. Other common presenting symptoms and signs are nipple retraction, local pain, nipple ulceration, nipple discharge and bleeding from the nipple. Nipple involvement occurs in 40–50% of patients.

The scanty breast tissue also results in lesion being close to the pectoral fascia and the skin and fixity to these structures is often observed at presentation. Bilateral MBC occurs less commonly than in women. Although men with history of breast cancer have a substantial elevation in relative risk (thirtyfold) of developing a second breast primary, the absolute risk is quite low (1.75%). This could be either due to later age at diagnosis in MBC resulting in death due to other causes prior to onset of contralateral disease. Paget's disease has been reported in less than 1% of MBC. More than 50% men with

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breast cancer present with stage II or more disease. Lymph node metastases, lymphovascular invasion and nipple involvement are thus more likely to be present at initial diagnosis of MBC.

DIAGNOSIS

As with symptomatic female patients, the diagnosis is made by triple assessment, viz. palpation, imaging and biopsy. Both mammography and USG have high sensitivity and specificity for male patients. When a man presents with a breast mass, the primary differential diagnosis is gynecomastia. Mammography is useful in distinguishing the greater number of benign from the smaller number of malignant lesions.

Despite the relatively small size of the male breast, mammography is feasible and can be used in men employing the same routine views as women and if necessary spot compression. At mammography, malignant lesions appear as high-density irregular masses with well-defined contours and margins that are spiculated or lobulated or micro-lobulated. Eccentric location is suspicious for carcinoma. Microcalcification is less common in MBC compared to FBC. It occurs primarily in ductal carcinoma in situ (DCIS) tumors, which comprise only 9% of MBC. Nipple retraction, skin thickening and increased trabeculation are helpful secondary signs.

Ultrasound is useful in patients in whom mammography is noncontributory. Ultrasound features are similar to those of FBC—nonparallel, discrete, hypoechoic masses with angulated/speculated/micro-lobulated margins. Ultrasound is useful in evaluating the axilla, as axillary adenopathy is seen in about 50% of patients with MBC. It is also useful in directing percutaneous biopsies in select cases, for instance MBC occurring in the setting of gynecomastia. Papillary carcinoma is more common in MBC. Most of the papillary cancers are intracystic. They appear as a solid mass or a complex cystic mass with thick walls containing both solid and cystic components. Other imaging techniques such as the Tc^{99m} Sestamibi uptake scan have been tried for the diagnosis of malignant masses in the male breast but have no specific advantage.

After appropriate local imaging, any suspicious mass needs to be biopsied to confirm the diagnosis. Fine-needle aspiration cytology (FNAC) has been found to have high sensitivity and specificity with 100% PPV in the diagnosis of MBC. The most important pitfall reported for FNAC is over diagnosis of florid hyperplasia in gynecomastia as carcinoma. Core biopsy is a useful adjunct to distinguish MBC from malignancy. As in women with breast cancer, core biopsies need to be done for evaluation of tumor grade, estrogen receptor (ER), PR and Her2/neu status as these have prognostic and therapeutic significance.

The extent of disease can be determined from laboratory evaluation, chest X-ray, radionuclide bone scan and computer tomography scan of the

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abdomen, as considered clinically appropriate. Tumor stage is determined using the TNM classification of the American Joint Committee on Cancer, identical to the system used for FBC.

PATHOLOGY

Almost all histological subtypes of breast cancer that have been described in women have also been reported in men. Approximately 90% of all breast cancers in men are invasive; the remaining 10% are noninvasive. The proportion of noninvasive cancer is higher than that seen in women before the introduction of mammography and could be due to the ease with which small masses are palpable in the male breast. Almost all in situ malignancies are ductal (DICS) in origin. Lobular carcinoma in situ is rare as terminal lobules are absent in the male breast.

Ductal carcinoma in situ of male breast differs from that of the female breast in that papillary DCIS occurs with much higher frequency than solid, cribriform and micro-papillary forms. In a study by Hittmair et al. (1998) on DCIS in males, 75% of all DCIS demonstrated a papillary architecture. They also noted a frequent extension of DCIS beyond the central macroscopically obvious lesion into the small ducts. This finding suggests that if these extensions are not excised completely, it could result either in recurrence of DCIS or progression to invasive carcinoma. In contrast to FBC, which arise predominantly in the terminal duct lobular unit (TDLU), MBC arises from the larger ductal structure of the central portion of the duct system. The periphery of the organ comprising of the TDLU or lobules differentiates only under the physiologic or pathologic influence of endogenous or exogenous estrogens or estrogen mimicking compounds. This could explain the predominantly papillary pattern of DCIS in MBC, which resembles that present in the more central portion of the ducts of the female breast. High-grade comedo type DCIS is rarely seen in MBC most probably because it originates from the TDLU.

Burga et al. (2006) investigated the frequency and distribution of various histological subtypes in a large data set of invasive MBC over a 40-year period. Pure infiltrating duct carcinoma not otherwise specified (IDC-NOS) was the most common histological subtype (84.7% of all cases). Overall, it was observed that invasive cancer of the male breast displays a morphologic spectrum and distribution of histological subtypes that is comparable to invasive cancer of the female breast. With the exception of papillary and lobular variants, no specific histological subtypes were under- or overrepresented. Papillary DCIS assumes an IDC pattern once it invades the stroma. Invasive papillary carcinoma accounts for about 2–4% of MBC compared to about 1% of FB. Lobular carcinoma has been noted rarely not only in Klinefelter's syndrome but also in genotypically normal men with no previous history of estrogen exposure or gynecomastia. Rare tumors like inflammatory

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carcinoma and sarcomas have also been reported to occur in men. A possibility of metastases to the breast has to be kept in mind when evaluating a breast mass in men known to have malignancy elsewhere. As in women, grade is an important prognostic factor. In one study, 85% of MBC were grade 3 tumors compared to 50% grade 3 tumors in women. In contrast, in a SEER database analysis encompassing breast cancers between the years 1973 and 2000, 39% of 1,180 tumors of MBC were grade 3. This was found to be comparable to the proportion in postmenopausal FBC, but less than that seen in premenopausal women.

IMMUNOHISTOCHEMISTRY/BIOLOGICAL CHARACTERISTICS

The vast majority of MBC are hormonally sensitive. MBC have a higher rate of hormone receptor positivity than do FBC when matched for tumor stage, grade and patient age. In the National Cancer Institute's SEER database, between 1975 and 2005, 92% of MBC were ER+ compared to only 78% of FBC. Similarly, men were more likely than women to have tumors expressing PR (81.2% versus 66.7%). ER positivity increases with increasing age in MBC as it does in women.

The proto-oncogene Her2/neu is a member of the erbB/Her type 1 tyrosine kinase receptor family. It is located on chromosome 17Q and encodes a transmembrane tyrosine kinase with substantial homology to epidermal growth factor receptor. These receptors mediate proliferation and differentiation in normal epithelial cells. Inappropriate overexpression may contribute to tumor growth and invasion. Amplification or overexpression of Her2/neu has been shown to a prognostic factor associated with resistance to some forms of adjuvant chemotherapy and sensitivity to others, short disease-free interval and short survival time in both node-negative and node-positive breast cancer patients. In addition, overexpression of Her2/neu on the surface of the tumor cell provides a potential target for the genetically engineered anti-Her2/neu monoclonal antibody, trastuzumab. Optimal use of this therapy, however, requires accurate determination of Her2/neu status. Approximately 25–30% of invasive FBC overexpress Her2/neu. In 90–95% of these cases, overexpression is a direct result of gene amplification. Data on Her2 expression in MBC are inconsistent. Studies have documented overexpression rates ranging from 2% to 42%. In a series of 58 men with breast cancer, only one tumor (1.7%), showed Her2 overexpression by immunohistochemistry (IHC) and none showed over amplification by fluorescence in situ hybridization (FISH). The study, however, was a retrospective one, most of the testing being done on archival tissue blocks and slides, factors which are known to reduce the antigenicity of Her2/neu protein. Rudlowski et al. (2004) analyzed formalin fixed paraffin specimens of MBC for Her2 overexpression by IHC and gene amplification using FISH. They demonstrated an 11% rate of gene amplification and overexpression (2+ or 3+ by Hercep test). This is much lower than rates of overexpression in FBC.

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Data on other biomarkers of interest are even more sparse and variable. p53 is a tumor suppressor gene that controls cell growth by inducing cell cycle blockade, apoptosis and cell differentiation. Its transcriptional regulated p21 protein, besides being related to cell repair and apoptosis appears to promote either growth arrest or proliferation depending on the cellular context and also mediates the activation of the estrogen signaling path in ER- neoplastic cells. *p53* gene alterations are present in approximately 30% of cases of FBC. Tumors of MBC express p53, but the rates of expression range from 3.7% to 20.8% of patients only. The prognostic significance of p53 mutation in MBC is not clearly established. Bcl-2 is a proto-oncogene that inhibits apoptosis and thereby promotes cell growth. In breast cancer in women, expression of Bcl-2 has been associated with favorable prognosis. Men may have significantly higher rates of Bcl-2 expression than FBC but the prognostic significance is unclear.

André et al. (2007) compared the immunohistochemical profile of cell cycle inhibitors of G1/S-phase transition (p21, p53 and pRb), Ki-67 cell proliferation markers and DNA ploidy between two groups of patients with invasive FBC and MBC matched for clinico-pathologic and therapeutic criteria. They observed that MBC tumors showed a higher frequency of DNA aneuploid tumors, p21 positivity and p53 negativity compared to FBC tumors. PRb and Ki-67 immunoexpression were similar between MBC and FBC. They concluded that the differences in DNA ploidy, p21 and p53 expression point to different genomic instability and to differences in the cell cycle proliferation control suggesting the existence of independent mechanisms of tumorigenesis in FBC and MBC.

It has been hypothesized that androgen pathways may be more active in MBC compared to FBC. Studies have found 34–95% AR activity in MBC. However, in the study by Pich et al., AR positivity did not correlate with clinical or pathological characteristics such as age, stage, PR and p53 overexpression. Further, a linear correlation was noted with ER expression.

In females, using IHC markers, several subtypes of breast carcinoma have been identified which may have prognostic significance. These subtypes are luminal A, luminal B, Her2/neu, Her2 driven, basal- like. In men, the predominant types have been found to be luminal A (75%) and luminal B (21%) with the others being very rare. Luminal A tumors are associated with older age and postmenopausal status in women. Men resemble postmenopausal women in their hormonal status and the majority of tumors in men are luminal A. All the Her2 positive cases in men were ER positive and were classified as in a study by Kornegoor (2012). The prognostic significance of luminal B in MBC is yet to be established. Basal-like breast cancer in FBC accounts for 16% of tumors and signifies an overall poor prognosis. This type is rare in MBC (< 3%) and patients are relatively younger as in FBC.

As in FBC, structural genomic rearrangements appear to be common in MBC. Comparative genomic hybridization in fresh frozen MBC with

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available data set from FBC tumors, demonstrated that male tumors were more likely to have genomic gains and less likely to have losses of genomic material and high-level amplifications. Performing GEX (gene expression) profiling on 66 MBC tumors, Johansson et al. were able to stratify them into two stable subgroups, luminal M1 and luminal M2 associated with different biological features and clinicopathological characteristics. The luminal M2 subtype of tumors had a more favorable outcome, were less frequently aneuploid, and displayed a lower S-phase fraction compared with luminal M1 tumors. Both MBC groups differed from the established intrinsic subgroups of FBC, indicating that they constitute two subgroups of breast cancer occurring only in males. It is thus possible that gender-related biological differences exist in breast cancer, and could have clinical and treatment implications for breast cancer patients.

TREATMENT

Local Therapy

Surgical options for men with early stage (non-metastatic) breast cancer include breast conserving therapy and mastectomy. The most common procedures are modified radical mastectomy (MRM) (70%), followed by radical mastectomy (8–30%), total mastectomy (5–14%) and wide local excision (1–13%). However, since the tumor is almost always in the central quadrant, which for oncological reasons necessitates removal of the nipple areola complex, there is little aesthetic advantage to conservative breast surgery in men. When primary skin closure is not possible, a transverse rectus abdominis or latissimus dorsi flap is used to cover the defect. Nipple reconstruction by surgery or tattooing may be done to restore body image. Axillary nodal involvement is seen in 50% of cases and is an important prognostic indicator. In patients with clinically N0 disease, sentinel lymph node (SLN) biopsy is required in men as in women. This is supported by a study by Gentilini et al. (2007) who investigated the predictive value of SLN in 32 males with breast cancer. Six patients had positive SLNs, in four of whom the SLN was the only lymph node harboring metastases. The value of sentinel node biopsy was further confirmed by a study from the Memorial Sloan-Kettering Cancer Center. SLNs were positive for tumor in 49% of their cases, and there was a failure rate of 3% as in women.

Radiation Therapy

As regards radiotherapy, most of the available data is what has been extrapolated from the experience in women. The indications for radiotherapy include tumors more than 3 cm, involvement of more than 4 lymph nodes or 1–3 lymph nodes with evidence of extensive lymphovascular invasion. Few studies have shown a survival benefit. The radiotherapy doses (2 Gy/fraction

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for 25 fractions) and the indications for boost radiotherapy in cases with positive resected margins are the same as in women. As in women, neo-adjuvant CT or RT is recommended for patients with inoperable primary tumors.

Systemic Therapy

The mainstay of systemic therapy for hormone-positive MBC is hormonal therapy. Standard adjuvant endocrine therapy for men includes 20 mg of oral tamoxifen daily for 5 years. The benefit approaches that in women in terms of both recurrence and overall survival. Studies have shown that 5-year disease-free survival increases from 28% to 56% and 5-year overall survival from 44% to 61% with adjuvant tamoxifen therapy. No data is available to suggest the duration of treatment in men, but improvement in survival has been shown with administration of adjuvant tamoxifen for 2 years. Some studies have suggested that male ER-positive tumors do not respond to tamoxifen therapy in the same manner as female ER-positive tumors do, resulting in male patients who had hormone receptor-positive tumors having inferior survival compared with female patients despite using similar endocrine therapy. Consequently, hormone receptor positivity does not translate into better prognosis for male ER-positive breast cancers. The smaller improvement for male hazard ratios, suggests a delay and/or underutilization of adjuvant therapy in males compared to females, in particular tamoxifen for hormone-positive MBC. Use of tamoxifen for MBC may also be limited by poor compliance due to its association with a high rate of treatment—limiting side effects in males. Treatment discontinuation among men due to adverse effects approaches 25%. Toxicities recorded include weight gain, sexual dysfunction, loss of libido, hot flashes, neurocognitive effects, thromboembolic events, depression, leg cramps and insomnia. By comparison, the corresponding discontinuation rate among FBC shows a wide range from 30% to 50%.

Aromatase inhibitors (AI), which prevent conversion of androstenedione to estradiol are the recommended drugs for postmenopausal women with HR positive breast cancer. Physiologically, 80% of circulating estrogen in men is produced by the aromatase pathway, the remaining 20% is produced directly in the testes. It is therefore postulated that AI alone would be insufficient for treating ER-positive MBC. Adding a gonadotropin-releasing hormone antagonist or orchiectomy is recommended when using AI to achieve complete estrogen suppression. The role of AI in adjuvant treatment of MBC is yet to be established, but the success of its use in FBC warrants additional studies in MBC. Side effects due to anastrozole and letrozole in men include loss of libido, mood alterations and hot flashes, but none of the patients in one study discontinued the treatment because of these side effects.

In a case series comprising of 35 men with breast cancer, reported form the MD Anderson Cancer Centre, 32 patients received CT, 19 of whom also received hormone therapy. Seventy two percent of those who received

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CT were treated with anthracycline-based regimens, about 9% received both anthracycline and taxanes and 16% were given CMF. Most of them received CT in the adjuvant setting. In MBC, CT reduced the risk of mortality (hazard ratio 0.78) without reaching statistical significance. The reason for this is that CT is best employed in HR negative women whereas most men with breast cancer are ER positive. The overall response rate for all chemotherapy regimens in men has been estimated at 40%. Response rates for various combinations have also been estimated: 5-fluorouracil, doxorubicin and cyclophosphamide 67%; doxorubicin and vincristine 55%; cyclophosphamide 53%; cyclophosphamide, methotrexate and 5-fluorouracil 33% and 5-fluorouracil (13%). No data are available on taxanes, capecitabine, vinorelbine or gemcitabine in men. Similarly, no information is currently available on the benefits of trastuzumab in MBC cases with Her2-positive tumors.

The sites of metastases in men are similar to those in women and include bone, lung, liver, brain and other sites. Unlike female breast carcinoma, due to rarity of MBC, the effect of treatment of metastatic breast carcinoma in men has been published only in small case series and not as controlled trials. Hormone therapy has been the mainstay of treatment for metastatic cancer of the male breast since the first description of the beneficial role of orchiectomy in 1942. Other ablative therapies practiced include adrenalectomy and hypophysectomy. Patients who respond to orchiectomy are more likely to respond to second-line ablative therapy and response translates into improved survival. These surgical procedures are rarely used today and have been replaced by additive hormonal therapies which have been shown to have substantial response rates in metastatic MBC. These treatments are more appealing compared to ablative therapies because they are reversible and avoid surgery. Additionally there is the psychological advantage of avoiding an orchiectomy. Rates of response to various additive therapies are 75% for androgens, 57% for antiandrogens, 50% for steroids, 32% for estrogens, 50% for progestins, 40% for aminoglutethimide and 49% for tamoxifen. In men, tamoxifen therapy has been useful in managing visceral metastases, bone metastases or soft tissue recurrence with the effect more prominent on those with higher degrees of ER positivity. It is recommended that at least one metastatic lesion should be biopsied to estimate Her-2/neu status, hormonal receptor status and proliferation which gives the opportunity to tailor the metastatic treatment therapy based on the tumor's biological characteristics in the relapse rather than in the primary tumor. Chemotherapy can offer substantial palliation to men with hormone refractory breast cancer. As in treatment of women with advanced breast cancer, sequential use of endocrine therapy and chemotherapy is preferred to simultaneous use of the two modalities of treatment in men.

Male breast cancer survivors have an increased risk of developing second primary cancers. Based on data from the SEER cancer registry database, Auvinen et al. (2002) reported that men with a history of breast cancer had

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a thirty-fold greater risk of contralateral breast cancer. The risk for other cancers, including melanoma and prostate cancer, may also be elevated in MBC survivors, particularly in mutation carriers.

PROGNOSIS AND SURVIVAL

As in women, important prognostic indicators include stage at diagnosis, lymph node status, grade and hormone receptor status. Overall 5-year survival is estimated between 36% and 66%. The largest published registry series to examine survival is from the National Cancer database which included 4,755 men diagnosed with breast cancer between 1985 and 1994. Observed survival was highest for in situ disease (overall survival 97%, disease-free survival 82%) and decreased with successive stages. When grouped by stage at presentation, 5-year survival is 75–100% for stage I disease, 50–80% for stage II disease falling to 30–60% for stage III disease. Although it appears that survival is worse compared to that of FBC, when matched for age and stage of disease, clinical outcome is similar to that in women. Gnerlich et al. (2011) conducted a retrospective, population-based cohort study of males and females with a first primary diagnosis of breast cancer recorded in the SEER Program database between January 1, 1988 and December 31, 2003. Breast cancer-specific mortality was greater for males than females only in stage I disease. They reasoned that males with T1 tumors were more likely to have larger T1 tumors than their female counterparts—"in-stage migration". Women are also more likely to have a T1 breast cancer identified asymptomatically by screening mammography, whereas males are more likely to have a T1 breast cancer identified by a palpable mass on examination. Unlike women, improvement in MBC mortality rates is solely attributable to adjuvant therapy as men do not have the benefit of screening for early detection. Because older age at diagnosis is associated with higher prevalence of comorbidities, there is an overall poorer survival among male compared with FBC patients. Only in stage IV disease was all-cause mortality similar between the sexes.

Stage of the disease at diagnosis, ER and PR positivity and negative lymph node status are found to have a beneficial effect on survival. In a series of 109 male patients with breast cancer at a mean follow-up of 70 months, Sun B et al. (2015) observed that adjuvant hormone therapy was related to good disease-free survival ($p < 0.05$) but not overall survival. Lymph node involvement is the most important negative prognostic factor for breast cancer in males. Five-year survival rates for node-negative disease approaches 90% compared to 65% for histological node-positive disease. The number of involved nodes is also predictive of survival.

A Veterans Administration Hospital study has looked at the prognostic value of various factors such as M1B1, Her2, p53 mutation and ER and PR positivity in MBC and found that only advanced stage and Her2 positivity in

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Stage III and IV MBC affected survival being associated with worse outcome. Her2 neu positivity was associated with a higher number of metastatic lymph nodes. Other factors mentioned earlier could not be linked to outcome clearly.

In a retrospective analysis of 91 males with breast cancer with a median follow-up of 51.5 months, Masci et al. (2015), observed that patients with grade 3 tumors had a shorter overall survival (53.3% of patients versus 85.7% for patients with grades 1 and 2 tumors) as did a higher Ki67 score (>20%).

Men with a diagnosis of breast cancer are at increased risk of a second primary malignancy and need to be closely monitored. In a SEER database review that included 4,873 men with breast cancer diagnosed between 1973 and 2003, there was a 1.9% incidence of second primary MBC. In this study, 21% of men with breast cancer developed a second nonbreast malignancy; the most commonly reported second malignancies were prostate, colon, and genitourinary cancers.

Little is known about short- or long-term toxic effects of chemotherapy and local treatments in men, nor about psychological sequelae of the disease in this population. A recent comparison of Behavioural Risk Factor Surveillance System telephone survey data between 198 men without cancer and 66 men with a history of breast cancer (on an average 12 years post-diagnosis) found poorer physical and mental health in the breast cancer survivors. Obesity, diabetes and activity limitations due to a physical, mental, or emotional problem were more common in men with a history of cancer. Breast cancer may be socially isolating for men, who may feel stigmatized by their diagnosis because it is so strongly associated with women. It is unknown if men with breast cancer have greater difficulties with adjustment than men with other prognosis matched cancers.

CONCLUSION

Male breast cancer is rare. It is a disease of older men and presents approximately 10 years later than FBC. The similarity of both the age-standardized and age-specific incidence rate trends over time raises the possibility that there may be breast cancer risk factors that are common to both men and women. The phenotype, pathology, treatment, prognosis and survival of MBC differ in some aspects with that of FBC. The descriptive patterns show that the biology of MBC resembles the late-onset and ER-positive type of FBC. The most common initial symptom is a hard painless subareolar nodule. Treatment is usually modified Patey mastectomy with dissection of axillary nodes. Sentinel node biopsy can probably be applied routinely to men with a clinically negative axilla. Mortality and survival rates for male and FBCs have improved substantially over time, but progress in men has lagged behind progress in women.

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