Male Breast Cancer

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Abstract

Breast cancer is observed in men 100-fold less often than in women. The risk of breast cancer in men is approximately 1 in 1,000 throughout life. The American Association of Cancer predicted that 2,360 men would be diagnosed with breast cancer in 2014 and that 430 male patients with breast cancer would die. Anderson et al. reported on male breast cancer (MBC) from the Surveillance, Epidemiology, and End Result (SEER) database during the period of 1973–2005 and found an annual increase in incidence of 1.19 %, with a peak in 2000 of 1.24 cases per 100,000 men. The frequency is 0.1 deaths per 100,000 cases at 35 years of age and reaches up to 11.1 deaths per 100,000 cases after 85 years of age. The mean age of diagnosis of MBC is 67.68, which is 5–10 years older than for female breast cancer (FBC) patients in the USA, but in other parts of the world, such as the Middle East and South Asia, the age gap is smaller.

In a study based on an international population, the world-standardized incidence rates of breast cancer were 66.7 per 105 person-years in women and 0.40 per 105 person-years in men.

Previous studies have shown that MBC cases are significantly different from female cases, whereas new studies have reported that breast cancer has similar characteristics at the same stages in both genders.

Keywords

Male breast cancer • Sentinel lymph node • Mastectomy • Axillary dissection • Adjuvant therapy

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Introduction

Breast cancer is observed in men 100-fold less often than in women [1, 2]. The risk of breast cancer for men is approximately 1 in 1,000 throughout life. The American Association of Cancer predicts that 2,360 men will be diagnosed with breast cancer in 2014 and 430 male patients with breast cancer will die [3, 4]. Breast cancer is responsible for 0.1 % of cancer-dependent deaths in men [5, 6]. Similar to women, breast cancer is observed more frequently in the left breast in men [7]. The bilateral case rate is 1.4 % [8]. The incidence is lower in Japan, Colombia, Singapore, Finland, and Hungary, whereas the incidence is higher in North America and England and very high in some African countries [9, 10].

Anderson et al. reported on male breast cancer (MBC) from the Surveillance, Epidemiology, and End Result (SEER) database during the period of 1973–2005 and found an annual increase in incidence of 1.19 %, with a peak in 2000 of 1.24 cases per 100,000 men [11].

There is no difference in the frequency of death from MBC between Europe and the USA [3]. The frequency is 0.1 deaths per 100,000 cases at 35 years of age and reaches up to 11.1 deaths per 100,000 cases after 85 years. One percent of MBC is observed in males younger than 30, and 6 % of cases are detected below the age of 40 [12]. The mean age of diagnosis of MBC is 67.68, which is 5–10 years older than for female breast cancer (FBC) patients in the USA, but in other parts of the world, such as the Middle East and South Asia, the age gap is smaller [3, 13–16].

In a study based on an international population [17], the world-standardized incidence rates of breast cancer were 66.7 per 105 person-years in women and 0.40 per 105 person-years in men. Women were diagnosed at a younger median age (61.7 years) than men (69.6 years).

Previous studies have shown that MBC cases are significantly different from female cases, but new studies have reported that breast cancer has similar characteristics at the same stages in both genders [12].

Epidemiology and Risk Factors

The majority of cases are sporadic. Only 5–10 % of all male breast cancer cases are considered to be related to a genetic predisposition [18–21]. In a study investigating the familial characteristics of men with breast cancer, FBC or ovarian cancer cases were reported by 30 % of the families that included men with breast cancer [22, 23]. The risk of breast cancer in the sister or daughter of a patient with breast cancer is increased by two to threefold [10]. Breast cancer was reported in two brothers, one of whom also had prostate cancer [24]. BRCA1 is a suppressor gene that has been isolated and located on chromosome 17q. The risk of breast cancer increases in the presence of this germline mutation, and the disease appears at early ages in patients with mutations in BRCA1. BRCA2, which has been localized to chromosome 13, has been reported to be responsible for 70 % of hereditary breast cancer cases [25]. The genetic presence of the BRCA2 germline mutation is a risk factor for early-age MBC. A mutation in BRCA2 is not likely to exist in MBC cases without a family history of breast cancer [16, 22, 26]. BRCA2 and BRCA1 were detected by 77 % and 19 % of cases with familial MBC, respectively [27]. Breast cancer eventually develops in 5–10 % of men with BRCA2 mutations (and in a smaller proportion of those with BRCA1 mutations) [28].

In a study conducted in Iceland, mutations in BRCA2 were found at rates of 0.6 % in the community, 7.7 % in patients with FBC, and 40 % in the patients with MBC [20]. Breast cancer cases with the BRCA2 mutation generally have similar prognostic characteristics as the cases without the mutation; however, the nuclear grade tends to be higher in those with the mutation, and the frequency of p53 mutation is increased [22]. In another collaborative multicenter study from Italy [29], BRCA2 mutations were associated with a family history of breast/ovarian cancer ($p=0.0001$), a personal history of other cancers ($p=0.044$), and contralateral breast cancer (BC) ($p=0.001$). BRCA2-associated MBCs presented with high tumor grade ($p=0.001$), PR- ($p=0.026$), and HER2+ ($p=0.001$) status. Ding et al. reported

from the USA that the difference in BRCA2 mutation frequencies between cases with and without a family history of breast cancer was not statistically significant ($p=0.145$), suggesting that in males, family history is not a strong predictor of carrying a mutation [30]. They observed that carrying a pathogenic BRCA2 mutation showed a highly significant association with a high tumor grade ($p=0.001$) and a weak association with positive lymph nodes ($p=0.02$). Of the 97 BRCA2-negative MBC cases, they identified one PALB2 mutation with confirmed pathogenicity and one mutation predicted to be pathogenic, corresponding to a prevalence of pathogenic PALB2 mutations of 1–2 %. Based on their results and previous studies, they recommend genetic testing for BRCA2 for any diagnosed MBC case, regardless of the family history of breast cancer.

Data are mixed regarding the relevance of other germline mutations such as those in PALB2, the androgen receptor (AR), CYP17, and CHEK2 [31–34]. Other mutations that increase the risk of FBC (e.g., BRIP1 and RAD51C) have not been found to increase the risk of MBC [35, 36], and one study reports that polymorphisms in the vitamin D receptor do not appear to be associated with risk [37]. Lists of main risk factors for male breast cancer are listed in Table 23.1.

Table 23.1 Main risk factors for male breast cancer

Genetics	**Endocrine**
Klinefelter's syndrome	Liver disease
Family history of breast cancer	Exogenous estrogens
BRCA2 mutations	Androgen deficiency (prolactinoma)
BRCA1 mutations	
Ashkenazi Jewish men	
Cowden syndrome	
Environmental, occupational, and other factors	
Chest wall radiation	
Testicular disorders	
Undescended testes, congenital	
Inguinal hernia, orchiectomy	
Orchitis, infertility	
Lifestyle	
Obesity, alcohol, diet	
Occupational and environmental exposures	
Occupational exposure to heat	
High ambient temperature	
Exhaust emissions	
Electromagnetic field radiation	

In the studies conducted on the BRCA1 and BRCA2 genes, MBC was shown to have a greater association with the BRCA2 gene [18]. BRCA2 is considered a useful marker for identifying men with higher risk of breast cancer [18].

Mutations in p53, a tumor suppressor gene, result in Li-Fraumeni syndrome. It is reported that the incidence of breast cancer and many other tumor types increases when suppression disappears upon p53 mutation [15]. There is no convincing evidence for the association of MBC with gynecomastia, which is considered to be related to common hormonal risk factors [38].

Klinefelter's syndrome (genotype XXY) is a syndrome including characteristics such as less developed sex organs, gynecomastia, small testicles, aspermatogenesis, and increased FSH. It is the strongest risk factor for MBC, and the risk increases by 50-fold compared to a male with a normal genotype [39–43]. Hypertrophy in the breasts of such men is secondary to gynecomastia and the development of acini and lobules [44]. Patients with Klinefelter's syndrome have significant hyperestrogenemia in their blood, and the incidence of breast cancer in such male patients reaches 6 % [25]. Whether causes of gynecomastia other than Klinefelter's syndrome increase, the risk for MBC remains unknown. However, when slides from Klinefelter's syndrome patients with MBC are examined histologically, microscopic findings of gynecomastia are observed in 40 % of cases [45]. The most common side effect of finasteride, which is used for the treatment of prostate hyperplasia, is gynecomastia; additionally, breast cancer was reported in three patients who used finasteride [46].

In the MBC pooling project [47] involving a consortium of 11 case-control and 10 cohort investigations involving 2,405 case patients ($n=1,190$ from case-control and $n=1,215$ from cohort studies) and 52,013 control subjects, individual participant data were harmonized and pooled. Risk of MBC was significantly associated

with weight (highest/lowest tertile: OR = 1.36; 95 % CI = 1.18–1.57), height (OR = 1.18; 95 % CI = 1.01–1.38), and body mass index (BMI; OR = 1.30; 95 % CI = 1.12–1.51), with evidence that recent rather than distant BMI was the strongest predictor. Klinefelter's syndrome (OR = 24.7; 95 % CI = 8.94–68.4) and gynecomastia (OR = 9.78; 95 % CI = 7.52–12.7) were also significantly associated with the risk, independent of BMI, and diabetes emerged as another independent risk factor (OR = 1.19; 95 % CI = 1.04–1.37). Additionally, there were trends indicating relationships with cryptorchidism (OR = 2.18; 95 % CI = 0.96–4.94) and orchitis (OR = 1.43; 95 % CI = 1.02–1.99). Although age at the onset of puberty and histories of infertility were unrelated to risk, never having had children was statistically significantly related (OR = 1.29; 95 % CI = 1.01–1.66). Among individuals diagnosed at older ages, a history of fractures was statistically significantly related (OR = 1.41; 95 % CI = 1.07–1.86).

In men, obesity is associated with high levels of estrogen and low levels of testosterone and sex-hormone-binding globulin [48], leading to greater estrogen bioavailability. Thyroid diseases, marijuana use, and external estrogen cause gynecomastia, but their associations with MBC are much weaker. Only 2 of more than 17,000 patients who were treated with estrogen because of prostate cancer developed breast cancer [20]. Increases in estrogen circulation and hepatic metabolism may explain the increased incidence for MBC as follows: hepatic dysfunction because of cirrhosis and chronic malnutrition is common in some territories of Africa and is connected with increased rates of MBC [49]. The incidence of MBC is increased in regions where schistosomiasis is common. This parasitic infestation causes hepatic failure and hyperestrogenemia. In Egypt, where schistosomiasis is endemic, MBC was reported more frequently than prostate cancer [25].

Chronic liver diseases with other etiologies have also theoretically increased the risk for the development of MBC; however, severe hepatic dysfunction has a high mortality rate; thus, the increased risk may become significant [38]. MBC accompanying liver disease is observed in younger ages (40–50) and more frequently (15 %) in Zambia [10].

In testicular abnormalities that cause androgen deficiency, an increase in the incidence of MBC was reported in men with orchitis, undescended testicles, and testicle injuries [50, 51]. Radiation is also a risk factor for men and women. Cancer develops 12–36 years after contact with radiation [52]. Exposure to radiation of over 50–100 cGy during childhood or adolescence increases the risk of cancer similarly in both sexes [44, 49]. Unlike in women, white race does not appear to be a risk factor in men [53].

Work and environmental factors may also play an increasing role in MBC. Based on a multicenter case-control study that was conducted in eight European countries and included 104 cases and 1,901 controls, it was concluded that some environmental chemicals are possible mammary carcinogens [54]. Petrol, organic petroleum solvents, or polycyclic aromatic hydrocarbons are suspect because of the consistent elevated risk of MBC observed in motor vehicle mechanics. Endocrine disruptors such as alkylphenolic compounds may play a role in breast cancer. The prevalence is increased in those who work in high temperature ovens and steel factories because of cancer potentialization; in other words, testicular failure appeared as a result of heat [12, 18]. Vapors of gasoline and other flammable substances were shown to play a role in the appearance of breast cancer in men [54, 55].

Long-term therapy with the drugs which are commonly used today and cause hyperestrogenemia such as digital agents, cimetidine, methyldopa, and spironolactone has higher risk of breast cancer [56]. Obesity of which the frequency gradually increases in economically developed countries has become a social problem. Especially, obesity under age of 30 is a risk factor for breast cancer in women as well as men. The suggested mechanism of appearance is the increase in conversion of androgens into estrogen in increased fat tissue. Other risk factors include being unmarried, being Jewish, the presence of previous benign breast disease history, late puberty, and hypercholesterolemia [56].

Clinical Progress

Patients with MBC generally refer with a hard and painless mass located centrally under the nipple. The mass secondly settles in the upper-outer quadrant [57]. Nipple ulceration is commonly observed, but first referral with an efflux from the nipple is rare [25]. However, if serous-hemorrhagic efflux comes out of the nipple, the underlying disease is cancer in general (75 %). If metastasis exists, patients may complain about cough and bone pain [10]. It is more common in the left breast [58]. Bilateral masses are very rare (0–1.9 %). The period between onset of the disease and diagnosis is 18 weeks to 6 months [10]. Moreover, easy invasion of the dermal tissue in MBC because its superficial and central location causes to diagnose the disease during advanced stages [59].

Diagnosis

Breast cancer biology is distinct in men, but diagnostic approaches and treatments for men are generally extrapolated from those in women due to inadequate research in men [60]. Perhaps due to poor awareness of the disease and diagnostic delays, most (but not all) studies suggest that men are diagnosed with higher stage tumors and have a poorer prognosis overall [61, 62]. It often presents as a painless subareolar lump [63].

MBC is diagnosed with biopsy. Fine-needle aspiration biopsy (FNAB) may be performed in medical centers where experienced cytopathologists are employed. If FNAB is not appropriate, tru-cut biopsy should be performed. Removal of sufficient tissue is important both for diagnosis and determination of hormone receptors [12, 49]. Two studies that compared FNA with core and/or excision biopsies demonstrated that the former had sensitivity and specificity that approached 100 % [64]. Chest X-ray, bone scintigraphy, and liver enzymes should be assessed to determine invasion of the disease before the treatment [41]. Clinical examination is invaluable, although it must be noted that concurrent gynecomastia, the most common breast-related diagnosis in men, may mask an underlying tumor [65].

Gynecomastia which is generally confused with MBC in mammography is observed as a nodular lesion with three edges and small extensions in subareolar area. Edges are irregular in general. It should be noted that cancers may be hidden well in such benign density increases and nodularities. Although microcalcifications are not cancer specific, they are the most important traces for malignancy in mammography. Evaluation with mammography only is difficult for men [16, 65] (Fig. 23.1). Calcifications are not in spot or stick form like observed in women; they are generally wider and round. The mass is solid, spiculated, and located eccentrically associated with the nipple (Fig. 23.2) in general [65]. The mass in gynecomastia is symmetrically associated with the nipple. Breast skin retraction may exist in malignancies. Enlargements on axillary lymph nodes may be observed via mammography [66, 67]. Male patients with cancer on one breast may be followed by mammography to search a secondary tumor on the other breast. Cases with non-palpable breast cancer were reported by mammography in the normal breast which seems clinically normal.

Subareolar triangular, anechoic, and hyperechoic fibroglandular appearances exist in gynecomastia by ultrasound. Ultrasonographic microcalcifications in MBC are not detected in the ultrasound. Structural distortion, asymmetric

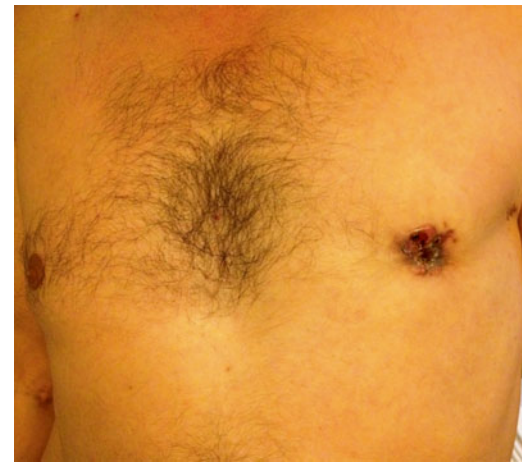

Fig. 23.1 Physical examination finding of a 45-year-old male showing ulceration around his nipple

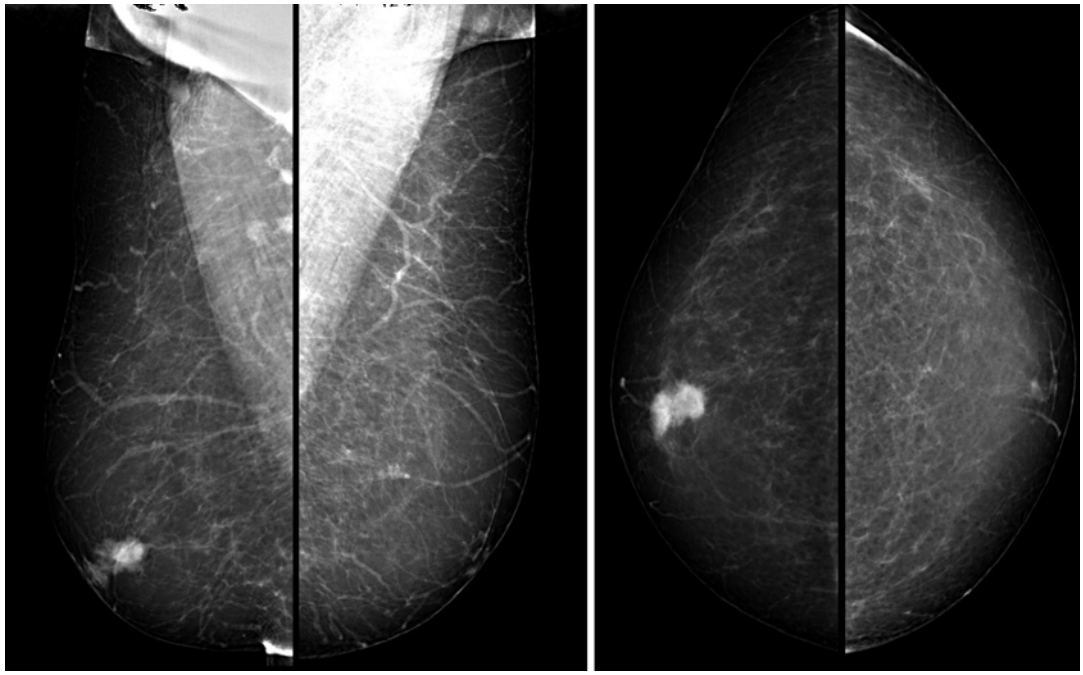

Fig. 23.2 Mammography imaging of a 65-year-old male patient with a malignant mass on his right breast

appearance in nipple shadows, and shadowing around the nipple may be detected by the ultrasound (Fig. 23.3). Ultrasonography generally visualizes a mass with hypoechogenicity and indistinct or irregular margins [65]. The use of ultrasound alone is deemed insufficient for male breast growths. However, much attention should be paid during diagnosis when suspicious changes are found by either ultrasound or mammography. In some cases, the combination of both techniques may be required for the final diagnosis [66, 67]. Clinical examination, ultrasound, and mammography may reduce the need for biopsy in patients who are considered to have a benign disease [68].

Smear examination is required for patients with nipple efflux. When a mass is detected on the breast of a man, a procedure should be run for histological diagnosis to definitively differentiate between benign and malign disease. This may be performed by fine needle aspiration, core needle biopsy, or open biopsy. A cytological examination performed by fine needle aspiration biopsy depends on the experience of the clinician and cytopathologist. In fact, the use of such a technique is safer with increased experience; however, fine needle aspiration biopsy is not commonly used for differentiation of the lesion on the male breast. The gold standard is open biopsy [49]. Cellularity, dyshesion, and morphism are important criteria for the diagnosis of cancer, which is also assisted by nuclear changes.

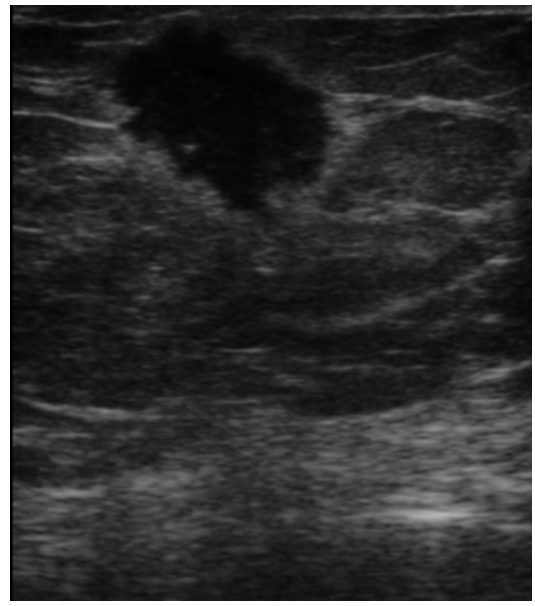

Fig. 23.3 Ultrasonographic imaging of a 65-year-old male patient with a malignant mass on his right breast

A mild cellularity or cellular failure exists in gynecomastia. Although anisonucleosis may exist in gynecomastia, a smooth surface of the membrane indicates a benign case. Honeycomb pattern, macronucleus, and mixed cell groups support malignancy [69].

Differential Diagnosis

The differential diagnosis should be made between gynecomastia and cancer for male breast masses. The most common unilateral or bilateral benign mass is gynecomastia [70]. It is generally detected by physical examination. Gynecomastia is characteristically a symmetrical, bilateral discoid under the nipple and areola. Carcinomas have an eccentric settlement and a hard mass; no sensitivity exists. Breast skin adjacencies may be observed both in gynecomastia and carcinoma. However, adjacency to the pectoral fascia, nipple efflux, nipple inversion, and ulceration are only detected in breast cancer. These characteristics are difficult to determine in adults, and a biopsy should be performed in any suspicious case [12]. Benign neoplasms are extremely rare in a male breast. Cystosarcoma phyllodes, phylloid papillomatosis, ductal papillomas, lipomas, and other tumor types that are not associated with the breast may be detected on the breast [49].

Pathology

The distribution of breast cancer in male and female patients differs because of the lack of lobule development in the male breast. Because a normal male breast does not contain any lobular elements, the most frequent cancer type detected in men is invasive ductal carcinoma (85–90 %) [71]. Invasive lobular cancer or lobular carcinoma in situ has been reported in several cases with a normal genetic profile and without any history of hormone use [8]. All histological types of the breast cancer observed in women (ductal carcinoma in situ, medullary, papillary, and colloid) can also be observed in men (Table 23.2). Inflammatory breast cancer and Paget disease were also reported in men. Granular cell tumor, adenoid cystic carcinoma, myofibroblastoma, carcinoid tumor, and metastatic tumors (generally originating from the lungs and prostate) are other possible tumor types [38].

Table 23.2 Frequency of histological types observed

Histology	Incidence (%)
Invasive ductal carcinoma	90
Ductal carcinoma in situ	10
Invasive papillary carcinoma	2
Medullary carcinoma	2
Mucinous carcinoma	1
Paget disease	1
Lobular carcinoma	1

The vast majority of MBCs are hormone sensitive [72, 73]. MBC shows higher estrogen (75–94 %) and progesterone (67–96 %) hormone receptor positivity than does breast cancer in women. In the National Cancer Institute's Surveillance, Epidemiology, and End Result (SEER) database between 1973 and 2005, 92 % of the 5,494 MBCs but only 78 % of the 838,805 FBCs were estrogen receptor (ER) positive [53]. Receptor positivity was not reported to be associated with age, histological grade, stage, and axillary lymph node involvement [8].

Information with other molecular and genetic markers is limited for MBC [74]. The Mayo Clinic assessed 111 cases and reported positive estrogen receptors in 91 % of cases; positive progesterone receptors in 96 % of cases; positive androgen receptors in 95 % of cases; the expression of bcl-2, which is a determinant for apoptosis, in 94 % of cases; p53, which is one of the proto-oncogenes, in 21 % of cases; HER-2 in 29 % of cases; and cyclin D1, which is one of the cell cycle regulatory proteins, in 58 % of cases [75]. The overexpression of cyclin D1 and c-myc may correlate with better outcomes [76]. In addition, studies have reported higher rates of HER-2 in 40 % of cases and p52 in 54 % of cases [10, 72, 77, 78].

Treatment

Treatment for Early-Stage Male Breast Cancer

Treatment in early-stage MBC patients is surgical followed by adjuvant endocrine, chemotherapy, or

radiotherapy according to the prognostic factors. A large population-based study conducted in Europe and Asia demonstrated that males with BC were significantly less likely to receive surgery and radiation therapy (RT) than females with BC. However, the rates of the use of chemotherapy and hormonal therapy were similar [17].

Surgical Treatment

Surgical options for men with early-stage breast cancer include breast-conserving therapy and mastectomy [79]. Standard treatment is mastectomy and sentinel node biopsy or axillary lymph node dissection [23, 80]. Radical mastectomy has been performed throughout the history of MBC. Today, this method is applied for wide chest wall invasions only. Currently, most patients undergo modified radical mastectomy [79]. The rarity of breast-protective therapy may be because men have less breast tissue than women and have tumors located more centrally; in addition, male patients do not request breast-protective therapy [18].

In a study from the USA, the Surveillance, Epidemiology, and End Result (SEER) database was used to identify all MBC patients who underwent either mastectomy or less than mastectomy between 1983 and 2009 [81]. A total of 4,707 (86.8 %) men underwent mastectomy and 718 (13.2 %) underwent lumpectomy. They mentioned that lumpectomy was performed in a small but growing proportion of MBC patients. These patients were not only older and more likely to have advanced disease at the time of diagnosis but were also less likely to receive standard therapies such as lymph node sampling and adjuvant radiotherapy. Despite those observations, breast cancer-specific survival was unaffected by the type of surgery. A recent report found a considerable desire by men to preserve their breast to maintain a positive self-image [82].

A retrospective analysis of MBC identified a total of 42 patients to undergo localized treatment [83]. Musculoskeletal functionality (tissue fibrosis, arm edema, and range of motion) and treatment outcome (local-regional control, disease-free survival, and overall survival) were evaluated. The actuarial overall 1-year fair-poor documented tissue fibrosis, arm edema, and decreased range of motion rates were 13 %, 23 %, and 27 % for patients receiving MRM; 25 %, 0 %, and 50 % for patients who underwent total simple mastectomy (TSM); and 13 %, 0 %, and 0 % for those undergoing BCS, respectively. The overall survival and disease-free survival were not significantly different between the groups. These data suggest that breast conservation therapy may be considered a reasonable local treatment option for male patients presenting with breast cancer because it may offer functional advantages over mastectomy with comparable rates of local control and disease-free survival and overall survival.

In the guidelines of the American Society for Clinical Oncology, sentinel lymph node biopsy is reported as acceptable in MBC [16, 84]. More radical surgical procedures do not improve survival. Preoperative chemotherapy may be useful for cases with a critical tumor load. Simple mastectomy or localized tumor excision can be performed for patients who have a metastatic disease or non-suitable overall status; this may be combined with postoperative radiotherapy [9].

Adjuvant Chemotherapy

The benefit of systemic adjuvant treatment for MBC was not assessed in randomized clinical surveys; however, progress and response to the therapy in patients with metastatic MBC is similar to that in female patients. Therefore, patients with early-stage MBC are considered to benefit from adjuvant therapy [4]. There is not yet sufficient information about various prognostic factors for selecting specific adjuvant chemotherapy. Generally, the prognostic factors used for women are also valid for men. Deciding on the treatment is difficult, particularly for lymph node-negative cases or cases with one to three positive lymph nodes and strongly positive for estrogen receptor. Chemotherapy is applied to lymph node-negative patients according to the indications in FBC. There is an indication for chemotherapy in those with positive lymph nodes [85]. The same chemotherapeutic drugs are used both for male and female patients. The agents generally used are CMF (cyclophosphamide, methotrexate, 5-fluorouracil) and FAC

(5-fluorouracil, doxorubicin, cyclophosphamide) regimes. However, treatment regimens including doxorubicin are superior to classical CMF [9]. Bagley [86] and Patel [87] reported in two small-scaled retrospective studies that survival was increased by adjuvant systemic therapy. Bagley reported a 5-year survey in which patients with stage II MBC who received 12 courses of CMF therapy showed a survival rate of 80 % and a mean overall survival of 98 months; he also suggested adjuvant therapy for its benefits. The precision of such data should be supported by prospective studies; however, because MBC is rare, it is difficult to perform large randomized studies.

Adjuvant Endocrine Therapy

Based on the positive clinical study results of adjuvant endocrine therapy solely or in combination with chemotherapy in female patients with early-stage breast cancer, adjuvant endocrine therapy is also recommended for male patients [88]. Likewise, in a Chinese retrospective single-institution study of 72 male patients over 40 years old, a multivariate regression found that the receipt of endocrine therapy was associated with better survival [89]. Tamoxifen or another hormone treatment is recommended for male patients with estrogen receptor-positive cancer, based on the prognostic factors for female patients [85]. Adjuvant therapy combined with radiotherapy was applied after surgery in 39 patients with Stage II and Stage III MBC with positive axillary nodes; the 5-year disease-free survival rate was reported as 55 % and the overall survival as 61 %. For former patients who were not treated systemically, the 5-year disease-free survival and overall survival were reported as 28 % and 44 %, respectively. Based on these indirect comparisons, tamoxifen increases both 5-year disease-free survival and overall survival. The long-term use of tamoxifen is suggested because it does not cause severe bone marrow toxicity or drug-induced death. However, tamoxifen may not be tolerated well in male patients. Men often experience bothersome symptoms from endocrine therapy, and approximately one in four discontinue treatment early because of hot flashes or sexual dysfunction [90, 91].

A limiting factor in the duration of tamoxifen therapy in men is the high incidence of adverse effects, with 20 % of participants in one study discontinuing therapy as a result. Common adverse effects include weight gain, sexual dysfunction, hot flashes, neurocognitive deficits, and thromboembolic events [91]. One study reported few adverse effects of tamoxifen [15]. However, further studies reported high rates of treatment-limiting side effects upon tamoxifen treatment in male patients, including a decrease in libido (29.2 %), weight gain (25 %), hot flashes (20.8 %), mental disorders (20.8 %), depression (16.6 %), sleeping disorders (12.5 %), and deep vein thrombosis (4.1 %). The rate of those who discontinued the treatment because of side effects was reported to be as high as 20.8 % within 1 year, compared with approximately 4 % for women who received tamoxifen [92]. Eggeman et al. [93] studied adjuvant therapy with tamoxifen compared to aromatase inhibitors for 257 hormone receptor-positive MBC patients. They found that the overall survival with MBC was significantly better after adjuvant treatment with tamoxifen compared to adjuvant treatment with an aromatase inhibitor. In conclusion, tamoxifen should be considered the treatment of choice for hormone receptor-positive MBC.

Adjuvant Radiotherapy

Postsurgical radiation criteria are generally extrapolated from data in women [94]. There are no prospective randomized studies evaluating the clinical effects of postoperative adjuvant radiotherapy in MBC. A case series of 75 men treated with curative intent in Ontario found significantly improved local recurrence-free survival in the 46 patients who received postmastectomy radiation, but their overall survival was not different [95].

Such studies have different technical characteristics, making clinical assessments difficult. Radiotherapy decreases local and regional relapse after mastectomy; however, it is not significantly effective for survival [41]. Radiotherapy should be considered based on similar criteria as for female cancer patients, and the indications are related to local findings. Tumors invading the skin and the chest wall require radiotherapy. Skin

and nipple invasion occurs more frequently in men than in women. This may be associated with breast size and the distance of the tumor to these formations. Radiotherapy is imperative for patients who choose breast-protective surgery [10]. Consistent with the results of two studies on the benefits of radiotherapy after mastectomy on overall survival for patients with FBC, radiotherapy was considered a requirement after mastectomy for male patients with positive axillary lymph nodes [96]. Raguse et al. [97] showed that radiotherapy reduced the first 2-year local relapse (from 60 % to 20 %) for the patients with positive nodes. However, a decrease in local relapse does not reflect overall survival. Postoperative radiotherapy is a basic component of the treatment plan for localized advanced tumors [9, 98].

Treatment in Advanced-Stage Male Breast Cancer

Metastasis and the relapse pattern in MBC are similar to that in women. Metastasis is detected in 4–17 % of patients during diagnosis. Metastasis will develop in 18–54 % of the patients who do not have metastasis at the beginning. Distant metastases are commonly observed on the bones, lungs, and brain [87]. Isolated metastases are best treated by excision or radiotherapy. Systemic treatment options include ablative hormone treatment, additive hormone treatment, and chemotherapy; however, ablative hormone treatment is no longer commonly used. Ablative hormonal treatments include orchiectomy, adrenalectomy, and hypophysectomy. In 1942, bilateral orchiectomy was shown to be effective as hormone therapy in the treatment of patients with metastatic MBC [86]. Orchiectomy has a low morbidity rate. The remission rate was reported as 55 % in a study including 271 cases between 1959 and 1987 [12]. Some researchers have reported a remission rate of 60–83 % by this treatment [99]. The basis for performing adrenalectomy was not clearly explained. The treatment response in an adrenalectomy series including 38 patients was shown to be 7.4 % [12]. In another study, the effect of adrenalectomy followed by orchiectomy was reported as 80 % [99]; however, when chemotherapy and hormone treatment options are available, adrenalectomy followed by orchiectomy is not preferred because of the low achievement rate and the presence of morbidity.

Tamoxifen and other antiestrogen substances used as additive hormonal treatments, such as clomiphene and nafoxidine, bind to estrogen receptors and reduce the hormone intake of the target tissue. Tamoxifen has fewer side effects and is more commonly used for FBC than are other drugs. A response rate of 48 % was obtained in 73 male patients with metastatic breast cancer who received tamoxifen treatment. All the patients responded to tamoxifen treatment, regardless of whether they responded to orchiectomy. Tamoxifen and orchiectomy are two individual treatment methods that do not show cross resistance [12, 41, 100]. Second-generation hormone therapy is currently used for FBC by inhibiting estrogen production through aromatase inhibitors, and good outcomes have been obtained. The role of aromatase inhibitors in male patients is limited. A case series including five patients who were treated with aromatase inhibitors was published [101]: three of the five patients had a stable period; however, those patients showed slow disease progress before adding aromatase inhibitors, and no objective response could be obtained from the patients. In another study, anastrozole was tested on healthy male volunteers [102]. Unlike in women, men treated with anastrozole did not show complete estrogen suppression; instead, a decrease of 50 % was observed in the estradiol concentration. Furthermore, testosterone levels were increased by 58 %. Two case studies reported responses to letrozole [103, 104]. Additional studies are required for evaluating both the adjuvant and metastatic efficiency of aromatase inhibitors on MBC. Luteinizing hormone-releasing hormone (LH-RH) agonists were reported as effective for the treatment of MBC with or without antiandrogens [105–107]. An LH-RH analogue drug called buserelin was introduced for use in advanced MBC. This drug first causes stimulation and then causes a paradoxical decrease in LH and FSH release; it presents an effect that can be called

medical orchiectomy. Partial remission was obtained for 12 months in one of five patients who were treated with buserelin only. This period was extended to 24 months by the addition of flutamide, which is a nonsteroidal antiandrogenic agent. A partial response for 15 months was observed in four of five patients who were treated with a combination of buserelin and flutamide [12]. Treatments including progesterone (megestrol acetate and medroxyprogesterone acetate) may be used for metastatic MBC; however, these studies included fewer patients. A 7-month partial remission was observed in five of six patients treated with a high dose of medroxyprogesterone acetate [12, 41, 100].

Prognosis

Men with breast cancer reportedly have poorer outcomes than matched women patients, even at the same disease stages, which might be because of variations in tumor biology between male and female patients [108]. Mortality in MBC has continued to improve over the past 30 years, despite its late presentation [12, 23]. The most important prognostic factor in MBC, similar to FBC, is positive axillary lymph nodes [45, 57, 72, 89, 98, 109]. The poorer progress in male patients was explained by the anatomic location of the tumor. It has been reported that nipple invasion occurs very early because of such placement, and increased lymphovascular invasion and higher axillary lymph node invasion were observed compared to FBC, despite the small tumor size; those characteristics and the referral of the patient at advanced stages result in poor prognosis [110, 111]. When matched by stage and age, men appear to have a similar or better prognosis compared to women [17, 112].

In an international population-based study including 459,846 women and 2,665 men diagnosed with breast cancer in Denmark, Finland, Geneva, Norway, Singapore, and Sweden over the last 40 years, male patients had a poorer 5-year relative survival ratio than women (0.72 [95 % CI, 0.70–0.75] *vs.* 0.78 [95 % CI, 0.78–0.78], respectively), corresponding to a relative excess risk (RER) of 1.27 (95 % CI, 1.13–1.42). However, after adjustment for age and the year of diagnosis, stage, and treatment, male patients had a significantly better relative survival from breast cancer than female patients (RER, 0.78; 95 % CI, 0.62–0.97) [13].

In a multivariate analysis of the prognostic factors performed on patients with MBC, tumor size and nodal invasion were presented as significant prognostic factors [72]. Published data also indicate that advanced age is a predictor of lower overall survival [113]. Guinee et al. [114] showed that both axillary lymph node involvement and clinical tumor size play important roles in prognosis in 335 patients. Patients with palpable axillary lymph nodes have a twofold greater risk for disease-related death, and a tumor diameter larger than 3 cm increases the risk of treatment failure. Fixation of the tumor to the skin or chest wall and tumor ulceration was reported more often in men than in women, but these factors were not shown to affect prognosis in multivariate analyses [49].

In a retrospective analysis of Egyptian patients, the collective 5-year survival in this cohort was 46.4 % [115]. Kiluk et al. reported that the 5-year survival estimates for node-positive and node-negative diseases were 68.5 % and 87.5 %, respectively, ($p=0.3$) [80]. Ethnic differences might also affect the prognosis of MBC [116]. In a Turkish cohort of 86 male patients treated over 37 years, Selcukbiricik and his coworkers reported a 65.8 % 5-year overall survival rate [117]. Similar in an Iranian cohort of 64 patients, the 5-year overall survival rate was 66 % [13].

The most significant protective factor is ER and PR receptor positivity. The significance of HER2 status in MBC remains unclear because there are few studies that have assessed its significance in terms of treatment options and prognosis [23]. There is no demonstrable correlation between Ki-67 expression and MBC prognosis [118]. To identify risk factors, the period between the appearance of the symptoms and diagnosis and less differentiated tumor must indicate a bad prognosis [12]. The prognosis of ductal-type carcinoma is worse than that of the medullary, col-

loidal, and papillary types [41]. In another study, no connection could be found between C-erbB2 and c-myc oncogenes, p53 suppressor genes, and survival [119]. The overexpression of cyclin D1 and c-myc may correlate with better outcomes [76]. One recent study identified more high-grade, progesterone-receptor negative, HER2-positive disease male patients who carried BRCA2 mutations [29], and earlier research found a poorer prognosis in men with BRCA2-associated tumors.

Survivorship issues in men may include sexual and hormonal side effects of endocrine therapies and unique psychosocial effects of the disease [60]. In a quality of life and symptom survey over MBC survivors, patients experience substantial sexual and hormonal symptoms [120].

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