Male Breast Cancer

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63.1 Introduction

Breast cancer (BC) is often mistakenly thought of as a female-only disease. Aside from the expected cultural explanations, the simple fact is that male BC (MBC) is rare. To date, in Western countries, MBC accounts for less than 1% of all cancers in men and less than 1% of all BCs, but its incidence is increasing [1, 2].

The earliest reference to BC in the Edwin Smith Surgical Papyrus from Egypt (3000–2500 BC) appears to have referred to a man [3, 4]. The first clinical description of an MBC case is in the early fourteenth century and is attributed to John of Arderne (1307–1390) who recorded the several-year evolution of nipple ulceration in a priest, with the subsequent development of BC [5]. Many years later, in 1842, Domenico Antonio Rigoni-Stern showed to the Congress of the Italian Scientist that the risk of BC was greatly increased in nuns compared to other women, and, intriguingly, he concluded his presentation saying that "the four men found to have died of BC were all priests" [6].

Because of its rarity, MBC is often compared with FBC, and our current understanding regarding MBC biology, pathology, and treatment strategies has been largely extrapolated from the more common female counterpart. Current epidemiologic and pathologic data, such as age-frequency distribution, age-specific incidence rate patterns, and prognostic factor profiles, suggest that MBC is like postmenopausal FBC [7]. Although MBC resembles postmenopausal FBC, clinical and pathologic characteristics of MBC do not exactly overlap FBC. Compared with FBC, MBC occurs later in life with more advanced stage, lower histologic grade, and more frequent estrogen receptor (ER)- and progesterone receptor (PR)-positive (ER/PR+) status [8, 9]. Higher stage and advanced age at diagnosis are negative prognostic factors, and, although rare, MBC remains a substantial cause for morbidity and mortality in men.

There is very little research on the management and care of MBC, and, due to the low incidence of MBC, studies are often small and underpowered. Thus, to date, therapy has been based largely on biomarkers developed for FBC, and MBC treatment generally follows the same indications as postmenopausal FBC. The outcome for men is the same as women stage for stage, but overall the prognosis tends to be worse in MBC [7]. This is usually due to a delay in presentation, leading to a large proportion of patients presenting with advanced-stage disease, and older age at diagnosis, leading to the coexistence of possible comorbidities. Overall, BC mortality and survival rates have improved significantly over time for both male and female BC, but the improvement for male is smaller if compared to female patients [9]. The different treatment outcomes may suggest a non-appropriate utilization of treatment options and a possible existence of different underlying pathogenetic mechanisms between male and female BC.

Today, thanks to the increasing number of collaborative studies and to the combination of data derived from new high-throughput technologies, we are now able to hypothesize that despite the similarities between female and male BC, MBC could be rather considered a distinct pathology.

63.2 Epidemiology

MBC incidence varies greatly in different geographical areas and ethnic groups and is correlated with FBC incidence worldwide [10]. Indeed, the worldwide variation of MBC resembles that of FBC, with higher rates in North America and Europe and lower rates in Asia [11]. A substantial high proportion of MBC cases have been reported in Africa, particularly in Uganda and Zambia [12]. These relatively high rates have been attributed to endemic infectious diseases causing liver damage leading to hyperestrogenisms. Overall, black men have a higher incidence of MBC (1.8 per 100,000)

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compared to the average incidence. By contrast, the annual incidence of MBC in Japan is significantly lower (5 per 1000,000) than the average incidence (1 per 100,000), comparable to the lower than the average incidence of FBC in this country [8, 13].

MBC incidence is increasing [2]. Data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database indicates that in the USA the incidence of MBC has been increasing during the last 20 years, from about 1 per 100,000 to around 1.2 per 100,000 (SEER 13 Registries Database). Data from the United Kingdom Association of Cancer Registries (UKACR) have reported that in the UK, MBC incidence is on the increase and parallels US data over a similar period of time [14].

Age-specific incidence rates for MBC increase linearly and steadily with age with a peak incidence in the late 60s. In contrast, FBC increases rapidly until around age 50 and then increases at a slower rate for older women (Fig. 63.1). MBC cases are diagnosed at a more advanced age than FBC. Age of BC presentation in males is mostly in the late 60s, which is about 10 years greater than in female. In the SEER database, the median ages at diagnosis of BC were 68 and 61 years in males and females, respectively. The differences in incidence rates and time trends between males and females may reflect gender-related differences in risk factors and/or different underlying pathogenetic mechanisms. On the other hand, the correlation between male and female BC incidences indicates the existence of common risk factors for BC in both genders.

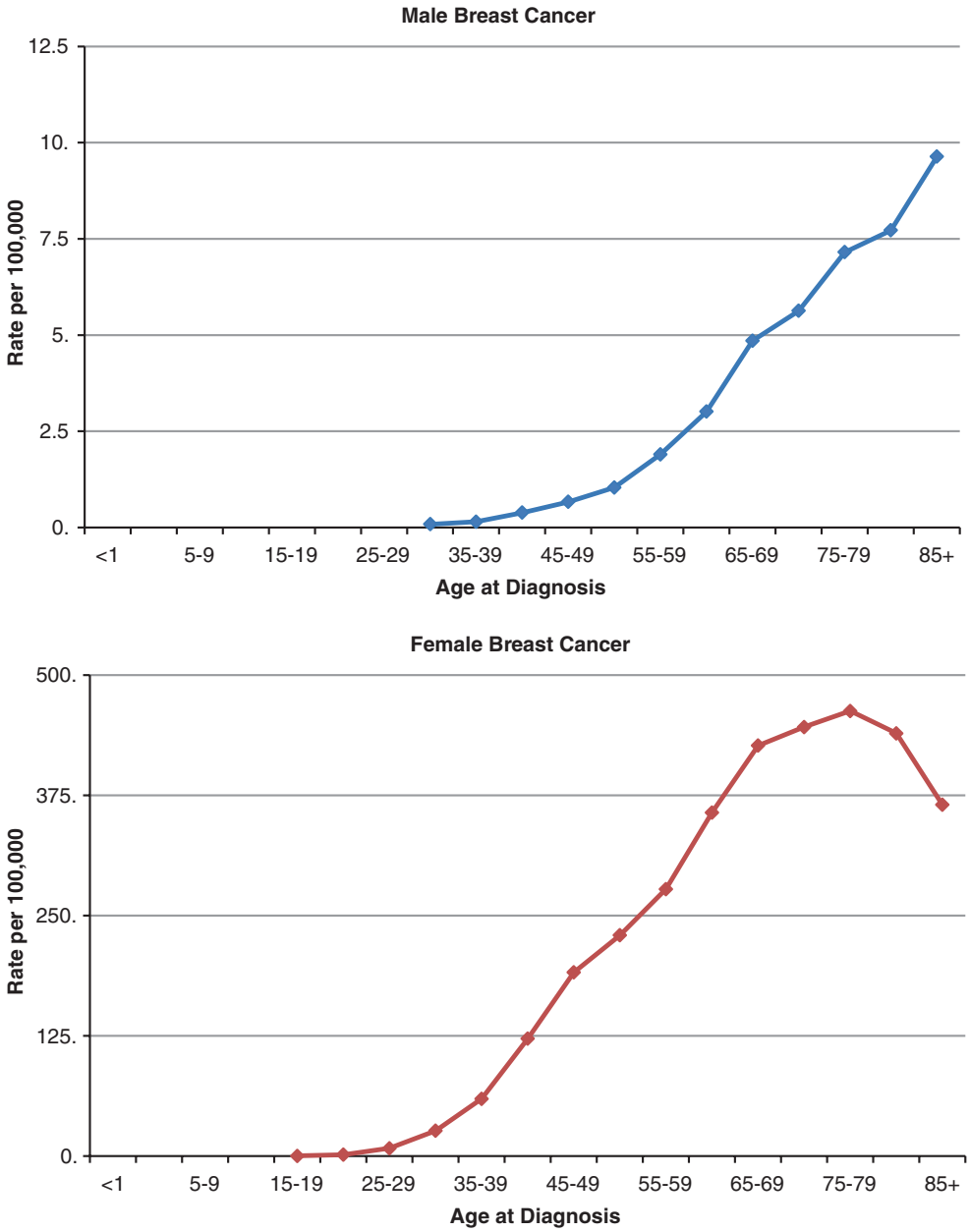

Fig. 63.1 Age-specific incidence rates (per 100,000) for male and female invasive breast cancer in white US population. Data source: SEER 18, years 2003–2012

Table 63.1 Risk factors for male breast cancer

Risk Factors	Genetic	Hormonal	Environmental
Well established	Breast cancer family history	Increased estrogen exposure	Radiation
	BRCA1/BRCA2	Deficiency of testosterone	
	Klinefelter's syndrome	Testicular disease	
Possible	*CHEK2*	Obesity	Heat
	PALB2	Diabetes	Electromagnetic fields
	SNPs	Liver damage	Polycyclic aromatic hydrocarbons
Suspected	Cowden syndrome	Gynecomastia	Alcohol
	Lynch syndrome		Tobacco

63.3 Risk Factors

Risk factors for MBC include genetic, hormonal, and environmental factors (Table 63.1).

63.3.1 Genetics

About 20% of male patients with BC have positive family history for BC. Men with a positive first-degree family history have a twofold increased risk of BC. The risk increases with increasing numbers of first-degree relatives affected, and a particularly enhanced risk (more than ninefold) is reported for cases with both an affected mother and an affected sister [15]. About 2% of male patients with BC develop a second primary BC, and more than 20% develop a second non-breast tumor, more frequently prostate, colon, and genitourinary cancer. Men who have family members with Cowden syndrome and Lynch syndrome are also at increased risk for BC [16, 17]. As both these syndromes and MBC are rare, it is difficult to determine as to whether germline mutations in these genes increase the risk of MBC.

Mutations in the two major high-penetrance BC genes, *BRCA1* and, predominantly, *BRCA2*, account for approximately 10% of MBCs, outside populations with *BRCA* founder mutations [18]. In Icelandic population, for example, the *BRCA*2 999del5 founder mutation is implicated in about 40% of MBC cases [19]. Mutations in *BRCA1* and *BRCA2* genes are often found in MBC patients who have multiple cases of breast and/or ovarian cancer in their family, but have also been found in MBC patients with no breast and/or ovarian cancer family history. This evidence and the rarity of the disease indicate that every man who has BC should be routinely screened for *BRCA1* and *BRCA2* mutations, regardless of family history, which could prove to contribute invaluable genetic information to family members. Men with *BRCA1/2* mutations have an increased risk of BC compared with general population and develop BC at younger age compared with non-mutation carriers. The lifetime risk of developing MBC has been estimated to be in the range of 1–5% for *BRCA1* and 5–10% for *BRCA2* mutation carriers, compared with a risk of 0.1% in the general population [20, 21]. The median age at BC diagnosis in male *BRCA1* and *BRCA2* mutation carriers is earlier (62 years) than that of the general population (68 years) (SEER 13 Registries Database).

Two genes, *CHEK2* and *Partner/Localizer of BRCA2* (*PALB2*), both functionally related to *BRCA1* and *BRCA2* in DNA repair pathways, also play a role in MBC susceptibility as moderate-penetrance genes. In certain populations, the *CHEK2* 1100delC mutation confers an increased risk of MBC, particularly in *BRCA1* and *BRCA2* mutation-negative BC families. However, this association is not so evident in MBC cases unselected for family history, and the contribution of the *CHEK2* 1100delC variant to MBC predisposition varies from one ethnic group and from one country to another [22–24]. Mutations in *PALB2* have been reported in families with female and male BC cases [25–27]. A fourfold higher frequency of MBC among relatives of *PALB2* mutation carriers has been shown. BC risk estimates for male *PALB2* mutation carriers still remain to be precisely assessed; however, *PALB2* may have an important role in MBC predisposition, at a comparable extent as for FBC [28].

A number of single nucleotide polymorphisms (SNPs) are implicated as low-penetrance alleles in MBC genetic predisposition [29]. The majority of SNPs that are associated with MBC risk are the same as those associated with FBC risk, but it appears that the magnitude of risk conferred by them differs between the two diseases. In particular, two SNPs (rs3803662 and rs1314913) have been identified significantly associated with MBC risk [30]. The rs3803662 localizes to the TOX High Mobility Group Box Family Member 3 (*TOX3*) gene (mapping to 16q12.1) and is a known modifier of FBC risk [31]. As shown for rare variants in *BRCA2* and *CHEK2* genes, the association with risk for this SNP is greater in males compared with females [30]. The rs1314913 SNP, located in intron 7 of the *RAD51B* gene (mapping to 14q23-24.2) belonging to RAD51 DNA repair family, is specifically associated with increased MBC but not FBC risk, supporting defined difference between male and female disease [32]. While the risk associated with these SNPs is low, they are likely to be

responsible for a substantial percentage of hereditary and sporadic MBCs because of their high frequency in the population.

63.3.2 Endocrine

MBC is recognized as being a hormone-dependent malignancy, and it is widely accepted as an estrogen-driven disease, specifically related to hyperestrogenism [33]. Clinical disorders associated with imbalanced estrogen/androgen ratio that result in abnormal estrogen exposure represent a major risk. Men affected with Klinefelter's syndrome, a rare congenital condition characterized by a 47 XXY karyotype and high levels of estrogens and low levels of testosterone, have been shown to have 20- to 50-fold increased MBC risk [34].

Other medical conditions linked to altered endogenous hormones including diabetes, orchitis, cryptorchidism, and gynecomastia have possible influences on MBC risk [35]. In addition, liver disease, leading to hyperestrogenism, emerged as a significant risk predictor of MBC, particularly among black men [36]. Conditions increasing exposure to estrogen or decreasing exposure to androgen, such as the long-term use of antiandrogens and estrogens in the treatment of prostate cancer, the exogenous administration of estrogen to transsexuals, or abuse of steroids for physical performances, have also been implicated as causative factors for MBC [37–39]. Elevated risks of MBC have also been related to a variety of other conditions associated with altered endogenous hormones, with the most consistent association being observed with obesity [40, 41]. Obesity is associated with an increased risk of postmenopausal FBC, presumably through peripheral conversion of androgens to estrogens. In men, obesity is associated with decreased testosterone and sex hormone-binding globulin levels but increased estrogen levels [42, 43], thus leading to greater estrogen bioavailability.

63.3.3 Environmental and Lifestyle Risk Factors

Ionizing radiations, occupational exposure to heat, and electromagnetic radiation have been considered as possible causal cofactors in the etiology of MBC [12]. Additional clues to a potential importance of other occupational exposures derive from studies showing elevated MBC risks among men exposed to polycyclic aromatic hydrocarbons [18, 44]. Some lifestyle factors have also been involved in the etiology, including alcohol and tobacco exposures, although results have varied across investigations [45].

63.4 Histopathology

63.4.1 Histology

The histology of BC occurring in men is generally similar to that occurring among women although the distribution of the histological types is different. The majority of MBCs are invasive ductal carcinoma (more than 80%) followed by ductal carcinoma in situ (about 10%). Lobular histotype is much less common in men (1.5%) than in women, due to the absence of terminal lobules in male breast tissue [46, 47]. Lobular histotype has been reported in association with Klinefelter's syndrome and, rarely, in men with no previous history of estrogen exposure. The rare tumor types, such as medullary, tubular, mucinous, and squamous carcinomas, are also reported in men although they are rarer than in women. On the other hand, papillary carcinoma is more frequent in men than in women. Both Paget's disease and inflammatory carcinoma are observed with equal frequency (about 1%) in both genders [12]. The majority of MBCs are low histologic grade [46, 47]. Data from the SEER 13 database show that 13% of MBCs are Grade 1 (G1), 50% Grade 2 (G2), and 39% Grade 3 (G3) tumors (Table 63.2) [43].

63.4.2 Biomarkers

The great majority of MBCs are ER+ and PR+ with more than 90% of tumors being positive for ER and about 85% for PR (SEER13, [43]). As reported for FBC, the percentage of men with ER+ BC significantly increases with patient age [1, 8]. Rates of androgen receptor (AR) expression in MBC have been variable in different cohorts, ranging from 39 to 95% [12, 48, 49]. Data about HER2 expression in MBC are inconsistent most likely because of small studies and of not standardized technical approaches. Studies performed by using both immunohistochemical (IHC) and fluorescence in situ

Table 63.2 Histopathology of male breast cancer

Histology	%
Invasive ductal carcinoma	85–95
Ductal carcinoma in situ	5–10
Invasive papillary	2–5
Lobular	1–1.5
Medullary	2
Mucinous	1
Paget's	1
Biomarkers	**%**
ER	90
PR	85
AR	39–95
HER2	15

hybridization (FISH) analyses report HER2 overexpression in about 15% of MBCs [50, 51].

Based on immunophenotypic characteristics, MBC can be classified into different molecular subtypes [50, 52]. Luminal A (ER+ and/or PR+, HER2-) subtype has been reported as the most common subtype in MBC (more than 85%), whereas Luminal B (ER+ and/or PR+, HER2+) subtype has been less frequently observed (about 12%). Triple-negative (ER-, PR-, HER2-) subtype and HER2-positive (ER-, PR-, HER2+) subtype have been rarely identified in MBC (about 1%).

63.4.3 BRCA1/2 Male Breast Cancer

Generally MBC presents with lower histologic grade tumors than FBC. In contrast, MBC associated with *BRCA2* mutations presents with higher histologic grade compared both with FBC in *BRCA2* mutation carriers and with MBC in the general population from SEER [53]. In particular, high histologic grade breast tumors are more frequent among male *BRCA2* mutation carriers diagnosed at younger ages (below 50 years) than among those diagnosed at older ages. Thus, the identification of a specific *BRCA2*-associated phenotype suggestive of an aggressive behavior may define a subset of MBC patients (i.e., patients with high-grade breast tumors and with young age at diagnosis) who might particularly benefit from adjuvant chemotherapy. A similar trend is also observed for *BRCA1* mutation carriers. Overall, *BRCA1/2* MBCs display distinct pathologic characteristics compared to *BRCA1/2* FBCs. These findings should lead to the development of gender-specific risk-prediction models and guide clinical strategies appropriate for MBC management.

63.5 Clinical Presentation and Diagnosis

Men with BC are more frequently diagnosed at a more advanced age and with a more severe clinical presentation, with greater tumor size and a more frequent lymph node involvement, than women with BC. In general, this is thought to reflect diagnostic delay in a population unaware of its risk and not appropriately encouraged to undergo routine BC screening. Despite increasing awareness of MBC, there remains an average delay from the onset of symptoms to diagnosis of 6–10 months [54].

The most common symptom of BC in men is a painless lump. The majority of MBC patients present a palpable subareolar mass. Because of the unique anatomy of the male breast, characterized by the presence of the rudimentary breast ducts located directly beneath the nipple, other initial symptoms may include nipple involvement such as retraction, ulceration, discharge, and bleeding [54]. BC primaries in men more often have locoregional metastasis at presentation. More than 40% of MBC patients present with stage III/IV disease, often due to early chest wall spread. Clinically suspected axillary nodes are identified in about 40% of patients at the time of diagnosis [46]. Bilateral involvement is rare, less than 2% of MBC cases [55].

Clinically suspicious lesions identified by palpation are evaluated with mammography and/or ultrasonography scans to select patients who will undergo to further examination generally made by fine-needle aspiration (FNA) or core biopsy. The primary differential diagnosis of a breast mass in a man includes gynecomastia that affects 30% of healthy men [56]. The evaluation of the extension of disease and stage classification follows the guidelines for FBC.

63.6 Prognosis and Survival

Prognosis depends upon tumor size, histologic grade, nodal status, and hormone receptor status. Stage classification of male patients with BC is similar to that of female patients, according to AJCC or UICC guidelines. As postmenopausal FBC, in general MBC have more favorable prognostic factor profile, including low histologic grade and hormonal receptor-positive expression [9]. Despite this, men experience worse prognosis than women, probably due to both an advanced stage and older age at diagnosis. As in FBC, the most important prognostic indicators are tumor size and lymph node status. Men with breast tumor diameter > 2 cm have a 40% higher risk of mortality than men with tumors <2 cm. Similarly, men with lymph node involvement have a 50% higher risk of mortality than men without lymph node involvement. Furthermore, an increasing number of lymph node metastases are positively correlated with a poorer prognosis [1].

Compared with women, overall survival rates are lower in men; however, when adjusted for older age at diagnosis and poor life expectancy, the relative survival rates are quite similar for men and women [9]. This likely reflects the influence of serious comorbidities as result of an older age at diagnosis. The overall 5- and 10-year survival rates of MBC patients are around 60% and 40%, respectively. When grouped by stage at presentation, overall survival rate is 78% and 55% for stage I, 66% and 39% for stage II, and 39% and 21% for stage III disease, at 5 and 10 years, respectively [57]. Overall, survival rates differ significantly according to race/ethnicity. Compared to white men, black men have features of more aggressive disease as higher histologic grade, larger tumor size, and higher rate of nodal involvement. Worse prognosis in black men after

adjustment to clinical, demographic, and treatment factors has been shown [58].

BC mortality and survival rates have improved significantly over time for both male and female BC, but the relative improvement was less significant for men compared with women [7]. Decline in FBC mortality rates are attributed to adjuvant systematic therapy and screening mammography. Decline in MBC mortality would likely reflect just the impact of adjuvant systematic treatment since men do not receive screening mammography. However, the improvement for male is smaller if compared to female BC patients, suggesting underutilization or non-appropriate utilization of adjuvant therapy.

63.7 Oncogenetic Counseling, Screening, and Surveillance

Genetic counseling should be offered to MBC patients based on their increased risk of *BRCA* mutations, particularly in the context of a family history of breast/ovarian cancer. The National Comprehensive Cancer Network (NCCN) recommendation indicates that all MBC patients should be offered genetic counseling and testing based on their risk of carrying a deleterious mutation that might be relevant to their own care or the care of their family members. Risk assessment models to estimate the risk of carrying a *BRCA* mutation, such as BRCAPRO, have been validated for use in male patients [59–61].

Because the age-standardized incidence of MBC is only 1/100,000 person-years with lifetime risk of about 1/1000, there is no role for breast screening in the general male population. On the other hand, screening for BC in men at higher BC risk, including those with *BRCA1/2* mutations, strong family history of BC, such as affected mother and/or sister, Klinefelter's syndrome, or transgenders [62, 63], should be undertaken and should be available preferably in a clinical trial. Extrapolating from FBC, NCCN recommends that men at higher BC risk have a clinical breast exam every 6 to 12 months and consider having a mammogram at age 40. However, as the value of breast imaging remains uncertain in men, mammography and ultrasound should be considered. Men with a *BRCA1/2* gene mutation should also have prostate cancer screening starting at age 40. Men at higher BC risk should also be aware of the warning signs of BC and should be taught for breast self-examination.

The risk of a new BC is higher in MBC survivors. MBC patients had a 30-fold increased risk of developing a contralateral BC, and this risk is greatest in men who were younger than 50 years at BC diagnosis. Thus, male survivors of early stage BC could benefit most from breast screening. MBC survivors are also at risk of certain non-breast second malignancies, prostate and colon cancer being the most common [47]. Thus, MBC survivors should be offered the same screening programs for non-BC as men in the general population, unless they are found to carry deleterious genetic mutations for which specific follow-up is recommended. Overall, there is a clear need for protocols for both screening and surveillance and, more in general, for information and support to men diagnosed with BC.

63.8 Treatment Options

To date, because there have been few evidences supporting a specific therapeutic approach in MBC, the majority of clinicians base their treatment recommendations on their personal experience with this disease and on the data of FBC. Indeed, the small numbers of MBC seen in any unit annually have precluded significant trials being carried out, and treatment of MBC often mirrors that of FBC despite some not negligible differences. Overall, with some minor variations, MBC treatment follows the same indications as female postmenopausal BC, with surgery, radiotherapy, and systemic therapy.

63.8.1 Treatment of Early-Stage Disease

63.8.1.1 Surgical Management

The goals of BC surgery include complete resection of the primary tumor with negative margins to reduce the risk of local recurrences and pathologic staging of the tumor and axillary lymph nodes to provide prognostic and/or predictive information.

In early-stage MBC patients, primary standard treatment is a modified radical mastectomy with axillary dissection [64]. This is primarily due to a paucity of breast tissue in men as well as the fact that in male breast, the tumor usually affects central quadrant. Locoregional disease control to this treatment is generally similar to those seen in women with BC. Conservative breast surgery has produced encouraging results for the treatment of early-stage MBC patients, although in males a larger tumor size and a higher rate of chest wall infiltration are found compared to female patients. Overall, breast conservation has also been used, and results have been similar to those seen in women with BC [65].

Surgical assessment of the axillary lymph nodes is an essential part of primary BC therapy; although men with

early-stage disease typically undergo axillary lymph node dissection, the use of sentinel lymph node biopsies is increasing [66, 67]. If the sentinel lymph node contains cancer, a full axillary lymph node dissection may be needed, depending on the size of the cancer in the lymph node as well as what other treatment is planned. In a recent SEER analysis, 19% of men were treated with lumpectomy [68]. Obviously, if breast-conserving surgery is done, it is usually followed by radiation therapy. External beam radiation is the usual type of radiation therapy for men with BC. This usually includes the chest wall where the breast was removed and, depending on the size and extent of the cancer, may include the underarm area, supraclavicular lymph nodes, and internal mammary lymph nodes.

Rates of contralateral preventive mastectomy in men who received a diagnosis of unilateral invasive BC nearly doubled between 2004 and 2011. In fact, in 2004, about 3% of men had contralateral preventive mastectomy while, in 2011, men who had contralateral preventive mastectomy were 5.6%, with a relative increase of 86.7% [69]. However, this increase has occurred despite the lack of evidence for a survival benefit from bilateral surgery.

Although breast reconstruction is an integral part of BC treatment plan and methods of reconstruction after mastectomy in women are well described, to date, postmastectomy deformity of the male chest has not received sufficient clinical interest. However, body image has emerged as an area of concern for MBC patients, thus deserving gender-specific attention [70].

63.8.1.2 Adjuvant Therapy

Currently, due to the rare occurrence of this disease, no controlled studies have compared adjuvant treatment options in MBC. In this setting, responses are generally similar but not identical to those seen in women with BC, and hormonal therapy has been recommended in all receptor-positive patients. In men with ER+, node-negative BC, endocrine therapy with tamoxifen is usually recommended [71]. In men with node-positive tumors, both chemotherapy and tamoxifen have been used and can increase survival to the same extent as in women with BC. However, there are limited data regarding adjuvant chemotherapy use; to date most clinicians offer either an anthracycline or anthracycline-taxane-based schedules to men who are classified at a high risk of recurrence based on the presence of axillary lymph nodal disease, larger tumors, younger age, and ER-negative tumors [72].

While the data supporting adjuvant chemotherapy in women are strong, there is little information on the effectiveness of adjuvant chemotherapy in men. However, most clinicians use similar guidelines for adjuvant chemotherapy in male and female patients. To date only one study has been performed to determine which male patients would derive benefit from adjuvant treatment as measured by the standardized 21-gene RT-PCR assay [73]. A similar gene expression profile has been found in male compared with female BCs. If these preliminary data will be confirmed by prospective studies, this testing may also be a reasonable help to guide the treatment of early stage, ER+, lymph node-negative MBC (Table 63.3) [74].

63.8.2 Treatment of Metastatic Disease

Advanced-stage disease at BC diagnosis is more frequently observed in men than in women; although a very small selected subset of patients with metastatic BC should be approached with curative intent, it is a generally held belief that once the patient with BC develops clinically detectable metastases beyond the regional lymph nodes, the disease is incurable [64]. The goals of care are to optimize both length and quality of life.

To date, clinical management of metastatic BC is similar in male and female patients. Treatment choice should take into account at least these factors: tumor burden, metastatic de novo or recurrence, hormonal receptors and HER2 status, previous therapies and/or toxicities, and disease-free interval. Given that the vast majority of men have ER+ tumors, hormonal therapy is the upfront approach. Tamoxifen has an established efficacy and toxicity profile in metastatic male BC, with an approximate 50% response rate, and is considered the standard first-line approach.

For male patients with hormone-refractory disease or rapidly progressing visceral metastases, chemotherapy can provide significant palliation. The type of chemotherapy is similar to the one used in the adjuvant setting, with anthracycline and taxanes as the backbone of the chemotherapy regimens. In particular, in the absence of medical contraindications, anthracycline- or taxane-based regimens, preferably as a single agent, would usually be considered as first-line chemotherapy for HER2-negative MBC, in those patients who have not received these regimens as adjuvant treatment and for whom chemotherapy is appropriate (Table 63.3). Similarly to female, in MBC patients pretreated with an anthracycline and a taxane and who do not need combination chemotherapy, single-agent capecitabine, vinorelbine, and eribulin are the preferred choices. The effectiveness of anti-HER2 agents in her2-neu overexpressing male breast cancer is unproven, but certainly it seems reasonable given the strong evidence in support of trastuzumab in women with breast cancer. Finally, no gender-specific trial have been designed so far testing mTor or CDK4/6 inhibitors.

Table 63.3 Drug options

Early stage			Advanced stage		
Chemotherapy regimens[a]:	Hormonal treatments[b]:	Target therapy[c]:	Chemotherapy regimens:	Hormonal treatments[d]:	Target therapy[e]:
AC (doxorubicin and cyclophosphamide)	Tamoxifen	Trastuzumab	Nab-paclitaxel	Tamoxifen	Anti-HER2 agents (trastuzumab, pertuzumab, TDM-1) in her2-neu overexpressing male breast cancer
AC or EC (epirubicin and cyclophosphamide) followed by T (doxorubicin and cyclophosphamide, followed by paclitaxel or docetaxel, or the reverse)	Aromatase inhibitors plus luteinizing hormone-releasing hormone agonist[f]		Doxorubicin	Luteinizing hormone-releasing hormone agonist with or without total androgen blockage (antiandrogen)	Bevacizumab
CAF (cyclophosphamide, doxorubicin, and 5-FU)			Paraplatin	Progesterone	plus LHRHa
CEF (cyclophosphamide, epirubicin, and 5-FU)			Cyclophosphamide	Aromatase inhibitors	CDK4/6 inhibitors
CMF (cyclophosphamide, methotrexate, and 5-FU)			Doxorubicin	Fulvestrant	
EC (epirubicin, cyclophosphamide)			Epirubicin		
TAC (docetaxel, doxorubicin, and cyclophosphamide)			Fluorouracil		
TC (docetaxel and cyclophosphamide)			Gemcitabine		
			Eribulin		
			Ixabepilone		
			Methotrexate		
			Vinorelbine		
			Paclitaxel		
			Docetaxel		
			Vincristine		
			Capecitabine		

[a]The role of taxanes and dose-dense regimen, however, remains to be elucidated
[b]The use of aromatase inhibitors for male BC is controversial; while these have been shown to increase disease-free survival in women, mixed results have been found in men
[c]There is currently few data on the benefits of trastuzumab in male breast cancer
[d]There is currently few data on the benefits of aromatase inhibitors and fulvestrant in male breast cancer
[e]The role of bevacizumab, mTor inhibitors and CDK4/6 inhibitors remains to be studied
[f]The effectiveness of anti-HER2 agents (trastuzumab, pertuzumab, TDM-1) in HER2 overexpressing male breast cancer is unproven but certainly seems reasonable given the strong evidence in support of trastuzumab in women with breast cancer

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