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Scientific Research

Male Breast Cancer Clinical Features, Risk Factors, and Current Diagnostic and Therapeutic Approaches

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Abstract

Objective: To review presentation, diagnosis, treatment and prognosis of male breast cancer. Method: A systematic review of the English language literature between 1990 and 2013 was conducted to identify studies relevant to the objective. Searches were carried out on the database PubMed, by using the title term "male breast cancer". Results: The majority of male patients present with a painless, firm, subareolar lump. Experience of male breast imaging is good but limited. However, there is no definitive therapeutic algorithm. Men are often treated with mastectomy instead of breast conserving surgery and mostly tamoxifen is used as an adjuvant therapy. The most important prognostic factors are tumor size and lymph node status in the armpit. Conclusion: More increased awareness and further research are needed to improve the diagnosis and treatment of this disease.

Keywords

Breast Cancer, Male Breast Cancer, Treatment, Diagnosis, Prognosis

1. Introduction

Male breast cancer is a relatively rare disease, which accounts for less than 1% of all instances of cancer in men and about 1% of all breast cancer cases [1]-[7]. It accounts for less than 0.2% of all cancer related deaths among men [8]-[11]. Because of the rarity of the disease, most information about male breast cancer has been obtained from small, mono-centric, retrospective studies or through extrapolation from randomized prospective studies or from clinical experience of breast cancer in women [12]. But this enormous volume of data on female breast

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cancer may not be completely relevant to men, particularly with regard to differences concerning the hormonal environment for men and women, and also in terms of gender differences that may affect the cancer patient's condition, medical and/or psychosocial side effects from treatments, and survival priorities. Men with breast cancer have a higher occurrence of ductal histology [5]. Infiltrating ductal carcinoma (ICD) represents more than 90% of all MBC cases [1] [3] but in women, the frequency of ductal histology is 70% to 75% [5]. Tumour types such as infiltrating lobular carcinoma (ILC), medullary lesions, tubular or neuroendocrine tumours are very rare in the MBC cases [1] [3]. Oestrogen and progesterone steroid receptor expression is also higher in male breast cancer [5] [12].

2. Method

This study is a systematic review of the literature. The literature review was conducted in order to describe the current state of knowledge and to compile the scientific literature within the field of breast cancer in men. The study processes the scientific papers in a systematic manner, which consisted of both empirical studies of quantitative and qualitative design, and theoretical or meta-analytic and overview studies. All of them had a clear link to breast cancer in men. The search for scientific literature was conducted in the PubMed database by searching for the key words "male breast cancer" and some articles were also selected from bibliographies from other publications.

Articles that were included in this study met these criteria:

-Articles were published between 1990-01-01 and 2013-09-30, which were in English.

-Articles were about primary breast cancer in men.

-Articles touched heredity and genetic aspects, clinical features, clinical histopathology, diagnosis and diagnostic methods (mammography, ultrasound, fine needle aspiration biopsy/core needle biopsy and sentinel lymph node biopsy), treatment (surgery, radiotherapy, hormone therapy and chemotherapy), prognosis (prognostic factors and survival), and psychosocial aspects.

-Articles made a clear comparison of breast cancer in men and breast cancer in women.

Articles were excluded if one or more of the following criteria were matched:

-Articles that were case studies or studies with less than 10 patients (with the exception of case studies of unknown/rare genetic factors to MBC or articles with qualitative approach and in-depth interviews).

-Articles that affected other aspects of MBC disease including local epidemiological aspects and demographic patterns, studies of environmental risk factors or the effects of various drugs and medications or relationship between MBC and races, research into the mechanisms of MBC tumors in cell level and in molecular subgroups or if a special or rare MBC tumor, etc.

-Articles that were studies of a certain group of people e.g. breast cancer in transsexual men or in HIV-infected men or among Jews.

-Articles that were about MBC metastasis.

-Articles that were irrelevant e.g. studies of gynecomastia or causes of death among a profession, etc.

Of the total of 812 articles, some were excluded. These included 11 papers on local demographic studies or about demographic patterns, 45 studies of environmental risk factors, drug or medication effects and the relationship between race and MBC, 90 studies on the mechanisms at cellular level, chromosome studies, DNA analysis and treatment mechanisms, 25 studies on rare types of MBC tumours, 111 case studies or studies with less than 10 patients, 53 studies whose abstract was missing in the database, 52 studies that were not in English, 4 studies on MBC in a particular group of people, 15 studies on metastases, metastasis sites or about secondary breast cancer, and finally, 101 studies that did not deal with MBC.

Due to the extensive information about MBC disease divided the study into two parts. The first part deals with the clinical features, diagnosis, treatment and prognosis aspects of MBC disease and the other part on genetic, histopathology, and psychosocial aspects of MBC and also comparison between MBC and FBC.

3. Results and Discussion

3.1. Clinical Features

MBC patients are usually in their sixties at presentation, but in the Middle East, China and South Asia and also in Africa, they are more often in their fifties (**Figure 1**). Symptom duration before diagnosis has decreased [13] [10], but there are large geographical differences *i.e.* less than eight months in western countries [14]-[16] and at

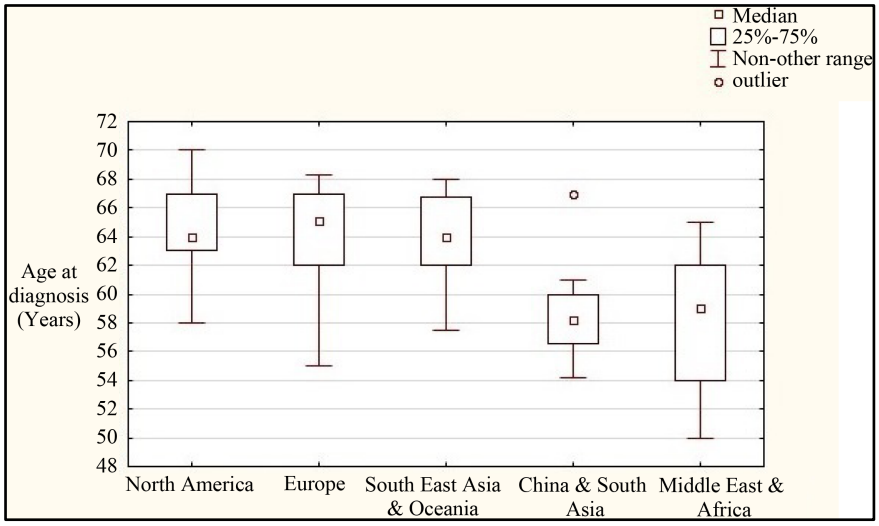

Figure 1. The correlation chart between median age at MBC diagnosis and parts of the world. North American clinical series of MBC patients: 3 Canadian +14 American, European studies om MBC patients: 2 British +3 German +1 Finnish +1 Swiss +1 French +1 Austrian +2 Spanish +1 Portuguese +2 Italian +1 Croatian +7 Turkish, South-east Asian clinical series of MBC patients: 4 Japanese +1 from Singapore +1 Korean +1 Malaysian +2 Australian, studies about MBC patients from China & South Asia: 5 Chinese +4 Indian +3 Pakistani and studies about MBC patients from the Middle East & Africa: 1 Iranian +1 Kuwaiti +1 Lebanese +2 Moroccan +1 Libyan +1 Egyptian + 6 Nigerian +1 Tanzanian +1 West African.

least one year in Asia and in Africa [17] [18]. Rarity and hence a low index of suspected cases by both patients and their doctors are important factors for long duration of symptoms before diagnosis [19]-[21]. A painless but noticeable solid lump under the areola of the nipple is the most frequent symptom of MBC [4] [14]-[17] [22]-[29] [30]-[37] which may, in the intermediate stage, be painful to the touch and accompanied by clinical gynecomastia [16] [31] [38] with nipple retraction [6] [15] [16] [38]-[40] At the later stage, spontaneous pain with tenderness appears [6] [16] or with bloody nipple discharge [6] [16] [37] [38] [40] or with watery nipple discharge [14].

In the absence of other clinical signs, the presence of nipple discharge may be an indicator of a non-invasive disease, and early identification of this symptom is therefore important [41] [42]. The primary tumour may be of varying size between 1.8 and 3.5 cm [6] [25] [27] [40] but older patients have larger tumours in more advanced stages at diagnosis, compared with younger patients [43]. Carcinoma in situ (CIS, stage 0) occurs in less than 10% of MBC cases. Tumours ≤ 2 cm (stage 1) have been reported between 22% and 35%. Tumours between 2 and 5 cm (stage 2) have been reported from 27% to 41%. It has also been reported that up to 27% of male breast tumours are more than 5 cm (stage 3) or any size growing into the chest wall or skin (stage 4) [1].

The Male breast tumours are more often located centrally [6], with skin and muscle disorders [6] [38] and with enlarged lymph nodes in the armpit [6] [16] which are clinically detected in nearly half of the patients at primary diagnosis [14]. In 33% - 46% of the cases, four or more lymph nodes are involved [1]. Because of the dominant central position and the anatomical proximity, nipple involvement occurs at an early stage [19]. Bilateral forms of male breast cancer are much rarer compared to unilateral forms of cancer, and occur in less than 2% of MBC cases [14].

3.2. Risk Factors

3.2.1. Genetic Factors

A family history of breast cancer, in both men and women, is certainly a risk factor [19]. A family history of breast cancer confers a relative risk of 2.5 [3], 20% of men with breast cancer have a first-degree relative the disease [19]. Genetic predisposing factors include abnormalities of both somatic and sex chromosomes [13]. Between 4% and 40% of male breast cancer are thought to result from autosomal dominant inheritance, particu-

larly BRCA 1 and BRCA 2 mutations [3]. The mutation of the BRCA 2 appears to be risk factor for breast cancer in men more important than BRCA 1 [3] [13]. Between 3% and 7% of men with MBC, have the sex chromosome genotype of 47, XXY (Klinefelter's syndrome) with testicular dysgenesis, gynecomastia, low testosterone concentrations, and increased gonadotrophins [3]. These men may have up to a 50-fold increased risk of MBC [3] [12].

3.2.2. Acquired Aetiological Factors

Hormonal imbalance between oestrogen and testosterone has been suggested as a possible mechanism of MBC [1] [13] [19], which may occur endogenously due to testicular diseases or infertility or cirrhosis of the liver or by increased peripheral aromatisation of androgens [3] [12]. Endemic infectious diseases causing liver damage, leading to hyper-oestrogenism maybe explain the substantially higher proportion of MBC cases in some countries in Africa [19]. Exposure of the breast to ionising irradiation increase risk of cancer in women, which may be similar in men if they exposed to therapeutic or diagnostic radiation [3]. Chronic heat exposures or electromagnetic fields, which are supposed to suppress testicular function, maybe increase risk of MBC [13] [19]. Increasing age and obesity can also increase the risk of MBC, possibly because of the changed hormonal levels in the body [12].

3.3. Diagnosis

In order to obtain a better understanding of the male breast, it is essential to develop a differential diagnosis for male patients with breast problems [44]. Breast enlargement (gynecomastia) in men is a common condition with increasing age [34] [45], which is the most common breast disease in men [33] [44]-[48] and the most common mammographic finding [45] [49] and the main problem regarding the differentiation from breast cancer [34] [49]-[51], Breast enlargement may be caused by reduced testicular function in older males, leading to a reduction in testosterone but with continued normal oestradiol [33]. Breast cancer is a rare cause of breast enlargement [52]. Patients with gynecomastia are more likely to have pain and tenderness on clinical examina- tion [34]. Besides gynecomastia, radiographic examination of male breasts is also performed to evaluate other clinical abnormalities such as breast tenderness, an apparent mass in the breast, and nipple or skin changes, which in most cases are benign and malignancy is less frequent [53]-[55]. However, breast cancer in men is considered separately when evaluating a lump in the breast, even though various benign causes are more common [56]. MBC must be excluded in patients with unilateral breast mass, particularly in patients presenting with painless mass [34]. Breast cancer in men is usually suspected in connection with clinical examination [57] [58]. Clues to the diagnosis are provided by a history of cancer or a family history of breast cancer [34]. The patient's medical history may therefore identify important suspicions about malignancy or about benign diseases [56]. But the differentiation between benign and malignant mass in the male breast is critical and can cause anxiety in patients and lead to unnecessary procedures, which should be avoided [55]. Mammography seems unnecessary in most cases and should not be used as a routine imaging of the male breast. One should also consider only imaging the clinically suspected cases in order to avoid unnecessary imaging, especially in younger patients [58]. Since the male breast can be affected by a wide range of different diseases, some of which have characteristic radiological appearances which can be correlated with their pathological diagnosis [48] [59], mammography and ultrasound should be performed along with clinical examination in the evaluation of the male breast [48]. Mammographically, the male breast is characterized by a solid mass under the areola with separation from the nipple and with irregular edges [33] [39] which on ultrasound usually appears as a hypoechoic area [60] whose edges are angled or with micro-channels and points on the surface [61]. The appearance of a complex cystic mass in a male breast with ultrasound suggests possible malignancy, which requires a biopsy [62]. Micro-calcifications are uncommon [37] [48] [57] [59] but in case of any presentation, they tend to be large, round and scattered [33] [59] [63] Clinical examination is as effective as mammography in order to differentiate the benign from the malignant disease changes, and both of these diagnosis modalities have been reported with high levels of accuracy for the identification of malignancy [56], but the male breast is not easily examined with mammography because of its limited volume [60]. On the other hand, ultrasonic images of cancer tumours are not easily distinguished from benign lesions [54]. Ultrasound is very effective for the detection of isolated lesions [60] and it is a natural complement to the diagnostic work with clinical examination and mammography [53] [60]. Ultrasound has an established role as a biopsy guide for both female and male breasts [60] [62]. Correct identification of pathological

male breast lesions using ultrasound is necessary in order to establish appropriate measures and diagnostic recommendations and to avoid unnecessary biopsies [53]. For example, ultrasound is important for demonstrating axillary lymphadenopathy [39] [55] [64] [65]. Mammography is undoubtedly superior to ultrasound for the identification and characterization of micro-calci-fications, but these are quite rare in male breast cases [60]. Several studies show that mammography has both high sensitivity and high specificity (**Table 1**), but there is conflicting information about the sensitivity and specificity regarding comparisons between mammography and ultrasound. For example, in a study by Muñoz Carrasco *et al*. (2013) [43], mammography had higher sensitivity, and in a study by Patterson *et al*. (2006) [66], mammography has higher specificity compared to ultrasound for breast cancer diagnosis in men. But on the other hand, Taylor *et al*. (2013) [67] reported in their study that ultrasound has higher sensitivity than mammography, and another study by Adibelli *et al*. (2009) [45] found that the sensitivity, specificity and validity of ultrasound is not only satisfactory, but is also superior to mammography. Morrogh & King (2009) [68] have also reported that ultrasound, with 100% sensitivity and 100% specificity, is superior to mammography. But several studies have shown that both techniques with a negative predictive value (NPV) close to 100% make it possible to avoid a large number of unnecessary surgical interventions in men [42] [66] [50]. Since experience with male breast mammography is limited, with a high rate of false positive results due to gynecomastia and cysts [69], biopsy biopsy, in order to allow a definitive diagnosis in most breast cancer cases in men [57] [70]. Fine needle aspiration biopsy (FNA) of the male breast has been studied in more depth, as demonstrated with high sensitivity and high specificity, and with almost 100% PPV or positive predictive value for the diagnosis of malignancy [40] [69] [71]-[76]. FNA biopsy allows accurate diagnosis in many medical changes that occur in the male breast. But this technique is less helpful when it comes to male patients with DCIS, especially in lesions that are cystic, such as papillary DCIS, which has been described as having a strong cystic component [62]. Core needle biopsy or fine needle aspiration biopsy should be used more often, because these procedures can help to avoid unnecessary surgery and may help in the planning of any surgeries for cancer cases [77]. The decision on a biopsy should be taken on the basis of clinical and mammographic findings, together with the medical history [54].

3.4. Surgical Treatment

Surgery as a form of therapy is generally a key part of the treatment of breast cancer [78] [79] and is a "gold standard" for MBC treatment [80] [81]. Mastectomy is usually the primary treatment for early breast cancer in men [82]. Historically, radical mastectomy has been the most popular surgical option based on the logic that male breast tumours tend to be in the vicinity of the large breast muscle and are usually detected at a more advanced stage [14]. Surgical treatment has become less aggressive in recent years, from radical mastectomy to modified radical mastectomy and total mastectomy [78] [83] [84], since radical mastectomy involves high risks of post-operative complications [78], and because several retrospective studies have shown that there is no difference between these surgical procedures with regard to local cancer recurrence and/or cancer survival [14] [15] [36] [84]-[87]. Today, modified radical mastectomy is a standard treatment for MBC treatment [78] [79] [88] and the majority of patients undergo modified radical mastectomy [78] [89]-[91], except for MBC patients with

Table 1. Sensitivity and/or specificity of mammographic diagnosis of MBC.

Study (year)	Purpose	Sensitivity (%)	Specificity (%)
Muñoz Carrasco *et al*. (2013) [42]	Evaluation of mammography and ultrasound regarding men with nipple discharge	100	100
Taylor *et al*. (2013) [67]	Evaluation of mammography and ultrasound and clinical examination in order to establish new proposals for age-specific guidelines for imaging of the male breast	92	90
Patterson *et al*. (2006) [66]	Evaluation of mammography and ultrasound in the diagnosis of benign and malignant breast problems	100	90
Adibeli *et al*. (2009) [45]	Evaluate the diagnostic validity of mammography and ultrasound regarding male breast diseases and provide a diagnostic record	69	87
Stewart *et al*. (1997) [63]	Evaluation of radiological imaging regarding the male breast	92	90
Evans *et al*. (2001) [50]	Evaluation of the validity of mammography regarding male breast diseases	92	90

tumour spread in the thoracic muscle [92]. Modified radical mastectomy, together with radical mastectomy, is now the most common surgical treatment of MBC, which is over 70% of the total surgical MBC treatments [10] [14] [38] [87] [93] [94]. It is believed that the cosmetic result of mastectomy is not a problem for men, but lumpectomy or breast-conserving surgery may be preferred for certain MBC patients, in part because of a significantly lower post-operative morbidity [95]. Lumpectomy is performed in a small but growing percentage of MBC patients [96], but this treatment procedure is usually not considered to be feasible for men, even at an early stage of the disease, because of the paucity of breast tissue in males [12] [83] [92] and the central location of the majority of male breast tumours [92]. Also in conjunction with mastectomy, a few studies have shown that lumpectomy is correlated with poorer local control of the disease [83] [87], but nevertheless, this surgical technique can be used in patients with poor general state of health [12] [61]. Axillary lymph node dissection (ALND) is also an important part of the surgical treatment of men with invasive breast cancer [1] [3] [13] [97] [98], but because of its complications, sentinel lymph node biopsy (SLNB) will be used in future to identify node metastases with a high level of accuracy [1] [3] [97] in men with clinically node-negative breast cancer, which has produced good results with high sensitivity and/or specificity in several small retrospective studies [99]-[107]. This technique should be used in patients with primary tumours of less than 2.5 cm in size, without clinically suspected lymph node involvement [1] [2].

3.5. Radiotherapy

Post-operative radiotherapy reduces the risk of local cancer recurrence and improves long-term survival rates in women [3]. The criteria for its use for MBC treatment is generally extrapolated from data about FBC treatment [108] [109]. Standardized indications for irradiation of the thorax and lymph node in the armpit regarding female breast cancer include: large tumour and its spread to the nearby skin, to the areola or to the large chest muscle, and lymph node involvement in the armpit [3], with a radiation dose of 50 Gy divided into 25 fractions [3] [19]. Radiation therapy should be used for tumours that are larger than one centimetre in diameter or with more than one metastatic lymph node [1] [2] [12] or where there is a high risk of chest wall metastasis [110]. Adjuvant loco-regional irradiation should be used more extensively for male breast cancer, compared with female breast cancer, due to the higher proportion of locally advanced disease and in particular, the central location of male breast tumours and with greater likelihood of lymph node involvement in the armpit [2] [11] [12] [87] [111]-[114]. Men who undergo breast-conserving surgery should also be treated with post-operative radiation [70], because lumpectomy results in unacceptably high rates of local cancer recurrence, which can be reduced with the combination of local radiation therapy [87]. Radiation therapy is also recommended because of the fact that rudimentary breast tissue in MBC patients complicates tumour margins in the operation [115] and there is also a clear indication for radiation therapy when it is impossible to surgically remove the entire tumour from the armpit [116]. There is limited data regarding the need for radiation therapy after surgery [92] [12]. The use of radiation therapy in men with breast cancer has varied greatly over the past few years and has been very irregular. A careful evaluation is very difficult, therefore, because this treatment has been used after several different types of surgical treatments and also with different radiation techniques [1].

Adjuvant radiation therapy is considered to reduce the risk of local cancer recurrence associated with large tumours with lymph node and muscle involvement [61]. There are a few retrospective studies showing that post-operative radiotherapy in men can improve local control of the disease [10] [16] [78] [87] [117]-[120], but does not affect long-term cancer survival [5] [10] [15] [38] [87] [116] [117] [121] [122]. Historically, no survival advantage has been observed for the use of adjuvant radiation therapy for male breast cancer cases [91]. Post-operative radiation is routinely used in all stages of male breast cancer, but the risk of local cancer recurrence is small, especially in the early stages, and it is therefore better to use the same indications for post-operative radiation as apply for female breast cancer [123]. Radiation therapy after surgery is correlated with longer survival in men with breast cancer at disease stage III, but men with breast cancer at lower stages of the disease do not appear to benefit from radiation therapy [124]. Due to the fact that the most common location for local cancer recurrence in MBC patients is on the chest and above the clavicle, this should be taken into account when planning adjuvant radiotherapy [19]. Because MBC patients are also generally older than FBC patients, they are more likely to have cardiovascular problems and/or lung problems, and more sophisticated radiation therapy techniques must therefore be used to avoid unnecessary exposure of the heart and lungs [3].

3.6. Hormone Treatment

Because of the high sensitivity to oestrogen in male breast tumours, a large proportion of MBC patients have a good response to hormonal treatment [1] [13] [41] [79] [125]. Historically, orchiectomy, adrenalectomy and hypophysectomy have also been useful surgical methods for the treatment of male breast tumours [126] by altering the hormonal state of the male body [127], but today Tamoxifen is accepted as a standard adjuvant hormonal therapy for hormone-sensitive breast cancer [13] [92] [128], which has been shown to produce results comparable with orchiectomy [129] and with high levels of patient acceptance [7]. Several retrospective studies have shown good results with adjuvant Tamoxifen, resulting in improved five-year overall survival and/or five-year disease-free survival [78] [83] [94] [130] [131], but there are a few retrospective studies questioning Tamoxifen treatment of MBC [10] [132]-[134]. The relationship between oestrogen positivity and survival with Tamoxifen is less clear among men compared with women, because these studies include few patients and are often without a clear difference in survival outcome in terms of disease-specific or overall mortality, and with much shorter duration of Tamoxifen treatment, *i.e.*, a 5-year optimal duration of Tamoxifen has not been studied in men [1] and there is a major need to address the issue of Tamoxifen compliance in this patient group [135]. On the other hand, male patients experience more side effects from Tamoxifen, such as weight gain, sexual dysfunction, nausea, depression and hot flushes [136]-[138], which may affect their compliance with the prescribed treatment [138] [139].

Tamoxifen is still the first treatment option for men with hormone-receptor positive breast tumours. But there are also other anti-endocrine and endocrine therapies that can be applied, such as aromatase inhibitors, androgens, anti-androgens and corticosteroids [31] [79] [140], but their use is dependent on the clinical response or cancer recurrence [31] [79] [140]. It was hoped that aromatase inhibitors will be useful in the treatment of MBC patients with metastases [141] [142], but ongoing case studies have unfortunately produced poor results [143]. Because the hormonal environment in male patients is different from that in female patients, the role of aromatase inhibitors is not clear in male patients [144]. A recent German study by Eggemann *et al*. (2013) [145] compared the effect of adjuvant Tamoxifen treatment aromatase inhibitor therapy on survival in men with hormone-sensitive breast cancer. 207 MBC patients had received Tamoxifen and the other (n = 50) aromatase inhibitors. 37 patients (18%) treated with Tamoxifen and 16 patients (32%) with aromatase inhibitor died during the follow-up period of 42 months. After adjusting for patient age, tumour size, lymph node status and tumour grade, it has been shown that patients treated with aromatase inhibitors had 50% higher risk of death compared with patients treated with Tamoxifen (HR = 1.55, 95% CI: 1.13 - 2.13; p = 0.007). This means that overall survival was significantly better after Tamoxifen treatment compared to aromatase inhibitors. But more research is needed to evaluate the role of aromatase inhibitors for the treatment of MBC. Moreover, due to the biological differences between men and women, it is probably not wise to advocate the use of aromatase inhibitors as the only drug for the treatment of MBC [146].

3.7. Chemotherapy

Adjuvant chemotherapy in men with breast cancer is less established. However, the limited data shows good resultants [3] [12] [147], especially regarding high-risk subgroups and possibly younger patients [1].

Systemic treatment with cytostatics should be administered to male patients at stage II or greater [128] and to patients who are either hormone receptor-negative or resistant to various available hormone treatments [1] [61], [84] [148] [149], to patients with a significantly higher risk of relapse [12] or to patients with a tumour size above 1 cm or with positive node lymph status [110]. In clinical practice, chemotherapy is routinely recommended for male patients with positive lymph node status in the armpit [150]. But at the time of diagnosis, a large proportion of male patients are older and it is therefore very likely that there will be medical contraindications to receiving this treatment [88]. Surgery, radiation therapy and hormone therapy are used to the same extent in both elderly and younger patients, but older patients are less likely to receive adjuvant chemotherapy [43]. Several retrospective studies have evaluated adjuvant systemic chemotherapy in male breast cancer [10] [83] [94] [98] [128] [151]. Two of them have confirmed significantly improved survival [98] [151] and the third showed significantly reduced risk of recurrence [128] in male patients who received this systemic treatment.

The retrospective study by Izquierdo *et al*. (1994) [128] for the evaluation of adjuvant therapy (chemotherapy, hormone therapy or both) reported better disease-free survival for 17 patients who received adjuvant therapy, compared to 21 patients who had not received any form of adjuvant therapy (72% vs. 47%). Furthermore, the retrospective study by Giordano *et al*. (2005) [94] showed that 51 patients, including 66% with positive lymph

node status, were treated with Tamoxifen, chemotherapy or both. Patients who received adjuvant systemic treatment had 43% lower risk of death, compared with patients who received no form of adjuvant therapy. During tumour progression in male breasts, a combined hormonal and cytostatics treatment can be used with considerably good results [152]. However, these reports should be interpreted with caution, given the small populations, limited follow-up times, and the inconsistencies in the stage of the disease and in studying the adjuvant treatment modalities [150]. With regard to adjuvant chemotherapy, MBC is probably an under-treated disease [147]. For example, an American study by Scott-Conner *et al*. (1999) [90] has shown that after adjustment for age and cancer stage, 27% of male patients treated with adjuvant chemotherapy, compared with 41% of women with the same disease. Decisions about adjuvant chemotherapy for MBC patients can be made by assessing the drawbacks and benefits in the same way as for FBC patients [3] [13] [147] [151] [153]. But the approach to this decision should take account of the experiences from treatment of post-menopausal women, rather than pre-meno-pausal women with early breast cancer [150] because male breast cancer behaves in many respects like post-menopausal breast cancer [27]. We also need further investigation of the role of adjuvant chemotherapy in the treatment of male breast cancer patients and the determination of optimal chemotherapy in the treatment of the disease with metastases [154].

3.8. Prognosis

3.8.1. Survival of Male Patients with Breast Cancer

The number of studies that have examined the survival rate of male breast cancer patients is quite small compared to the population-based studies on female breast cancer, and most studies on men with breast cancer have focused on overall survival, with the exception of a few recent studies that report disease-free survival [57]. Some studies show that other primary cancers, especially melanoma, prostate cancer and gastric and colon cancer, affects one in ten men with breast cancer during follow-up [155]-[157] and many men with breast cancer also have various cardiovascular, neurological and respiratory diseases [1] [3] [112] [158] and male breast cancer patients are more likely to die of other causes than female breast cancer patients [84]. This is important in order to better understand the differences between overall survival and disease-free survival [1]. In these retrospective series, as shown in **Table 2**, it is sometimes seen that the 5-year disease-free survival rate is larger than the 5-year overall survival rate, for example in the studies by Cutuli *et al*. (1995) [87] (74% vs. 65%), Donegan *et al*. (1998) [10] (66% vs. 51%), Selcukbiricik *et al*. (2013) [93] (72% vs. 66%) and Müller *et al*. (2012) [159] (79% vs. 66%), which is due to the fact that some of the patients in these retrospective series, die during the follow-up period due to other primary cancers, or from other related diseases or from various complications and unknown causes [1]. “Disease-specific survival” is therefore a more suitable marker for studying the MBC prognosis, compared to “overall survival” [10] [87] [90] [158] [160]-[163]. In general, disease-specific survival is 10% higher than overall survival in MBC patients [115] [164]. The 5-year overall survival rate in male breast cancer patients varies greatly in different studies, with a range from 7% to 92%. In retrospective series from western countries, the 5-year overall survival rate was reported with a range between 43% and 85%, which in the older series is often below 70%, but in the newer series over 70%. These figures for Asian series are from 27% to 92% and for African series they are between 7% and 61%. The 10-year survival rate is from 24% to 60% and the five-year disease-free survival rate is from 41% to 79% in Western series. In Asian series, the 10-year survival rate is from 28% to 77%, and the 5-year disease-free survival rate is between 46% and 92% (**Table 2**). These differences are partly explained by variations in study periods, the patients’ co-morbidity and health care standards and quality of healthcare in the country where the study is conducted. These large ranges are also probably related to differences associated with cancer stages at diagnosis and treatment guidelines [57].

3.8.2. Prognostic Factors

Breast cancer has similar prognostic factors and behaviour in men and women [12] [61] [80] [88]. Survival in men is significantly associated with: 1) The degree of histological differentiation [15] [81] [134] [165]-[168], which means that a higher degree of differentiation of the tumour is associated with a poorer prognosis; 2) Clinical cancer stage [40] [87] [167]-[169] *i.e*. tumours at higher stages produce a worse prognosis; 3) The hormone receptor status [10] [82] [125] [170] [171], which means that tumours with ER+ and/or PgR+ have a better prognosis; 4) The tumour size [31] [38] [43] [98] [115] [134] [159] [167] [170] [172]-[174], which means that larger tumours are correlated with shorter 5-year survival rates (**Table 3**); 5) The most documented factor *i.e*.

Table 2. Survival rate (%) in MBC patients in different studies.

Study (year)	Country	Number of patients	Diagnosis-period	5-year overall survival rate (%)	10-year overall survival rate (%)	5-year disease free survival rate (%)
Borgen *et al*. (1992) [14]	USA	104	1975-1990	85		68
El-Tamer *et al*. (2004) [84]	USA	53	1980-1998	77	56	
Gough *et al*. (1993) [36]	USA	124	1933-1983	57	31	
Donegan *et al*. (1998) [10]	USA	215	1953-1995	51	24	66
Williams *et al*. (1996) [51]	USA	17	1959-1990	47		41
Giordano *et al*. (2004) [31]	USA	2537	1973-1998	63	41	
Chakravarthy & Kim(2002) [109]	USA	44	1967-1995	75		
Schaub *et al*. (2008) [89]	USA	28	1975-2005	43(51)		
Yu *et al*. (2012) [117]	Canada	75	1977-2006	74	37	66
Goss *et al*. (1999) [83]	Canada	229	1955-1996	53		47
De Ieso *et al*. (2012) [175]	Australien	63	1977-2007	85		
Schuchardt *et al*. (1996) [116]	Tyskland	21	1972-1993	59	46	
Sandler *et al*. (1994) [16]	Tyskland	28		43		
Foerster *et al*. (2011) [170]	Tyskland	108	1995-2007	71		53
Zabel *et al*. (2005) [119]	Tyskland	31		57	44	
Müller *et al*. (2012) [159]	Tyskland	40	1982-2007	66	43	79
Herman *et al*. (2000) [177]	Poland	65		70	60	
De Perrot *et al*. (2000) [178]	Schweiz	37	1968-1998		44	
Stierer *et al*.(1995) [38]	Österike	169	1970-1991	62		55
Cutuli *et al*. (1995) [87]	Frankrike	397	1970-1992	65	38	74
Cutuli *et al*. (2010) [112]	Frankrike	489	1990-2005	81	59	
Marchal *et al*. (2009) [179]	Frankrike	58	1980-2002	59	34	
Dabakuyo *et al*. (2012) [180]	Frankrike	75	1982-2008	69		
Salvadori *et al*. (1994) [167]	Italien	170		73	56	
Izquierdo *et al*. (1994) [128]	Spanien	50	1964-1990	75		59
Thalib & Hall (2009) [181]	Sverige	269	1970-1997	79		75
Liukkonen *et al*. (2010) [27]	Finland	58	1981-2006	75		
Arslan *et al*. (2012) [173]	Turkiet	118	1986-2009	82		60
Atahan *et al*. (2006) [121]	Turkiet	42		77		45
Atalay *et al*. (2003) [81]	Turkiet	55	1990-1998	73		45
Eryilmaz *et al*. (2012) [24]	Turkiet	25		53		49
Selcukbiricik *et al*. (2013) [93]	Turkiet	86	1973-2010	66		72
Ulutin *et al*. (1998) [182]	Turkiet	15	1980-1995	60		
Engin & Unsal (1993) [183]	Turkiet	26	1980-1988	27		
Anan *et al*. (2004) [160]	Japan	14		92	77	

continued

Tajima *et al*. (2001) [184]	Japan	182	1966-1995	58		
Chung *et al*. (1991) [185]	Sydkorea	16	1970-1990	57	28	
Parker *et al*. (2008) [186]	Sydkorea	20	1985-2007	86	76	92
Xia *et al*. (2010) [158]	Kina	35	1969-2004	82		60
Zhou *et al*. (2010a) [82]	Kina	72	1969-2009	72		
Liu *et al*. (2011) [187]	Kina	87	1961-2008	77		66
Chen *et al*. (2013) [188]	Kina	150	1980-2012	74	54	66
Baojiang *et al*. (2012) [189]	Kina	42	1982-2006	75	52	61
Rai *et al*. (2005) [190]	Indien	30	1996-2000	40		
Shah *et al*. (2012) [23]	Indien	28	2001-2008			46
Salehi *et al*. (2011) [25]	Iran	64	1989-2008	66		
Temmim *et al*. (2001) [165]	Kuwait	41	1979-1996	67		58
El-Beshbeshi & Abo-Elnaga (2012) [191]	Egypten	37	2000-2009	61		53
Ahmed *et al*. (2012) [192]	Nigeria	57	2001-2010	23		
Ihekwaba (1994) [193]	Nigeria	57	1971-1990	7		

Table 3. The 5-year survival rate (%) with respect to tumour size in different studies.

Study (year)	T1	T2	T3	T4
Selcukbiricik *et al*. (2013) [93]	92	74	41	0
Zhou *et al*. (2010) [82]	100	74	57	0
Giordano *et al*. (2004) [31]	78	67	40	19
Vaizey *et al*. (1999) [194]	88	50	27	5
Ribeiro *et al*. (1996) [86]	76	66	43	-

lymph node status [5] [25] [31] [38] [43] [83] [87] [115] [119] [125] [163] [172] [173] [175] [176], which means that positive lymph node status results in a lower 5-year survival rate (**Table 4**) and with the number of positive nodes in the lymph nodes in the armpit [38] [87] [115] [163].

4. Conclusion

Breast cancer in men is a rare disease compared to women and it is frequently diagnosed with more advanced stage of disease. Because of high median age for occurrence and also high hormone positivity rate, hormone therapy such as tamoxifen is generally considered a standard adjuvant therapy [1] and theoretically very promising [12]. However, the relationship between hormone positivity and survival benefit with hormonal therapy is less clear in men than in women. The role of adjuvant aromatase inhibitors in MBC has not been determined, and preclinical data suggest that aromatase inhibitors may be less effective in men [19]. Therefore, tamoxifen remains as first line hormone therapy till further large-scale data are available [13]. The role for adjuvant chemotherapy in men is also not adequately established [19], but the limited data do suggest a benefit [12]. It is not simple to evaluate the relative benefit of hormonal therapy and chemotherapy, but it seems that the patients being treated with systemic therapies have had longer time to disease recurrence and survival [1]. Limited data are available for determining which patients need radiation therapy after operation [12], and the use of radiation therapy is extremely heterogeneous in the literature [1], but this therapy should be delivered more often in men with breast cancer than in women, due to the high proportion of locally advanced disease, axillary nodal

Table 4. The 5-year survival rate (%) with repect to lymph node status in different studies.

Study (year)	Node negative	Node positive
Goss *et al*. (1999) [83]	68	47
Stranzl *et al*. (1999) [120]	91	71
Guinee *et al*. (1993) [163]	78	45
Borgen *et al*. (1992) [14]	87	30
Giordano *et al*. (2004) [31]	76	54
Teo *et al*. (2012) [22]	70	<54
Kiluk *et al*. (2011) [195]	87.5	68.5
Salehi *et al*. (2011) [25]	68	45

involvement and central tumour location [1]. We need a greater awareness of male breast cancer to guide evidence-based treatment and to encourage enrollment in future studies aiming at optimizing management of this rare disease. The role of adjuvant hormonal treatment and chemotherapy deserves more researches, especially to determine which subgroup of men will benefit.

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