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The Etiology, Diagnosis and Treatment of Breast Cancer in Males

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1. SUMMARY

Male breast cancer receives increasing attention during the recent years and more and more studies are being conducted. But, since male breast cancer is a very rare disease, large clinical trials are difficult to conduct, and therefore specific diagnostic and treatment guidelines still remain based on the experience from female breast cancer.

However, several milestones have been archieved until now. These include the male-specific identification of risk factors like positive family history, black ethnecity, genetic mutations in the CHEK2, PALB2, CYP17, BRCA1, and BRCA2 genes, alterations of the estrogen to androgen ratio, and primary testicular conditions. Male breast cancer typically presents as a unilateral, painless, retroareolar mass with possible additional signs and symptoms. Furthermore, two main subtypes have been identified in male breast cancer: luminal A and luminal B.

Histologically, invasive ductal carcinoma is the most common type and represents approximately 90% of the cases. The diagnosis is mainly established by the triple assessment, which includes clinical assessment, mammography/ultrasound and core biopsy. The staging process consists of the identification of the tumour size, lymph node involvement, estrogen receptor and progesterone receptor levels, human epidermal growth factor receptor status and tumour grade, and is classified according to the tumour-node-metastasis system.

The rising knowledge about the prevalence of hormonal receptors such as estrogen receptor, progesterone receptor, androgen receptor, and human epidermal growth factor receptor, and the genetic and hormonal influence in the pathogenesis, contributes to a positive view of the future. It will help to create male-specific treatment guidelines for each cancer stage, type and hormonal status with surgery, radiotherapy, endocrine therapy, chemotherapy, and biological targeted therapy.

2. KEYWORDS

Male breast cancer; etiology of male breast cancer; epidemiology of male breast cancer; risk factors male breast cancer; genetics and family history in male breast cancer; BRCA2 mutations in male breast cancer; alterations of the estrogen-to-androgen ratio in male breast cancer; klinefelter´s syndrome; primary testicular conditions in male breast

cancer; signs and symptoms of male breast cancer; clinical and pathological characteristics of male breast cancer; male breast cancer subtypes; diagnosis and staging of male breast cancer; mammography in male breast caner; ultrasound and other diagnostic methods in male breast cancer; biopsy in male breast cancer; staging of male breast cancer; differential diagnosis of male breast cancer; treatment of male breast cancer; adjuvant therapy in male breast cancer; radiation therapy in male breast cancer; chemotherapy in male breast cancer; endocrine therapy in male breast cancer; bisphosphonates and male breast cancer; prognosis and surveillance of male breast cancer.

3. INTRODUCTION

Although MBC (male breast cancer) remains a rare disease, it's incidence is rising (1). The age at diagnosis differs between men and women. While in men the average age at diagnosis is 69,6 years, for women the age is significantly lower (61,7 years) (2). In the United States, each year, approximately 2600 new MBC cases and 440 MBC deaths are expected. For females these incidence and mortality numbers are much higher (246.660 new cases and 40.450 deaths) (3).

The treatment of MBC is mainly based on the knowledge of FBC (female breast cancer), even though there are differences regarding pathogenesis, biology, and genetics between the two diseases (4).

4. METHODS

A literature review was conducted using PubMed and Google scholar as the main databases. The sources used were limited to English language. A particular priority was laid on the recent publications from 2012 until 2022. The goal was to summarize the recent publications in order to understand the specific features, diagnostic methods and treatment possibilities in male breast cancer.

5. RISK FACTORS

5.1 Genetics and family history

Positive family history has a strong association with the development of breast cancer in males (5). Around 17% of MBC patients have a positive first-degree family history with ovarian and/or breast cancer. Another 13% of the patients have a positive family history for cancer in second-degree relatives, instead (6). Several studies about men from different countries show that having a first-degree relative with breast cancer increases the relative risk of breast cancer by approximately 2 % (7,8).

According to demographics, there are different incidence rates all over the world. Black men are at increased risk for MBC compared to white men. The incidence ratio among black to white men is 1.41 (9). In African countries, the male-to-female ratio is 0.042 (10).

Variouss genes have been identified and mutations in these genes are linked to MBC. These mutations include CHEK2, PALB2 and CYP17.

CHEK2, also known as checkpoint kinase 2, is a gene involved in the process of DNA repair. A mutation of this gene (CHEK21100delC) is frequently found in families with MBC (13.5%) compared to healthy individuals (1.1%). It is associated with a 10-fold increase in risk for MBC and 2-fold increase in risk for FBC (11).

PALB2 is a gene that has shown to interact with BRCA2 in several diseases, e.g., Fanconi anaemia. A genetic mutation in the PALB2 gene increases the risk for female breast cancer by 2,3-fold (12), but even though it is identified as potentially pathogenic, this mutation is rare in MBC (1-2%) (13).

The next gene that was found to be associated with an increased risk of MBC is CYP17 gene. CYP17 gene is located on chromosome 10 and is responsible for the production of P450c17 alpha. P450c17 alpha is important for the biosynthesis of androgens (14). A case-control study from Scotland has shown that polymorphism of this gene increases the risk of breast cancer in male. The genetic variant is more frequent in MBC patients compared to the control group (15).

5.2 BRCA2 MUTATIONS

BRCA2 mutation is a major risk factor in the development of MBC. Approximately 4-10% of male breast cancer patients carry the mutation. The incidence of the BRCA1 gene mutation in MBC patients (approximately 1%) is much lower than the BRCA2 gene mutation (6,16). For BRCA2 mutation carriers, the risk of developing breast cancer increases 80 times compared to the general population (17). BRCA2, rather than BRCA1 gene mutations play an essential role in the development of MBC (6), and are related to a higher tumour grade ($p<0.001$) (18).

5.3 ALTERATIONS OF THE ESTROGEN TO ANDROGEN RATIO

Conditions that alter the estrogen-to-androgen ratio increase the risk of developing breast cancer in males (19). These include klinefelter´s syndrome (KS), obesity (20) and exogenous estrogen (estrogen-based prostate cancer therapy) (21) or testosterone (hypogonadism treatment with testosterone) use (22). Elevated circulatory levels of estradiol, rather than androgen levels, are the enhancing factors (23).

Klinefelter´s syndrome is a genetic disorder of the sex chromosomes first described by Harry F. Klinefelter in 1942. Affected males have an additional X chromosome in their genome (47,XX Y), which is associated with gynecomastia, aspermatogenesis, small testicles, hypoleydigism and increased excretion of follicle-stimulating hormone (FSH) (24). Among other conditions that enhance the risk for MBC, Klinefelter syndrome is one of the strongest with a relative risk of 29,64 (20). A retrospective study from Sweden (n=93) revealed that approximately 7.5% of MBC patients carry the genetic abnormality XX Y (25). Klinefelter syndrome increases the risk of developing male breast cancer by approximately 20 fold (19). Other studies suggest that the relative risk increases even up to 50-fold compared to normal males (26). The relation between KS and MBC is thought to be via the hormonal changes in KS, which leads to low testosterone and high gonadotropin concentrations (27).

5.4 PRIMARY TESTICULAR CONDITIONS

Thomas et al. have identified additional risk factors for the development of MBC. One of the most strongly associated conditions was undescended testis. Other conditions that increased the risk for MBC development were orchiectomy, inflammation of the testis, testicular injury, late puberty and infertility. A decrease in risk is associated with an increased number of offspring (28). These conditions are have impact on the hormonal balance and therefore increasing the risk of MBC development.

6. PRESENTATION

6.1 CLINICAL CHARACTERISTICS

The initial diagnoses of MBC usually takes place 5-10 years later than in women (29). MBC typically presents as a painless, retroareolar mass, which may be accompanied by additional symptoms listed in Table 1 (30). The majority of MBC´s are unilateral. Bilateral breast cancer represents only 1.4% of all breast cancers in men (31). Distant metastasis are present in 4% - 10.7% of the patients (32,33).

Table 1. Patient characteristics at presentation (34)

Signs and symptoms	Number of patients	Percentage
Breast mass	196	85.6%
Nipple ulceration	18	7.9%
Nipple bleeding	20	8.7%
Nipple discharge	13	5.7%
Nipple retraction	60	26.2%
Local pain	22	9.6%
Inflammatory skin	11	4.8%
Other	70	30.6%

Cited from Gross et al (2000).

6.2 PATHOLOGIC CHARACTERISTICS

Several hormonal receptors are identified in MBC. These include progesterone receptor (PR), estrogen receptor (ER), human epidermal growth factor receptor 2 (HER2/neu) overexpression and androgen receptor (AR).

Progesterone receptor positivity in invasive MBC is very abundant (92.3%) (35). MBC is highly ER positive. Around 96% of MBC patients with invasive carcinoma carry this receptor (35).

HER2/neu is a transmembrane glycoprotein that helps to control the epithelial cell´s growth and differentiation (36). HER2/neu overexpression is present in 16% of invasive MBC patients (35) and is associated with a lower overall survival compared to HER2/neu negative patients (36).

AR is present in 34%-87% of MBC patients (37,38). Furthermore, AR positivity is more related to the well-differentiated type of breast cancer ($p=0.08$), rather than to tumour stage, patient age, or expression of progesterone receptor and p53 protein (38). Most of the clinicopathologic features have no relation to AR positivity (38).

Triple-negative tumours (ER negative, PR negative and HER2/neu negative) are rare in primary invasive MBC (3.6%) (39).

In general, MBC is related to high rates of receptor positivity and therefore provides specific treatment opportunities in targetting these hormones and receptors.

6.3 BREAST CANCER SUBTYPES

There are 2 different molecular subtypes identified in MBC: luminal A and luminal B. The luminal A type is more common (83%). The mean age for both subtypes slightly differs (subtype A: 58 years; subtype B 64 years). Histologically, there at least 2 types of cancer identified: invasive ductal carcinoma and invasive papillary carcinoma (40). Other types include lobular carcinoma and several forms of ductal carcinoma (mucinous, tubular, scirrhous, inflammatory, etc.), but these are rare (41). Invasive ductal carcinoma (IDC) is the most common and represents approximately 90% of the cases.

The subtypes have some differences in their nuclear grade. Nuclear grade 1 is rare and belongs to luminal A subtype. Nuclear grade 3 cancers are more frequently in luminal B subtype. Lymph node involvement is more common in luminal B subtype (71%) (40).

Immunohistochemically, the luminal subtypes express Immunostains in different frequencies. In total there are at least 6 different immunostains identified in MBC: ER=estrogen receptor; PR=progesterone receptor; HER2/neu=human epidermal growth factor receptor 2; CK5/6=cytokeratin; EGFR=epidermal growth factor receptor; NF-κB=nuclear factor-κB. Estrogen receptor and progesterone receptor expression are more prevalent in luminal A type (ER:83%; PR:88%). HER2/neu immunostain exist only in luminal B subtype. CK 5/6, EGFR and NF-κB exist in both subtypes (42,43).

7. DIAGNOSTIC EVALUATION AND STAGING

7.1 MAMMOGRAPHY AND OTHER DIAGNOSTIC METHODS

Data about the different diagnostic procedures is very limited in MBC. Compared to women, men are usually not included in mammography screening programs (44). Despite that, mammography is a highly sensitive (90%) and specific (90%) method to diagnose MBC (45). It is part of the so called tiple assessment, which is widely used to diagnose MBC. It includes clinical assessment, mammograpy/US and core biopsy (46). When suspicious lesions are found during physical examination, a mammography is the next step (47).

MBC has characteristic mammographic signs, which sometimes differ from female breast cancer. Cancerous lesions are frequently located subareolar and are commonly oriented eccentric to the nipple. Compared to female breast cancer, male breast cancer lesions have more often well-defined margins, and calcifications are rarer and coarser. Benign lesions typically appear lucent, just like in female breast cancer (48).

Ultrasound (US) can be useful, when the mammography is not applicable or has unclear findings (47). Invasive cancers often present as a solid mass on US. After discovering a suspicious or complex cystic mass on US, a biopsy should be performed to rule out the possibility of malignancy (49). US is further useful as a guidance during biopsy (46).

During the physical examination, MBC patients typically present with a unilateral, painless mass in their breast. Additional possible symptoms are listed above in Table 1. It is also important to discuss the patient´s family history of breast cancer, past medical history and possible exposure to estrogen (30,50).

7.2 BIOPSY

In general, there are 4 types of biopsy to confirm the diagnosis, fine-needle biopsy, core biopsy, surgical biopsy and image-guided biopsy (30,51,52). Core biopsy is highly effective at diagnosing invasive breast cancer and does not require surgery. It should generally be used more preferably (30).

7.3 DIFFERENTIAL DIAGNOSIS

Gynaecomastia, meaning enlargement of the glandular tissue, is the most common disease of the male breast which must be differentiated from MBC (54). It is very common in older men and is usually associated with a hormonal imbalance resulting from abnormal changes of the testis, prostate gland, thyroid gland, pancreas, and liver (55,56).

Gynaecomastia can either be pubertal/hormone induced or idiopathic/non-hormonal. Hormone induced gynaecomastia is usually bilateral and diffuse, whereas idiopathic gynaecomastia tend to be unilateral. With temporal progression, the disease usually becomes more fibrous (57).

Histologically, gynaecomastia presents as ‘‘a vascular fibroblastic stroma with periductal cuffs of loose connective tissue and by actively proliferating ducts… In specimens of gynecomastia of longer duration, including those due to the administration of estrogen, there was progressive fibrosis and hyalinization of the stroma associated with regression of the epithelial proliferation and later with a gradual reduction of the number of ducts.“ Symptoms like pain or tenderness are typically more associated with an acute onset (58).

Another differential diagnosis is Pseudogynaecomastia. It is associated with an increase in subareolar fat, but glandular tissues are not enlarged (56). Gynaecomastia can be

differentiated from Pseudogynaecomastia by physical examination. During palpation, gynaecomastia presents as a soft, elastic or firm tissue mass that is concentric to the nipple-areolar complex, whereby in pseudogynecomastia this is not found. Cancer presents as a firm or hard mass outside the areola, is more often unilateral and may have skin changes, nipple retraction and bleeding (56). If the physical examination does not provide enough clinical findings to distinguish carcinoma from benign breast diseases, a mammography (90% sensitivity and specificity) should be performed (45).

7.4 STAGING AND WORKUP

Staging workup, meaning to analyse the extent of spread of cancer cells in the body. It is important in order to select the appropriate treatment option. The spread of cancer cells into lymph nodes and other regions of the body is generally similar for men and for women (41).

The full workup for suspected breast cancer includes 3 steps: confirmation of diagnosis, evaluation of the stage and the selection of therapy (41). The stage is mostly determined by the tumour size, lymph node involvement, ER and PR levels in tumour tissues, HER2/neu status and tumour grade (41).

According to most literature, MBC is staged using the Tumour-Node-Metastasis classification and is identical to the female staging system. It includes the extent of the tumour, regional lymph node involvement and distant metastasis involvement (41). Masci et al. have identified that out of 91 MBC patients with invasive carcinoma from 2000 until 2013, 33% presented at stage 1, 39% at stage 2, 22% at stage 3 and 4% at stage 4 (with metastasis) (35). According to a study from Denmark, 35% of the cases were stage T1, 11% T2, 42% T3 and 12% T4 (59).

ER, PR and HER2/neu status are determined via biopsy (41). ER and PR levels are meastured by immunohistochemistry and HER2/neu expression are assessed by immunohistochemistry or in situ hybridisation (60).

Other possible diagnostic methods for metastatic staging include ct scan, pet scan, bone scan and chest x-ray. Ct scan and pet scan can detect tumours outside the breast (lung, liver, bone, lymph nodes). Bone scan and chest x-ray can determine the cancer spread into lung and bone tissue (51).

7.5 DIFFERENCES COMPARED WITH THE APPROACH IN WOMAN

MBC is diagnosed 5-10 years later, and at higher stages than in FBC (61,62). According to a population-based study of the National cancer institute, 94.4% of females with a positive first-degree family history underwent mammography screening and 78.8% underwent clinical breast exaination. Breast self examination was performed in 45% of these patients (50,63).

To my knowledge, there is no routine screening program in men due to the low incidence of the disease, even though it could be beneficial for high risk MBC patients (positive family history, BRCA2 mutation, testicular disease, obesity, KS).

8. SURGICAL TREATMENT

Surgical removal of cancer tissue is a major component of treatment, especially for stage I and II (40). There are several surgical techniques that have been used in the last decades. These include breast-conserving surgery (BCS) and different types of mastectomy (total/simple mastectomy, radical mastectomy and modified radical mastectomy) (64,65).

The American National Cancer Database from 1998 until 2012 with 23.305 non-metastatic MBC patients and 2.678.061 FBC patients revealed different treatment patterns. Breast conserving therapy was used more often in female patients, and non-metastatic MBC patients received mastectomy more frequently. Radiation therapy after mastectomy or breast-conserving surgery was less frequently used in MBC patients (66).

One of the largest cohort studies that analysed treatment patterns for MBC over the years was conducted by S. Yadav et al., relying on the data from the National Cancer Data Base in the United States from 2004 until 2014, and included 10,873 MBC patients (65).

The different types and frequencies of surgery are listed in Table 2.

Table 2. Treatment patterns from 2004-2014 (65).

Type of surgery	Number of patients (percentage)
Breast-conserving surgery	2572 (23.7%)
Total mastectomy	7755 (71.3%)
Unknown	137 (1.3%)
No surgery	409 (3.7%)

Citing from Yadav et al. (2019).

The most common surgical treatment that was used is total mastectomy (TM) (71.3%). In contrast, breast-conserving surgery (BCS) was only used in 23.7% of the cases. During the study (2004-2014), the surgical treatment patterns have changed. BCS has dropped in usage, whereas TM was becoming significantly more popular. Contralateral prophylactic mastectomy (CPM) was rarely performed (6.1%). For those who underwent surgery, 95% of the patients also received sentinel and/or axillary node dissection (65).

According to a Chinese study, there was no difference in loco regional recurrence for radical mastectomy and modified radical mastectomy in MBC patients where 81.4% had infiltrating ductal carcinoma and 93.7% were ER (estrogen receptor)/PR (progesterone receptor) positive. Both treatment options appeared to have similar outcomes (67).

Compared to FBC patients, MBC patients were treated more frequently with radical mastectomy and modified radical mastectomy (68).

8.1 EARLY STAGE DISEASE

In the early stage of breast cancer there are 2 treatment options available: surgery (with or without radiation therapy) and adjuvant therapy (chemotherapy, endocrine therapy and HER-directed therapy). The treatment options are generally similar in male and female breast cancer. The primary surgical treatment includes the modified radical mastectomy with additional axillary node dissection. A more conservative treatment strategy includes breast conserving surgery (also called lumpectomy) combined with radiation therapy. Adjuvant therapy consists of either chemotherapy, endocrine therapy or HER2-directed therapy. Agents used in chemotherapy include cyclophosphamide plus methotrexate, doxorubicin and/or paclitaxel. Endocrine therapy agents include

tamoxifen and aromatase inhibitors (AI). In HER2-directed therapy, mainly trastuzumab and pertuzumab can be used (41).

8.2 MANAGEMENT OF THE REGIONAL NODES

Approximately 50-60% of MBC cases have axillary nodes affected (69).

Since the axillary node status a very important predictive factor and helps to determine prognosis and therapy, sentinel lymph node biopsy is essential for initial staging. Sentinely lymph nodes are defined as the lymph nodes (one or more) that drain directly from the primary breast tumour. Agents that can be used include technetium Tc99m-labeled sulfur colloid and vital blue dye (60).

Sentinel lymph nodes were successfully identified in 96% - 100% of the cases when SLN biopsy was performed. False negative results, meaning to detect a positive axillary lymph node via axillary node dissection after a primary negative SNL biopsy, could not be seen (70,71).

SLN biopsy can be useful in the staging process, especially when no lymph nodes can be clinically palpated (72).

8.3 LOCALLY ADVANCED DISEASE

Locally advanced disease refers to the tumour stages T3 and T4 (73), and is usually treated with neo-adjuvant therapy (74). Metastatic disease can be treated with initial hormone therapy and/or chemotherapy (41).

8.4 ADJUVANT THERAPY

Adjuvant therapy should be applied after the primary surgical treatment to treat early/localized MBC. Adjuvant therapy includes chemotherapy, endocrine therapy and HER2-directed therapy (biologic therapy) (41).

Adjuvant chemotherapy and adjuvant endocrine therapy are further described in the sections 8.7 and 8.8.

HER2-directed therapy includes trastuzumab, which is a humanized immunoglobulin G1 (IgG1) that binds to the extracellular HER2 domain (75,76). It leads to the activation of antibody-dependent cellular toxicity, stops intracellular signaling, and limits angiogenesis and DNA repair. Trastuzumab targets mainly the HER2-overexpressing cancer cells (76). Clinically, trastuzumab was beneficial in the overall survival when being used in combination with chemotherapy, compared to the use of chemotherapy alone. The adjuvant use is approved to be beneficial against HER2 positive cancers and reduces the recurrence risk for tumours >1 cm or for tumours with lymphatic spread of the disease (41,75). Since MBC overexpresses HER2 only in approximately 13%, the role of HER2/neu-directed therapy compared to chemotherapy and endocrine therapy must be further studied (36).

Orchiectomy, meaning the removal of testes, is another controversial type of adjuvant therapy for treating primary and metastatic breast cancer. According to literature extracted from FBC, there is the possibility that this procedure might cause disease regression for both types of breast cancer, especially for secondary bone manifestations (77).

8.5 RADIATION THERAPY

According to the National Cancer Data Base, around 40% of the total MBC patients were treated with adjuvant radiotherapy. Adjuvant radiation therapy was used more frequently after BCS (70.2%), than after mastectomy (29.2%). Adjuvant radiation therapy after mastectomy was used more frequently for higher tumour stages (stage 1 (6.7%); stage 2 (27%); stage 3 (64.3%). Regardless of the stage, combining radiotherapy after mastectomy has shown low overall survival rates. The use of radiotherapy after BCT has risen throughout the years (2004:66%; 2014:74.6%). When radiotherapy was used after BCS, the survival for all stages increased significantly (65).

One study from London has found that PMRT (post mastectomy radiation therapy) has shown to not benefit the overall survival ($p=0.872$), but has a positive impact on preventing local recurrence ($p=<0.0001$). Especially patients with high risk features (positive lymph node, ≤2mm, unknown margin during surgery or advanced stage) benefit the most from post mastectomy radiation therapy (78).

Another study has shown that the overall survival after 5 and 10 years improved with radiation therapy for non-metastatic MBC patients (p=<0.001) (66).

8.6 SYSTEMIC THERAPY

Systemic therapy includes the neoadjuvant, adjuvant or palliative treatment with chemotherapy, hormonal therapy or HER2-directed therapy (79).

According to recent studies, neoadjuvant therapy (NT) with chemotherapy or endocrine therapy did not improve the overall survival compared to those who did not undergo this treatment. NT was more frequently used and combined with BCS at higher tumour stages (T3-T4) (73).

Based on female guidelines, first line neoadjuvant therapy should be considered in all inoperable locally advanced breast cancers patients (74).

8.7 CHEMOTHERAPY

The use of chemotherapy in MBC remains an understudied field (72). Chemotherapy can be adjuvant, neoadjuvant and palliative (46), and includes the use of either cyclophosphamide plus methotrexate and fluorouracil (CMF), cyclophosphamide plus doxorubicin and fluorouracil (CAF) or doxorubicin plus cyclophosphamide with or without paclitaxel (AC, AC-T) (41). In the past, chemotherapy was more frequently used in FBC patients (68).

Relying on guidelines and experience in FBC, adjuvant chemotherapy has the largest benefit against hormone receptor negative MBC and taxanes can be added for lymph node involvement (74).

8.8 ENDOCRINE THERAPY

Generally, there is a lack of controlled studies that compare different adjuvant treatment options in MBC (41). Endocrine therapy includes the use of anti-oestrogens, anti-androgens and aromatase inhibitors with or without gonadotropin releasing hormone (GnRH) analogue. Male breast cancer has a high frequency of hormone-receptor

positivity (80). Tamoxifen is an anti-oestrogen, that retrospectively has shown to improve disease-free survival when being used as adjuvant therapy after primary treatment in patients with lymph node involvement, especially for ER positive patients (34,80,81).

Endocrine therapy is recently becoming more popular. In 2004, 48.6% of the ER-positive MBC patients received endocrine therapy, which increased to 69.5% in 2014 (65).

On the other hand, tamoxifen has several side effects that are frequently seen during the treatment. These include a decrease in libido, weight gain, hot flashes, mood alterations, deep venous thrombosis, depression, etc (82).

Anti-androgen therapy was used in small clinical studies and included the use of cyproterone acetate (CA). It has shown to be effective in treating metastatic breast cancer and has been responsible for lowering estradiol and testosterone levels. In contrary to expectations, the hormonal changes from this therapy were not responsible for the degree of tumour response (83), but due to the small amount of patients included in the study this remains not definitive. CA treatment was associated with a partial or complete tumour response in 7 out of 10 patients (83,84).

Aromatase inhibitors (AI) are poorly researched in MBC. According to a pooled analysis which included 15 studies of MBC cases with ER positivity and metastasis, third generation AI's (anastrozole, letrozole, exemestane) were given in first line to 61.5% of the patients. Gonadotropin-releasing hormone analogue was added in 37.1% of the cases and resulted in a 3 times better clinical benefit than solo administering AI´s, but changes in overall survival and progression-free survival were not found (85).

8.9 BISPHOSPHONATES

Bisphosphonates include the adjuvant treatment with zoledronic acid, sodium clodronate and others (86). Their use is mainly based on research and surveys in women (87).

Most of the women who were treated with bisphosphonates were postmenopausal (68.1%), received chemotherapy (78%), were hormone receptor positive (61.1%) and received bisphosphonates every 6 month for 3 years (73%). The purpose of the

treatment was to reduce bone recurrence (66.9%), to prevent cancer treatment complications (16.6%), to prevent bone loss (61.3%) and to prolong survival (23.9%). Bisphosphonate treatment was accompanied by several side effects. These include flue-like symptoms (44%), bone pain (42%), etc. The benefits of bisphosphonates in early FBC treatment have been seen in a significant reduction in recurrence, distant recurrence, bone recurrence and mortality, mainly in postmenopausal women (87).

Their tolerability and efficacy in men requires further research.

9. PROGNOSIS AND SURVEILLANCE

The diagnosis of MBC is usually made at a later stage compared to FBC which might explain the poorer outcomes found in numerous studies (1,88). MBC has a lower overall survival after 5 and 10 years compared to FMB of the same stage ($p<0.001$). The addition of adjuvant radiation therapy (for BCT and PMRT (postmastectomy radiation therapy)) has shown to improve the overall survival after 5 and 10 years ($p=<0.001$) for both MBC and FBC (88). Another study revieled that the 10 years survival of MBC with axillary node involvement is approximately 10% (89).

Strong negative predictive factors for survival are lymph node involvement and duration of symptoms. Receiving treatment within 6 months after onset of symptoms improves the survival compared to the start of treatment later than 6 months ($p=0.03$). Axillary node negative patients have a better relape-free rate (87%) compared to axillary node positive patients (30%) after 5 years ($p=<0.001$) (66,90).

Positive predictive factors that have were identified are a short time between onset of symptoms and diagnosis, less radical surgery and treatment with systemic adjuvant therapy (91).

Surviving male breast cancer is associated with an increased risk of developing contralateral breast cancer (30-fold). That is significantly higher than in females who survived breast cancer (2-4-fold) (92). MBC survivors who have additional risk factors like klinefelter´s syndrome or BRCA mutations are at even higher risk (93). These patients could benefit from follow up breast imaging. Even tho the importance of breast imaging in MBC surveillance is poorly supported by randomized clinical trials, annual

mammography is recommended to detect early residual disease in male patients who survived breast cancer (93).

As described for FBC in the National Comprehensive Cancer Network guidelines, male breast cancer survivors are suggested to follow up with history and physical examination twice a year for 5 years (93). Since there is a major relation between inherited genetic mutations and MBC, genetic testing should be recommended for all MBC survivors to improve self-care and possible consequences for relatives.

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