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Review

An Update on the General Features of Breast Cancer in Male Patients- a Literature Review

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Abstract: Male breast cancers are uncommon, as men account for less than 1 percent of all breast carcinomas. Among the predisposing risk factors for male breast cancer, the following appear to be significant: a) breast/chest radiation exposure, b) estrogen use, diseases associated with hyper-estrogenism, such as cirrhosis or Klinefelter syndrome, and c) family health history. Furthermore, there are clear familial tendencies, with a higher incidence among men who have a large number of female relatives with breast cancer and d) major inheritance susceptibility. Moreover, in families with BRCA mutations, there is an increased risk of male breast cancer, although the risk appears to be greater with inherited BRCA2 mutations than with inherited BRCA1 mutations. Due to diagnostic delays, male breast cancer is more likely to present at an advanced stage. A core biopsy or a fine needle aspiration must be performed to confirm suspicious findings. Infiltrating ductal cancer is the most prevalent form of male breast cancer, while invasive lobular carcinoma is extremely uncommon. Male breast cancer is almost always positive for hormone receptors. A worse prognosis is associated with a more advanced stage at diagnosis for men with breast cancer. And randomized controlled trials which recruit both female and male patients should be developed in order to gain more consistent data on the optimal clinical approach.

Keywords: male; breast; cancer; diagnosis; treatment; prognosis

1. Introduction

Female breast cancer is the most frequently diagnosed tumor and one of the leading causes of cancer-related mortality worldwide. Male breast cancer is uncommon, representing less than one percent of all breast cancers. It is more prevalent in elderly men and resembles postmenopausal breast cancer in its behavior, according to various studies, including that of Garreffa[1]. However, the incidence is increasing, reaching 15 percent in some patient groups over the course of their lives. A study by Abdekwahab Yousef [2] reports that: age, hormonal imbalance, radiation exposure, and a family history of breast cancer are the most significant risk factors for the development of male breast cancer. Instances of the latter can be linked to mutations in genes with high or low penetrance. A BRCA2 gene mutation is the most important risk factor for the development of male breast cancer.

The majority of cases are diagnosed late due to a lack of awareness of the existence of this cancer in males and ignorance of the associated risk factors.

In addition to the above-mentioned issues, men with breast cancer have an elevated risk of developing a second cancer.

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2. Materials and Methods

In order to achieve an updated and extensive literature review on the theme of male breast cancer, an ample research was conducted between the 9th and the 23rd of May 2022 in several international databases, as follows: 1. On www.scicencedirect.com ,the search terms were : "breast cancer in male systematic review" between 2000-2022 and also "male breast cancer" , with the mention that "review" as type of article between 2018-2022 and having "medicine and dentistry" as a domain. Furthermore, another association of terms that were searched for was "breast cancer in men systematic review". 2. On www.pubmed.gov the terms " male AND breast AND cancer" and also "breast cancer in men" were looked up with the settings: systematic reviews from the year 2000, in Humans, articles in English. 3.Other quests on: www.pubmedncbi.nlm.nih.gov , www.oxfordjournals.org and www.sciencedirect.com, having as settings: reviews, in Humans, article in English, domain medicine and dentistry, looked also for meta-analysis and randomized control trials, using the terms: "male AND breast AND cancer" and "male breast cancer surgery" and "male breast cancer(treatment)(systematic) review study".

3. Results

3.1. Risc, biology, diagnosis

3.1.1. General facts

Taking into consideration that men's breast cancer causes, optimal treatments, and medical/psychosocial consequences are poorly understood, a systematic review of the literature in the English language was conducted by Ruddy [3]to identify various research materials, relevant to breast cancer in men, between 1987 – 2012,materials that included at least 20 patients.Known risk factors encompass BRCA2 mutations, (80 times the risk of the general population, according to Fox[4], Peshkin[5]), and according to Nguyen [6], there are 11 other gene mutations , apart from BRCA, that might trigger a similar outcome. Other factors implied are: age, conditions that alter the estrogen/androgen ratio, and radiation. Due to the incomplete clinical picture resulting from insufficient studies, diagnostic and treatment tactics in men are generally induced from those in women, even though disease biology is different between the two sexes. According to a research by Gucalp [7], male breast cancer is almost exclusively hormone receptor positive (+), including androgen receptor (AR), and is associated with a higher prevalence of BRCA2 germline mutations, particularly in men at an increased risk for developing high-risk breast cancer. To better characterize male BC, additional research is required. Men may experience sexual and hormonal side effects of endocrine therapies, as well as unique psychosocial effects of the disease, as part of their survivor issues.

In a systematic review by Liang[8] , CHEK2*1100delC is associated with an increased risk of breast cancer in both men and women. Furthermore, a recent systematic literature review by Chamseddine [9] looked at several male breast cancer (MBC) susceptibility genes. Different genes involved have been found, but the risk for individuals who have a pathogenic variant in each of these genes (i.e. penetrance) is not known until the moment. In order to better summarize current estimates of penetrance, an analysis of studies was done on the subject of reporting the penetrance of MBC susceptibility genes. From a number of 12,182 abstracts, fifteen studies measuring gene penetrance covering five putative male breast cancer genes were found: ATM, BRCA1, BRCA2, CHEK2, and PALB2. This study supports the conclusion that pathogenic variants in ATM, BRCA2, CHEK2 c.1100delC, and PALB2 increase the risk of MBC, while pathogenic variants in BRCA1 may not be associated with an increased risk of MBC. Moreover, Friebel [10]shows in a systematic review that the cancer risk of women who have inherited a BRCA1 or BRCA2 (BRCA1/2) mutation is highly variable.

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Although additional research is necessary to confirm certain associations, sufficient information is available to use certain risk factors in risk counseling or lifestyle modification to reduce cancer risk in BRCA1/2 mutation carriers.

A recent (2021) systematic review and meta-analysis by Davey looks at the relevance of the 21-gene expression assay in male breast cancer. The 21-gene assay provides prognostic information for early female breast cancer patients with estrogen receptor positivity and human epidermal growth factor receptor-2 negativity (ER+/HER2-).This signature in male breast cancer has not been validated (MBC). The results of the research showed that, for early-stage, ER+/HER2-breast cancer patients undergoing 21-gene expression assay testing, the expected scores for females and men are comparable.In the absence of stage matching, these results must be interpreted with caution.Validation of the 21-gene MBC assay is still necessary.

A study by Fentiman[11] underlines the endocrine risk factors. The significant increase in global age-standardized mean BMI in men is likely to lead to an increase in the incidence of diabetes of adulthood and metabolic bone disease (MBD).

Obesity is accompanied by metabolic changes that decrease androgens and sex hormone-binding globulin (SHBG), thereby increasing the availability of oestrogens. Klinefelter's syndrome (XXY) is associated with a 50-fold increase in MBC incidence compared to XY males; this is the strongest evidence for testicular dysfunction amplifying risk.

Symptomatically diagnosed cancers in men are typically advanced, indicating that earlier detection could improve prognoses. A research by Woods [12] identified potential screening benefits of screening high risk patients, such as: high sensitivity, and early detection.

In a review by Nofal [13], it was concluded that male breast cancer presents typically as a painless retroareolar mass requiring triple evaluation.The diagnosis requires a high index of suspicion due to the lack of awareness of this type of cancer in males.

3.1.2. Gynaecomastia and pediatric cases

Gynecomastia is the leading cause of male breast enlargement.This could be physiological, idiopathic, or pathological in nature, as stated in a review by Shaaban [14]. A review by Billa[15] finds that 45 to 50 percent of adult men with GM may have an underlying pathology, such as aggravating medications, systemic diseases, obesity, endocrinopathies, or cancer. Mammography and ultrasound are both sensitive and specific for distinguishing GM from breast cancer.When clinical findings suggest malignancy and imaging results are inconclusive, histological confirmation should be sought. It is essential to distinguish between gynecomastia, a common cause of male breast enlargement, and breast cancer for proper treatment.

In comparison with core needle biopsy, fine-needle aspiration biopsy (FNA) has been demonstrated sensitive and specific in assessing breast tumor lesions in female patients. Few studies of this nature have been conducted on men. In a research presented by Hoda [16], ana evaluation was done of the patients who had fine-needle aspiration (FNA) at Massachusetts General Hospital . The procedure had been performed for palpable breast lesions, in the timeline January 2007 - December 2016. The conclusion was that FNA allows for the evaluation and diagnosis of palpable male breast lesions in a sensitive, specific, and safe manner.

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As presented in a research by Ghilli [17], secretory breast cancer (SBC) is one of the rarest forms of breast cancer (BC), accounting for the vast majority of BC in children. Nonetheless, it generates a great deal of interest due to its peculiar morphology and genetic characteristics. SBC is a rare form of breast cancer characterized by triple-negative characteristics and an unexpectedly favorable prognosis. More information is required to fully comprehend this cancer's behavior, and genomic profiling may help improve its diagnosis and treatment.

Gynaecomastia has been described also as appearing after childhood cancer, as shown in a study by Shahriari [18] which shows that more than 80% of children with cancer today can be cured. The treatment of childhood cancer focuses not only on improving survival, but also on reducing late effects. The purpose is that children with a cancer diagnosis survive and enjoy a high quality of life. Gynecomastia and fertility outcomes of childhood cancer survivors should be considered in the follow-up of adolescents and young adults, and should be approached accurately and managed by multidisciplinary teams. Moreover, in a systematic review presented by Wang[19], subsequent male breast cancer(SMBC) in cancer survivors, compared to the general population can have an elevated risk of appearance , but the absolute risk is low. Male CCSs (childhood cancer survivors) with symptoms possibly related to SMBC should be thoroughly examined.

3.1.3. Metastases

A literature review by de Almeida Freire[20] draws attention towards uncommon metastatic sites. For instance, in the oral and maxillofacial region of male patients, breast metastases are exceedingly rare; however, clinicians should consider breast metastasis when evaluating reddish oral nodules in older patients, including men, particularly those with a history of malignancy.

Invasive lobular carcinomas(ILC) are rarer than ductal forms and are known to have unusual metastatic locations, and they can appear as primary tumors, such as may be the case of the pancreas, form instance, as described by Mor [21] .

Statistically, approximately 20% of cancer patients have brain metastases (BMs). This proportion rises with age to roughly 40 percent among those under 18 years old. However, the actual prevalence may be higher, as these estimates are typically restricted to individuals who are being evaluated for therapy. According to a study presented by Che [22], most BMs metastasize from lung cancer (40 percent –50 percent), breast cancer (15 percent –25 percent), and melanoma (5 percent –20 percent). However, cancer patients with BMs continue to have a poor prognosis, with a relatively low median survival (2,9 months for newly diagnosed malignancies) and 2-year survival rate (8 percent). Increasing evidence suggests that gender is associated with the survivability of the vast majority of malignant tumors. In addition, numerous studies have demonstrated that the male gender is an independent risk factor for a shorter survival rate in BMs patients. The conclusion of the study was that middle-aged females had an increased risk of developing BMs, whereas middle-aged males with BMs had an increased risk of poor survival.

3.1.4.Image-based diagnostic methods

Due to the small size of male breasts, physiological and pathological processes arising from the breast and anterior chest wall may have similar clinical manifestations, as presented by Yang [23]. As described by Mango [24], men presenting with breast symptoms may pose unique diagnostic difficulties for the radiologist, especially if imaging findings are not typical for gynecomastia or carcinoma. When radiological findings are ambiguous or suspicious, imaging is frequently necessary to localize and

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characterize the lesion and guide biopsy.Mammography, digital breast tomosynthesis (DBT), and ultrasound are the cornerstones of breast imaging evaluation. Symptomatic male breast imaging begins with a diagnostic mammogram and targeted ultrasound in patients 25 years old, as reported in a review performed by Chesebro [25]. If the breast finding is insufficiently imaged or occult on mammography, targeted ultrasound is required.

Similarly, mammography must be performed if the breast finding on targeted ultrasound in a younger patient is suspicious. Occasionally, additional imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and positron-emission tomography (PET) can supplement the investigation and aid in the planning of treatment.

In a systematic review by Dondi [26], which targeted to analyze the diagnostic performance and utility of 18F-FDG PET/CT in the evaluation of MBC, it was found that, despite the limitations of our review, 18F-FDG PET/CT appears to be an effective method for assessing MBC. The conclusion continued with the idea that further research is required to clarify the role of hybrid imaging with 18F-FDG in the evaluation of MBC, particularly in comparison to breast cancer in females.

In order to assess the potential added value of SPECT-CT quantitative analysis in the detection and differentiation of metastatic breast cancer lesions from degenerative lesions, a study was conducted by Gherghe[27]. The SUVmax value of metastatic bone lesions was significantly higher than that of degenerative bone lesions ($p< 0.001$).At an SUVmax cutoff value of 16.6 g/mL, the diagnostic accuracy of SPECT-CT quantitative data analysis revealed a sensitivity of 91.5 percent and a specificity of 93.3 percent. The conclusion of the research was that quantitative analysis of SPECT-CT data can improve the diagnostic accuracy of distinguishing metastatic bone lesions from degenerative bone lesions, leading to more appropriate treatment and improved follow-up in metastatic breast cancer patients.

In the given literature context that microcalcifications (MCs) are significant breast cancer disease markers, numerous studies have been conducted on their characterization in female breast cancer (FBC), but their composition in male breast cancer is unknown (MBC). According to Caldarone [28], as Raman spectroscopy (RS) is a molecular spectroscopy that can rapidly and without staining examine the biochemical composition of MCs, an algorithm to identify the mineral components present in MCs from raman images can be used to study and compare MCs identified on breast cancer pieces from male to female patients. This suggests that these patients have characteristics that distinguish them from the FBC previously studied.

In a review from 2018, Shin [29] found that the literature on the use of breast MRI in male patients is also extremely limited.

Although it is uncommon and not recommended as a standard clinical practice to perform breast MRI on male patients, even in the presence of a breast cancer diagnosis, there are a few instances in which MRI may be helpful to clinicians and surgeons.

3.1.5. Pathology

Shaaban[14] finds that the most prevalent histology is grade 2 ductal carcinoma with no special subtype. MBC is frequently of the luminous A phenotype comparable to postmenopausal breast cancer in women. A research by Fentiman[30] showed that using hierarchical clustering, ER was clustered with PR in FBC, but with ER and AR in MBC.

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Oncotype DX appears to be effective in determining recurrence risk in selected MBC based on limited data.

Papillary in situ and invasive carcinomas are not uncommon in the male breast, unlike the female breast. Zhong [31] finds in a review that papillary lesions of the male breast papillary carcinomas span a wide clinicopathological spectrum, and both invasive and noninvasive papillary carcinomas have a favorable prognosis, as it is also reported by Avau [32] .

As presented by Fox[4], metastases to the breast also occur , but according to Akinseye [33] are rare and a differential with a primary lesion should be done. Lymphoma or leukemia, lung cancer, melanoma, prostate, gastric, renal, endometrial, pancreatic, esophageal, and thyroid cancers are the most prevalent primary malignancies affecting the breasts (in descending frequency).In most cases, the presence of breast metastases indicates a widespread disease.The prognosis is typically poor, and treatment focuses on the primary cancer.

For instance, Anagnostopoulou[34] describes how male breast lymphoma is a rare extranodal lymphoma of the mammary gland that may be primary or secondary. A breast lesion's excisional biopsy revealed chronic lymphocytic leukemia (CLL) with plasmacytoid features and immunoglobulin Gkappa monotypic expression in the mammary tissue.

Atypical ductal hyperplasia (ADH) greatly increases a woman's risk of developing breast cancer.Nevertheless, little is known about the effects of ADH in men. In a research conducted by Coopey[35] with a mean follow-up period of 6 years, no males in the series have developed breast cancer. The data inferred that , either ADH in men does not have the same risk as ADH in women, or surgical excision of a symptomatic gynecomastia lesion in men can effectively reduce the odds of breast cancer.

As presented by Wu[36] ,male cases of accessory breast cancer and sweat gland cancer associated with extramammary axillary Paget's disease are uncommon. In clinical diagnosis and treatment, it is necessary to precisely identify the disease and devise an appropriate treatment plan based on the patient's condition. The differential of axillary lymphadenopathy caused by various agents and the corresponding treatment can be helped by the reports of these two cases and the rationale presented.

Phyllodes tumor is a prototypical fibroepithelial neoplasm that accounts for 1% of breast neoplastic lesions that are typically detected in females and rarely in males. On the basis of predetermined morphological criteria, the World Health Organization classifies tumors as benign, borderline, or malignant. Infrequently documented in the English literature, squamous differentiation in Phyllodes tumors represents epithelial metaplasia, as shown also by Panigrahi[37].

Dermatofibrosarcoma protuberans (DFSP) is a soft tissue sarcoma that accounts for approximately 1 percent of all tumors. In addition, DFSP is frequently observed on the trunk and extremities, whereas breast occurrences are uncommon, as stated by Bouhani [38] .

3.2.Treatment

According to the ASCO guideline published in 2020, as presented by Hassett [39], many of the treatments for breast cancer in men are similar to those used for women. Men presenting hormone receptor-positive breast cancer who are candidates for adjuvant

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endocrine therapy have an indication to receive tamoxifen for an initial duration of five years; those who cannot be given tamoxifen due to counterindications may be prescribed a gonadotropin-releasing hormone agonist/antagonist plus aromatase inhibitor. After five years of tamoxifen therapy, have tolerated the treatment, and continue to have a high odds of recurrence may be given an additional five years of treatment. Men with early-stage disease should not be administered bone-modifying agents to prevent recurrence, but these substnaces may still be administered to prevent or treat osteoporosis. With the exception of cases of visceral crisis or rapidly progressive disease, men with advanced or metastatic disease should receive endocrine therapy as the initial treatment option. Targeted systemic therapy may be used to treat advanced or metastatic cancer using the same indications and combination treatments available for women. Men with a history of breast cancer treated with lumpectomy should receive an ipsilateral annual mammogram regardless of genetic predisposition; men with a history of breast cancer and a genetic predisposition mutation may receive a contralateral annual mammogram. All men diagnosed with breast cancer should receive genetic counseling and testing for cancer susceptibility genes in the germline.

In a research done by Trapani[40] in 2021 on the global aspect of treatment standards in breast cancer, it was found that this global landscape of BC treatment standards reveals that the majority are not context-appropriate.Research on the formulation of cancer treatment standards and novel platforms for developing and disseminating resource-appropriate guidance are of the utmost importance.

As the extent of changes in estradiol levels in male patients receiving standard endocrine therapies for hormone receptor-positive breast cancer is unknown and the impact of these changes on sexual function and quality of life has not been adequately evaluated, as shown in a randomized clinicall trial conducted by Reinisch[41] . In order to complete the research, patients were randomly assigned to 1 of 3 treatment arms for 6 months: tamoxifen alone, tamoxifen plus gonadotropin-releasing hormone analogue (GnRHa), or aromatase inhibitor (AI) plus GnRHa. The primary outcome measure was the change in estradiol concentrations from baseline to three months.After 3 and 6 months, secondary endpoints included changes in estradiol levels, additional hormonal parameters, adverse effects, sexual function, and quality of life. This phase 2 randomized clinical trial revealed that AI or tamoxifen plus GnRHa versus tamoxifen alone resulted in a sustained reduction in estradiol levels.The decreased hormonal parameters were associated with diminished sexual performance and life quality.

Giving an expert opinion in which regards best methods of approach, Duso [42] presents that there is a significant medical need to include male breast cancer patients in (more) prospective clinical trials. The call for equality in breast cancer care can be pursued in two divergent ways: (i) a gender-neutral delivery of breast cancer information, and (ii) the creation of separate sections in common studies, one for the more prevalent female breast cancer and the second, for the rare male breast cancer. We propose to differentiate male breast cancer care, recognizing that males have distinct onco-sexual and social needs that can only be shared partially.

In a review by Ahmed Jang Khan [43], it was found that, *i*n certain cases, breast conserving surgery (BCS) with sentinel lymph node biopsy (SLNB) remains an alternative to mastectomy for men with early-stage breast cancer. The identification and false-negative rates for SLNB were comparable to those of breast cancer in female patients, according to a research presented by Lin [44], who also shows that survival is improved by post-mastectomy radiation to the chest wall and 5-year tamoxifen treatment.

In which concerns disease staging and sentinel lymph node biopsy, Carter [45] and Gherghe[46] show that standard treatment for women with clinically N0 breast cancer is senti-

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nel lymph node biopsy (SLNB). However, there are no randomized controlled trials determining the optimal surgical management of the axilla in men. In males with clinically N0 breast cancer, the use of SLNB alone has increased while ALND has declined. Patients who underwent SLNB alone during the later time period, however, exhibited worse clinical characteristics and experienced variations in adjuvant therapy. This indicates a growing acceptance of SLNB for axillary management. Methods of axillary staging and their influence on the prognosis of males with breast cancer warrant additional investigation.

Aquaporins are membrane channels that belong to the large family of major intrinsic proteins (MIPs), of which there are thirteen classes with tissue-specific distributions in humans, as summed up by [47] Khan. As important physiological modulators of water and solute homeostasis, mutations and dysfunctions in aquaporins have been linked to pathologies in all major organs.

AQPs 1, 3, and 5 are highly expressed in breast, endometrial, and ovarian cancers, consistent with their gene regulation by estrogen response elements, and AQPs 3 and 9 are associated with prostate cancer.

Continuing research is defining avenues for pharmacological targeting of aquaporins as potential therapies to reduce the growth and invasion of female and male reproductive cancer cells.

3.2.1. Breast conserving surgery versus mastectomy

Fentiman [48] underlined that it is possible to make a compelling case for the use of neoadjuvant endocrine therapy to facilitate breast-conserving surgery. Although nomograms for predicting nodal status are inadequately calibrated, sentinel node biopsies have been utilized successfully to stage MBC. Male mastectomy is associated with psychological side effects, and there is no evidence that the needs of those with MBC are being met. The conclusions drawn by the previously mentioned research was that: collaborative research is required so that men can participate in meaningful randomized controlled trials (RCTs) to provide a rational, evidence-based basis for the surgical treatment of MBC. Furthermore, Williams [49] discusses the context for neoadjuvant treatment in relation to advanced disease and aims at the determination of the prevalence of neoadjuvant therapy (NT) in MBC patients and its effect on BCT(breast conserving therapy). The conclusion was that males with invasive breast cancer are expected to have a low BCT rate, but NT appears to decrease the use of mastectomy in patients with locally advanced cancers. Understanding the effects of BCT on locoregional recurrence, disease-free survival, and overall survival for MBC requires additional research.

In a study by Bakalov[50], it was underlined that, while adj-RT after BCS is associated with decreased mortality in MBC patients, adj-RT is omitted in up to one-third of MBC cases after BCS, despite being the standard of care.

Breast conserving surgery (BCS) was studied in comparison with mastectomy in male breast cancer(MBC) in a study by Saunder[51] in which, given the context that surgical indications for male breast cancer (MBC) have been largely influenced by clinical trials with a female predominance, a systematic literature review was done on studies that reported one or more of the following: overall survival(OS), disease free survival (DFS) and disease specific survival(DSS) stratified(sorted, selected) by surgical treatment (BCS and/or mastectomy) and/or radiotherapy compliance with BCS.

The majority of studies found no differences between BCS and mastectomy for DFS, DSS, or OS. BCS is a viable treatment option for MBC because it was associated with comparable oncologic outcomes to mastectomy, as it was also shown by de La Cruz[52] . However, the low rates of radiotherapy adherence among male patients who

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underwent BCS are concerning and demonstrate the importance of involving patients with MBC in the selection of a surgical treatment strategy.

A study by Deldar [53]looks at the aspects of postmastectomy reconstruction in male breast cancer and concludes that the limited the availability of research on chest reconstruction after mastectomy in male breast cancer patients.

Nonetheless, the available evidence suggests that reconstruction can restore a patient's body image; therefore, it should be considered and discussed routinely with male patients.

3.2.2 Adjuvant treatment

Tamoxifen is the only endocrine agent approved for the prevention and treatment of premenopausal and postmenopausal estrogen-receptor-positive breast cancer, as well as the treatment of male breast cancer.

Endoxifen, a secondary metabolite resulting from CYP2D6-dependent biotransformation of the primary tamoxifen metabolite, N-desmethyltamoxifen (NDT), is a more potent antiestrogen than either NDT or tamoxifen, the parent drug. In addition to its effects on ER, endoxifen's antitumor effects may involve additional molecular mechanisms of action. In phase 1/2 clinical studies, as is presented by Jayaraman[54], the efficacy of Z-endoxifen, the active isomer of endoxifen, was evaluated in patients with endocrine-refractory metastatic breast cancer, as well as patients with gynecologic, desmoid, and hormone-receptor-positive solid tumors, and demonstrated promising antitumor activity.

A report by Kraus [55] investigated the advantages and disadvantages of palbociclib plus endocrine therapy (ET) in men with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2negative (HER2) metastatic breast cancer (MBC).

Review of the global safety database revealed no new safety signals in men treated with palbociclib. Real-world data indicated that palbociclib plus ET is beneficial for men with MBC, with a safety profile consistent with previous findings in women with MBC.

This report's data on palbociclib in women and men, including clinical trial data, real-world data, and a well-established risk/benefit profile, led to US approval of an indication expansion for palbociclib to include men with metastatic breast cancer.

Forooshani [56] mentions that, unfortunately, the prognosis for patients with hormone-negative tumors or patients with therapy-resistance and metastasis remains dismal. New biomarkers are urgently required to predict the disease's progression, make better therapy decisions, and increase patient survival. In this regard, the Androgen Receptor (AR), a member of the superfamily of nuclear hormone receptors along with ER and PgR, emerges as an intriguing characteristic widely expressed in human BCs. The precise tumorigenic mechanism of the androgen receptor (AR) and the role of its endogenous ligands are not yet well understood, despite recent advances.

3.3. Breast cancer in transgender patients

As summarized in a research by T'Sjoen [57], The Endocrine Society recommends estrogens in conjunction with androgen-blocking drugs for transgender women. Feminizing treatment with estrogens and antiandrogens results in desirable physical changes, including increased breast growth, decreased facial and body hair growth, and fat redistribution in a female pattern. Patients should be informed of potential adverse effects, particularly those at risk for venous thromboembolism.

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The Endocrine Society's recommendations for transgender men include testosterone therapy for virilization, voice deepening, cessation of menstruation, and increases in muscle mass and facial and body hair. Due to the lack of evidence, gender nonbinary individuals should be treated on an individualized basis. Teenagers may be administered a pubertal suspension containing GnRH analogs, followed by sex steroids. Before any hormonal intervention, options for fertility preservation must be discussed. Morbidity and cardiovascular risk are unaffected by cross-sex hormones in transgender men, whereas it is unknown in transgender women.

Cancers caused by sexual steroid use are possible, but uncommon. The term "Transgender" refers to people whose gender identity and/or gender expression is different from the sex they were assigned at birth. As the number of individuals undergoing gender-affirming hormone therapy and gender-affirming surgery increases, radiologists must know progressively more about this population in order to be able to attend them properly. Even if diagnostic imaging methods and approaches for transgender individuals are similar to those for cisgender women, screening guidelines are different. Several professional and institutional guidelines have been developed to address breast cancer screening in the transgender population, particularly mammography screening in transfeminine individuals undergoing hormone therapy, as emphasized by Parikh [58].

3.3.1. Male to female

The therapeutic transition from male to female usually begins in late adolescence or adulthood, with the average onset being around 30 years of age. Current hormonal treatment protocols in transgender women combine high doses of estrogen and antiandrogen treatment to reduce testosterone levels in the blood. Likewise, the concomitant administration of progesterone would reduce the potential risk of breast cancer and cardiovascular events, as described by Martinez Ramos[59]. Male-to-female (MtF) breast cancer cases have nevertheless been reported since 1968, but the breast cancer risk of MtF patients remains unknown at the moment in which Hartley [60]decided to study the subject by looking at literature updates. Among the conclusions, there was the fact that breast cancer is present in MtF patients, who typically present with a palpable mass at a younger age. Also, pathology confirmed breast implant-associated anaplastic large cell lymphoma was described in the context of breast augmentation with bilateral silicone implants , as reported by Ali [61].

3.3.2. Female to male

The breast cancer risk and screening recommendations for transgender men or Female-to-Male (FtM) patients are still unknown, according to a systematic review presented by Hartley [62] that looked at patient demographics, breast cancer characteristics, presentation, and treatment.The conclusion was that breast cancer is present in transgender men, with risk dependent on top surgery; those who have had top surgery appear to have a lower risk than natal females.

Female-to-male (FtM) transsexuals , in the context of their testosterone therapy for masculinization, can have a modified risk of developing breast cancer.The purpose of the study by Fledderus [63]was to examine the evidence regarding the risk of testosterone therapy on breast cancer in female-to-male transsexuals and to assess breast cancer screening in this subgroup.The research concluded that few cases of FtM transsexuals with breast cancer have been documented.However, cases such as these alert physicians

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to the possibility that FtM transsexuals may develop breast cancer. Radiological screening of FtM transsexuals for breast cancer prior to mastectomy and histological screening of the mammalian tissue after mastectomy should be taken into account; physicians should appreciate and furhter decide with each individual FtM transsexual if screening is imposed by clinical or paraclinical data.

In which regards the long term effect of hormone replacement therapy HRT , an analysis from 2020 by Patel [64] concludes that, due to the paucity of long-term studies tracking breast pathology among transgender men and women, information about the risks associated with HRT is limited and often contradictory in the current literature and in this setting. The study concluded that the long-term effects of off-label pharmaceutical use to modify hormone levels and sexual characteristics in transgender patients have not been adequately studied. The propensity of steroid hormones to promote the development of certain cancers raises concerns regarding the safety of varying drug doses and combinations. Additional clinical and laboratory research is required to better establish dosing and safety guidelines for transgender patients.

3.4. Paget's disease

Paget's disease of the breast is characterized by eczematous changes of the nipple-areolar complex and, in the majority of cases, is accompanied by an underlying in situ or invasive breast carcinoma, an aspect underlined by Vergine [65].

Paget's disease is characterized histologically by epithelial cells with an abundance of basophilic or amphophilic, finely granular cytoplasm and a large, centrally located nucleus, which are most prevalent in the lower epidermal layers.Due to the rarity of the condition among breast cancers and the rarity of breast cancer in men, knowledge of the disease's presentation, course, and optimal treatment in male patients is derived primarily from case reports and extrapolation of findings from studies in female patients.Paget's disease must be distinguished from eczema, Bowen's disease, squamous cell carcinoma, and melanoma, among others. In a research by [66] Adams, it was also emphasized that Paget's disease must be identified clinically and pathologically, as the superficial lesion may be the only indication of an underlying ductal carcinoma and its presence may have prognostic significance.

3.5. Geographical specifics and distribution pattern

3.5.1. General facts

In a research dating from 2021, Pizzato[67] looked at mortality data in male breast cancer by analyzing, from 2000 to 2017, official death certification data and population estimates for breast cancer in men, reported by WHO and Pan American Health Organization. Death rates standardized by age were computed for selected countries and regions worldwide. Between 2015-2017, Central-Eastern Europe had a rate of 2.85 per million people, and Russia had a rate of 2.22, placing them among the highest. North-Western and Southern Europe, the European Union as a whole, and the United States exhibited rates ranging from 1.5 to 2.0. Lower rates were observed in most Latin American nations, with values below 1.35/1,000,000, compared to 1.22/1,000,000 in Australia and 0.58/1,000,000 in Japan. Age-adjusted death rates decreased between 10 and 40 percent between 2000-2004 and 2015-2017 in North-Western Europe, Russia, and the United States, and between 1.5 and 25 percent in the other regions studied, with the exception of Latin America (+0.8 percent). With the exception of Central-Eastern Europe, the anticipated rates for 2020 were favorable.

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The favorable trends in male breast cancer mortality rates over the past several decades are likely primarily attributable to advances in management. In some areas, the higher mortality rate is due to delayed diagnosis and limited access to effective treatment.

3.5.2. Male breast cancer in Africa

Ndom[68] included in a literature review papers that contained data on both male and female breast cancers in Africa -and, if both male and female breast cancer were available, the article was included. If two publications covered the same geographical region, only the one with the longer study period was included. 1201 male and 36,172 female breast cancer patients from 27 African countries were analyzed using random effects models and meta-regressions with mixed effects. In addition, male breast cancer patients in Africa were diagnosed at an average age of 54,6 years, seven years older than female patients. Male breast cancers in Africa are characterized by their late onset, and the male-to-female breast cancer ratio in Africa is higher than in developed nations. Fentiman[11] emphasizes the fact that the higher rates of MBC in Northern and Equatorial Africa are largely attributable to liver damage caused by endemic bilharziasis and hepatitis B, which results in elevated estradiol (E2) levels from hepatic androgen conversion.

In a retrospective study on male breast cancer in Tunisia, Methamem[69] found that invasive ductal carcinoma was the most prevalent histological subtype (95 percent of our patients). The series was divided into three immunohistochemical groups, with luminal A (68.2%), followed by luminal B (27.3%), and a single patient with a triple-negative tumor (4.5 percent). At 5 and 10 years, the overall survival rate (OSR) was 83,2 percent and 76,8 percent, respectively. Recurrence-free survival (RFS) was 64.5 percent at 5 years and 58.6 percent at 10 years. Age, clinical and histological tumor size, the presence of distant metastases, and the occurrence of recurrence all had a significant impact on the OSR. Recurrence-free survival (RFS) was affected by age, clinical and histological tumor size, and dermal infiltration.

A research by SSentogo [70] finds that regional, subregional, gender, and racial disparities influence breast cancer survival rates in Africa.

Consequently, measures are urgently required per region- and race-specific public health interventions coupled with prospective genetic studies to improve breast cancer survival in this region.

3.6. Second cancers associated with breast cancer in men

Decades of research have been devoted to the risk of second cancers among breast cancer patients. Men's second primary tumors, in contrast, are poorly understood. Men's breast cancer risk factors, such as genetic, hormonal, and environmental factors, parallel the causes of breast cancer in women. A review by Grenader [71]examines the literature concerning the risk of developing a second cancer in male breast cancer patients. Patients with a history of male breast cancer are more likely to develop a second ipsilateral or contralateral breast tumor (standardized incidence ratio 30-110),a phenomenon also underlined by O'Leary[72]. The risk of subsequent contralateral breast cancer was greatest in men younger than 50 years old at the time of the initial cancer diagnosis. Diverse information is available on second primary cancers besides breast cancer. According to one study, the incidence of cancers of the small intestine, prostate, rectum, and pancreas, as well as non-melanoma skin cancer and myeloid leukemia, has increased. Other researchers did not find an increase in the overall risk of subsequent cancer development among men initially diagnosed with primary breast cancer. Although sarcoma, lung, and esophageal cancers

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are well-known complications of radiation therapy for breast cancer in women, there is no evidence that these cancers are associated with radiation therapy for breast cancer in men.

Cancer treatment is an especially trying time for the patients. They frequently experience multiple side effects concurrently, resulting in a decline in health-related quality of life (HRQoL). A study presented by Charalambous [73]provides evidence regarding the co-occurrence and interrelationships of pain, anxiety, depression, and fatigue in breast and prostate cancer patients. This research provides evidence that targeting fatigue, anxiety, and depression may have a meaningful effect on pain as a related symptom and may have a positive impact on the HRQL of breast and prostate cancer patients.

Resistant breast and prostate cancers continue to be a major clinical problem; consequently, new therapeutic approaches and more accurate predictors of therapeutic response are required. Due to the involvement of the unfolded protein response (UPR) in cell proliferation and apoptosis evasion, an increasing number of publications, as presented by Direito [74]support the hypothesis that dysfunctions in this network cause and/or aggravate cancer. In addition, UPR activation may contribute to the emergence of drug-resistant phenotypes in breast and prostate cancers. Consequently, targeting this pathway has recently emerged as a promising anticancer treatment strategy.

3.7. Prognosis

In an update on research concerning male breast cancer, Benassai [75] and Malinda[76] state that the outcome of the MBC is worse than the female one.

In a comparison between prognostic factors studied in both sexes, Yao [77]found that: compared to FBC patients, MBC patients had more advanced TNM stages, tumor grades, and a greater proportion of hormone receptor-positive tumors (all p 0.05).

In addition, the locations of breast tumors differed significantly between males and females (p 0.05).

Patients with FBC had a longer overall survival rate than those with MBC.

Matters of : age, race, T, N, M-stages, tumor grades, estrogen receptor (ER)/progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2) overexpression were found to be independent prognostic factors in female breast cancer patients (all p 0.05) according to multivariate cox regression and competing risks analyses.

MBC and FBC patients had the same risk factors, but PR and HER-2 status did not have an independent influence on survival (all $p > 0.05$).

In both sexes, tumor location was found to be an independent prognostic factor. Further conclusions were that, in the coming years, it is reasonable to anticipate an increase in the sensitivity of multigenic tests, allowing for a more accurate prediction of recurrence risk.

This could result in substantial changes in the selection and duration of treatment, with surprising outcomes.

Treatment adherence is a very important factor in which concerns prognosis, and a study by Ali[78] compared the endocrine therapy adherence, discontinuation, and survival outcomes of male and female breast cancer patients using the SEER-Medicare linked database. The primary endpoints were rates of endocrine therapy adherence and discontinuation (ET). Adherence was defined as a gap between Medicare prescriptions of less than 90

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days. A discontinuation was defined as a 12-month interval between Medicare prescriptions or longer. Secondary outcome measure was the association between ET use and overall survival (OS). Men were significantly more loyal than women, but there was no difference between the sexes in terms of abandonment. On ET, both men and women exhibited a significant survival improvement.

Pensabene [79] describes that, in addition to non-genetic risk factors, genetic alterations, such as pathogenetic variants in BRCA1/2 and other moderate-/low-penetrance genes, have been identified as pathogenic factors for MBC. The detection of alterations in predisposing genes, especially BRCA1/2, and the identification of oncogenic drivers distinct from FBC may have preventative and therapeutic implications. However, the approved treatments for MBC are identical to those for FBC. Cancer genetic counseling must be considered in the diagnostic workup of MBC, regardless of the presence or absence of an oncological family history.

In a research by Stahl[80] that had as a purpose to analyze men with de novo stage IV breast cancer and known estrogen receptor (ER) and progesterone receptor (PR) statuses who underwent systemic therapy with or without surgery. Patients who died in the first six months were excluded from the study. In male patients with de novo stage IV breast cancer who were ER+ or PR+, we discovered that those who received surgery, radiation therapy, and systemic therapy (trimodality) had a significant survival advantage over those who received only systemic therapy. The data also revealed a downward trend in the use of surgery in this cohort over time.

In a study based on the proteomic profiling of male breast cancer, Zografos [81] found a total of 2,352 proteins, corresponding to 1,249 single gene products with diverse biological functions, were identified. A panel of 119 differentially expressed tissue proteins was identified in MBC samples versus controls; 90 were found to be over-expressed in MBC tissues and 29 were found to be down-regulated. Concurrently, 844 proteins were detected only in MBC tumors, whereas 197 proteins were expressed exclusively in mammary samples from healthy controls. Differential proteomic expression was identified in MBC tissue, resulting in a better understanding of MBC pathology and highlighting the need for individualized care for male patients.

As presented recently by Campone[82] , CompLEEment-1 (NCT02941926) is a single-arm, open-label, multicenter phase IIIb study evaluating the safety and efficacy of ribociclib plus letrozole (RIB + LET) in a large, diverse cohort of patients who have not previously received endocrine therapy (ET) for advanced disease. Methods: Patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC) who had no prior chemoradiotherapy (ET) and 1 prior line of chemotherapy for advanced disease were administered RIB + LET.Also administered to male patients were goserelin or leuprolide. Safety and tolerability was the primary endpoint; efficacy was a secondary endpoint. Males exhibited the same clinical benefit and overall response rates as the entire population. This study supports the use of RIB + LET in male patients with HR+, HER2- ABC.

4. Discussion

Male breast cancer's (MBC's) causes, optimal treatments, and medical/psychosocial consequences are poorly understood. Known risk factors include BRCA2 mutations (80

times the risk of the general population), and 11 other gene mutations. Other factors implied are: age, conditions that alter the estrogen/androgen ratio, and radiation. Male breast cancer presents typically as a painless retroareolar mass requiring further evaluation. When initial radiological findings are ambiguous or suspicious, more imaging methods are frequently necessary to localize and characterize the lesion and to guide biopsy(core biopsy/fine needle aspiration).

The global landscape of treatment standards for male patients with breast cancer is not context-appropriate. A call for equality in breast cancer care can be pursued in two divergent ways: a.a gender-neutral delivery of breast cancer information, and b.the recruitment in randomised controlled trials of both sexes.

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