Male breast cancer: an update

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PURPOSE: *To summarize and compare the most recent data from the literature to clarify the management of male breast cancer.*
METHODS: *A review article.*
RESULTS: *Diagnosis and Treatment of Male Breast Cancer have been derivative for years. Nowadays MBC is a nosological entity in its own right with biological, molecular and clinical features that require a multidisciplinary approach and the involvement of specific skills. Multimodal treatment involves surgery, radiotherapy and chemotherapy. It is evident that the outcome of the MBC is worse than the female one. MBC is often diagnosed in advanced stages. Screening programs in the male population need to be strengthened to obtain an earlier diagnosis. It is necessary to know even more in depth the endocrine-metabolic and behavioral risk factors related to the neoplasm. Finally in the coming years it is reasonable to expect an improvement in multigenic tests: the sensitivity of these methods could predict the risk of recurrence even more precisely. This could lead to substantial changes in the choice and duration of treatment with results that could be surprising.*

KEY WORDS: Male breast cancer, Management, Review, Update

Introduction

Male breast cancer (MBC) has been a rare and neglected disease for years. Diagnosis and treatment strategies have been derivative until recently: the absence of randomized control trials allows to apply scientific evidences obtained on female population [1]. The biological behavior of MBC has been compared to the post-menopausal female one [9]. Over the past twenty years this belief has been progressively shelved. Nowadays male breast cancer is considered a nosological entity in its own right, with biological, molecular and clinical features that require a multidisciplinary approach and the involvement of specific skills. Multimodal treatment involves surgery, radiotherapy and chemotherapy just like female breast cancer. Unfortunately MBC is often diagnosed in advanced stages [7]. The absence of a screening program comparable to the existing one for women reveals substantial prognostic differences between the two sexes. Therefore our study aims to collect and compare the most recent data from the literature to clarify the management of male breast cancer.

Epidemiology

Male breast cancer is a rare tumor. American Population studies estimate its prevalence among all neoplastic diseases in the western world around 1%. Among the causes of male mortality from cancer, it affects just 0.1% [2]. Data collected by SEER (Surveillance, Epidemiology, and End Results) in a 2018 study suggest however a substantial increase in its incidence (corrected by age) in the general population: from 0.85 cases per 100,000 male individuals in 1975 to 1.43 out of 100,000 in 2011 [3]. As happens in tumoral pathologies, MBC is more frequent in old patients and its incidence increases in

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advanced age; the mean age of affected is 67 years (compared to 62 years observed in women) [4]. Subjects with a first degree relative affected by breast cancer have a two-fold increased risk to be affected by the same pathology [6]. Moreover African population seems to be more affected than Caucasian, because of endemic infectious diseases (Bilharziosis, Hepatitis B, Hepatitis C) associated to chronic liver damage and a substantial increase in estrogen levels [4, 5]. Compared with female, MBC patients are more frequently elderly, married, and are diagnosed at a more advanced stage of the disease; lymph nodes are often involved at the time of diagnosis. All this also occurs due to the absence of a valid screening program. In male subjects ER and PR receptors are more often positive, while positivity for HER2 is rare [7, 8]. In terms of mortality, a recent study has shown that MBC patients have a five-year survival rate lower than female patients (82.8 vs 88.5%) and 43% higher mortality [7].

Pathogenesis and Risk Factors

Male breast cancer recognizes a multifactorial etiopathogenesis as female breast cancer. There are several endocrinological changes involved in its development [9]. As reported by the first studies, an increase in serum Sex Hormon Binding Globulin (SHBG) levels was observed in patients with MBC compared to the control population [10]. An increased risk was found in individuals with epididymitis, mumps orchitis or cryptorchidism [11,17]. A study in the male population also demonstrated a statistically significant association between the pre-diagnostic levels of serum estradiol and the incidence of breast cancer [12]. Male hyperestrogenism, caused by endocrine-metabolic dysfunction [12,13] or external intake, is in fact associated with a higher incidence of the neoplasm. Iatrogenic damage can occur in the treatment of prostate cancer [14], and also in hormone replacement therapy for sex changes [15]. In the field of metabolic disorders there is evidence of a greater risk of disease among obese subjects [10]: there is a linear correlation between BMI and the incidence of male breast cancer [16]. It is interesting to observe how gynecomastia can represent an independent risk variable compared to BMI [16]. However the issue is still debated. There are studies that deny the existence of a clear correlation between gynecomastia and MBC [18,19]. Klinefelter syndrome (determined by the 47XXY karyotype) is associated with low testosterone levels and high concentrations of gonadotropins: the incidence of breast cancer in subjects with this chromosomal alteration is 20 fold higher than in the male control population [20]. Insufficient hepatic detoxification of endogenous estrogens can also increase the risk of MBC [4,5]. In fact, in cirrhotic patients there is an increased conversion of Androstenedione into Estrone, Estradiol and Testosterone; serum Testosterone, converted in turn to Estrone, decreases in favor of Estradiol levels [21]. Among the environmental risk factors, the effect of ionizing radiation is known (also in radiotherapy treatments for other malignancies): a higher incidence of male breast cancer has been described, especially among those who have been exposed in young age [22]. There are genetic mutations that have a decisive impact on the probability of developing cancer. In particular, BRCA mutations represent the risk factors that show the strongest statistical association with male breast cancer [1]. BRCA1 and BRCA2 are immunosuppressive genes involved in DNA repair mutated in 5-10% of women with breast cancer [23]. BRCA2 mutation predominate among male individuals: it is found in 4-16% of breast cancer patients [24]. In Deb et al has been analyzed the different impact of these mutations among males and females individuals. In the examined population (male and female with breast cancer) BRCA2 was mutated in 43% of men and in 8% of women; BRCA1 only in 5% of men vs 14% of women [25]. Several studies come to similar conclusions on the prevalence of BRCA mutations in MBC [26,27,28]. There are also other less common genes which represent a risk factor: CHECK2 which codes for a kinase involved in DNA repair [29,30,31]; PALB2 associated with BRCA2 [32,33]; ATM, RAD51C, BAP1 and EGFR [34]; finally PTEN (Cowden's disease) [35].

Clinical Presentation and Diagnosis

Clinical presentation of MBC in 60-70% of cases is characterized by an asymmetrical, not mobile, painful retroareolar mass, with an hard consistency and irregular margins. Serum-blood spilling from the nipple may be present in 5-10% of cases, while ulceration is rare [11, 36]. In 5% of cases, the neoplasm can present as Paget's disease with eczematous alterations of the nipple, serous secretions and itching [11]. There are several conditions that go into differential diagnosis with breast cancer: gynecomastia, epidermal cysts, subcutaneous lipomas, fibroadenomas, hematomas, retroareolar metastases from other neoplasms [37]. Clinical examination and clinical history are often insufficient to discriminate these lesions from breast cancer. For this reason, an instrumental diagnostic study is always indicated [38]. The process is no different from that of female breast cancer: a suspicious mass must be investigated by bilateral ultrasound and mammography [39]. The American College of Radiology suggests performing the first level ultrasound exam only in subjects under the age of 25. For all other cases, bilateral mammographic examination should be prescribed in the first instance; breast ultrasound above the age of 25 is recommended as a second level investigation [38]. The non-inferiority of unilateral mammography compared to bilateral mammography has recently been demonstrated in the evaluation of asymmetric lesions [40]: in women the comparison between the glandular tissues of both breasts

is fundamental to interpret the images [41,42]; in men the prevalence of adipose tissue [43] makes easier to evaluate the lesion with the unilateral examination [40]. In mammography the lesion appears as an eccentric thickening with irregular margins, with or without microcalcifications [39,40]. Whether it is a first level investigation or not, an ultrasound is always indicated [38,44]: it provides numerous details about pathology. Doppler US analysis gives the possibility to study the vascularization of the lesion; in addition, ultrasound allows early identification of axillary lymphadenopathies [44]. Magnetic resonance imaging is indicated only in cases of difficult interpretation and in multifocality [45]. Certainty diagnosis is possible only by histological analysis and influences the subsequent treatment choices: if the Fine Needle Cithology (FNC) is useful for determining the malignancy of the lesion, the needle biopsy allows the removal of a real tissue whip and therefore the possibility to obtain an histological and immunistochemical typing of the neoplasm [46]. Pre-surgical staging of male breast cancer follows the same criteria as indicated for the female population [46]. Chest CT, ultrasound or abdomen CT and bone scan should always be performed in patients with a higher probability of metastasis. PET / CT is indicated only if the other tests have not been conclusive [47-49].

Pathological Characteristics

There are several histotypes of male breast cancer: the most frequent variant is the Invasive Intraductal Carcinoma observed in 75.4% of cases in isolated form, and in 7% of cases with other tumor variants. Lobular form is diagnosed in 3.3% of the population. All the other histotypes (adenocarcinoma, cribriform carcinoma, papillary carcinoma, intraductal papillary adenocarcinoma) represent 5.8% of cases [50]. Exactly as recommended by the St. Gallen consensus conference for women, there are five molecular classes of MBC, that differ in receptor status and gene expression profiles [51] (Table I). In particular: 41.9% of cases are Luminal A-like; 48.6% are Luminal B-like (HER2-negative); 8.9% is Luminal B-like (HER2-positive); 0.2% is HER2-positive (non-luminal) and 0.3% is triple negative (or basal-like) [52]. In conclusion 90-95% of cases of male breast cancer are Luminal A-like or Luminal B-like [52,53], unlike what has been observed in women where the percentage is 73% [54]. The different receptor expression patterns of these five classes of breast cancer influence the response to treatment and therefore the prognosis [51,54]. In Table II we compared the most recent studies on MBC (Table II) [50,52,55]. 80-85% of patients have Invasive Ductal

Table I - *St Gallen Consensus Conference 2013 -Classification*

Subtype	ER	PR	HER2	Ki67
Luminal A-like	+	+	–	↑
Luminal B-like (HER2-negative)	+	–	–	↓
Luminal B-like (HER2-positive)	+	+/–	+	↑↓
HER2-positive (non luminal)	–	–	+	↑↓
Triple negative (basal-like)	–	–	–	↑↓

Table II - *Most Recent Studies*

Variabiles	Sarmiento 2020 (50)	Andrè 2019 (55)	Cardoso 2018 (52)
No. of patients	14882	196	1822
Mean Age	63	41,3% >70	68,4
Tumor Size	1,7 cm	-	-
C. Ductal	80,07%	-	84,80%
C. Lobular	3,35%	-	0,60%
Others	16,58%	-	5,10%
ER +	91,30%	93,10%	99,30%
ER –	8,70%	6,90%	0,70%
PR +	82,60%	75,30%	81,90%
PR –	17,30%	24,70%	18,10%
N +	40,90%	56,40%	38,30%
N –	59,10%	43,60%	56,2% + Nx 5,5%
M +	7,00%	9,20%	3,80%
M –	93,00%	90,80%	71,1% + Mx 25,1%
Stage 0	12,90%	3,60%	-
Stage I	31,50%	39,20%	-
Stage II	34,40%	44,90%	-
Stage III	14,70%	3,10%	-
Stage IV	6,60%	9,20%	-

Table III - *Restrepo DJ et al.(2019) didn't include Stage IV Patients*

Variabiles	Restrepo 2019 (56)
No. of Patients	10258
Mean Age	-
Tumor Size	-
C. Ductal	84,80%
C. Lobular	3,90%
Others	11,30%
ER +	82,80%
ER –	7,40%
PR +	-
PR –	-
N +	50,30%
N –	49,70%
M +	-
M –	-
Stage 0	14,40%
Stage I	33,90%
Stage II	36,10%
Stage III	15,70%
Stage IV	Not included

Carcinoma; ER receptor positivity is expressed in more than 90% of patients [50,52,55]. More than half of the patients in Sarmiento et al. (2020) have no lymph nodes involved at the time of diagnosis [50]. Conflicting results are reported in André et al (2019), even if conducted on a smaller population [55]. At the time of diagnosis, 60-70% of breast cancer cases are in Stage I or Stage II, 90% do not have distant metastases [50,52,55]. Restrepo et al. (2019) (Table III) excluded stage IV patients, focusing on pathology up to Stage III: out of 10258 patients enrolled, also in this case ductal carcinoma proved to be the prevalent histotype; lymph nodes were involved just in half of the cases at the time of diagnosis [56].

Treatment

For a long time management of MBC followed existing recommendations for female breast cancer. Indeed therapy is multidisciplinary and includes, in addition to surgical treatment, also radiotherapy and medical treatment, depending on the stage and immunohistochemical characteristics of the primary neoplasm. 85% of male patients are subjected to mastectomy [58,78]. Conservative therapy is not a common approach in male patients for several reasons: the low amount of breast tissue, the frequent retroareolar localization of the lesion, the advanced stage (56% of patients receive Stage II, III or IV diagnosis) [50], the modest aesthetic value and the less psychosocial implications [57]. Surgical procedure consists of an elliptical incision of the periareolar skin which includes the cutaneous projection of the lesion; all the glandular parenchyma is removed up to the pectoral muscle fascia, ensuring accurate hemostasis. In patients with known BRCA1/2 mutation, contralateral mastectomy can be performed simultaneously. Lymphadenectomy has the same indications as for female sex [52,60]. For the treatment of the axillary cavity the sentinel node technique is possible both with vital stain and radioactive tracing: in the presence of macrometastasis (greater than 2 mm) lymphadenectomy is performed [63,64]; in presence of micrometastasis (from 0.2 to 2 mm) lymphadenectomy is discussed [68]. As demonstrated by Zanghi et al. (2015) patients with micrometastasis are less likely to develop recurrence, compared to the ones with macrometastases [61]. In Scomersi et al (2010) axillary dissection should be the first option in all the patients with positive sentinel node biopsy [62]. After surgery, the indications for radiotherapy do not differ from those for female breast cancer [52]. 42% of patients who did conservative treatment undergo adjuvant radiation therapy [57]. In cases with lymph node involvement, radiotherapy treatment has brought undoubtedly benefits [65,66,67]. The choice of adjuvant medical therapy is the same for female population. ASCO recommendations (February 2020) indicate Tamoxifen as the drug of choice for patients with hormonal positivity [70-72,79], as confirmed by a recent cohort study in which treatment is associated with a statistically significant increase in DFS [73]; Tamoxifen therapy should last at least 5 years: if at the end of this time the predictive risk of recurrence is still high, it is reasonable to offer the patient 5 years of supplementary treatment, especially if well tolerated. Patients for whom Tamoxifen is contraindicated should perform adjuvant therapy with the GnRH agonist/antagonist and aromatase inhibitor combination. Patients with advanced Luminal A pathology (ER positive and HER 2 negative), should undergo endocrinotherapy with Tamoxifen, or alternatively with the above drugs. CDK4/6 inhibitors can also be used. In metastatic disease, chemotherapy should be reserved for patients who are no longer responsive to hormone therapy. Target therapy for HER2, PDL-1, PIK3CA and BRCA mutations are indicated in advanced or metastatic pathology according to the same modalities already approved for the female sex [69].

Prognosis

The risk of recurrence in patients treated for breast cancer is present in the following 15 years and beyond [69]. Kate et al (2017) reported a recurrence rate of 33% in a 59-month cohort study [8]. For this reason, an ultrasound and radiological follow-up is indicated: in particular the ASCO guidelines suggest performing an annual mammogram in patients who underwent conservative surgical therapy [69]. Multigenic expression tests, can establish a predictive probability of tumor recurrence 10 years after diagnosis [74]. In particular the Oncotype DX by analyzing the activity of 21 genes, expressed in the tumor tissue, is able to misure a Recurrence Score: this value is between 0 and 100 and gives information on the possible benefit of chemotherapy; 18 or lower score indicates a low risk of recurrence; a value greater than 31 indicates an high risk [75,76]. According to the SEER data [3,7] synthesized effectively in Giordano et al 2018 [1] there is a substantial difference between the male and female sex: a recurrence score greater than 31 was calculated in 12.4% of male patients, against 7.4% of women; the 5-year survival of these patients (with scores> 31) is 81% in men, compared to 94.9% observed in women. In other words, in men there is a greater probability of recurrence and a worse outcome than the female population [1]. Even when calculating the 5-year survival, regardless of the results of the Oncotype DX, the percentage in men is lower (82.8% against 88.5% observed in the female sex), with a 43% higher risk of death than women [7]. In a recent cohort study that recruited 227,122 patients in the period 1999-2016 (1094 cases of male breast cancer and 226,028 cases of female breast cancer), survival at 5 years from diagnosis was 88.8%, with this difference between the two sexes: 76.2% in men, 88.9% in women, confirming the worst prognosis in men [77,78].

Future Prospects

It is evident that the outcome of the MBC is worse than the female one. Screening programs in the male population need to be strengthened to obtain an earlier diagnosis. It is necessary to know even more in depth the endocrine-metabolic and behavioral risk factors related to the neoplasm. Finally, in the coming years it is reasonable to expect an improvement in multigenic tests for both sexes: the sensitivity of these methods could predict the risk of recurrence even more precisely. This could lead to substantial changes in the choice and duration of treatment with results that could be surprising.

Riassunto

Le strategie di diagnosi e trattamento del carcinoma mammario maschile sono derivative da anni: in assenza di studi di controllo randomizzati si applicavano le evidenze scientifiche ricavate sulla popolazione femminile. In particolare il comportamento biologico del tumore della mammella maschile veniva paragonato alla controparte femminile dell'eta postmenopausale. Negli ultimi venti anni questa convinzione e stata progressivamente accantonata. Oggi la neoplasia mammaria del sesso maschile è considerata un'entità nosologica a sé stante, con caratteristiche biologiche, molecolari e cliniche che richiedono un approccio multidisciplinare e il coinvolgimento di competenze specifiche. Il trattamento multimodale prevede terapia chirurgica, radioterapica e chemioterapica proprio come avviene per il carcinoma mammario femminile, con la differenza che nel maschio la diagnosi avviene quasi sempre ad uno stadio più avanzato. L'assenza di un programma di screening paragonabile a quello esistente per le donne rivela delle sostanziali differenze prognostiche tra i due sessi. Pertanto il nostro studio si propone di raccogliere e confrontare tra loro i dati più recenti della letteratura al fine di facilitare la gestione dei pazienti con carcinoma mammario maschile.

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