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REVIEW ARTICLE

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Male breast cancer: a budding and unaddressed issue

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ABSTRACT

Incidence of male breast carcinoma (MBC), although rare, recently has an increasing trend. The increase in incidence is associated with increasing age, and poor clinical outcome seen with MBC is mostly because of illiteracy and lack of health education and shyness in reporting to the clinical physician. In this context, a comprehensive review regarding this forth bursting clinical scenario is important. The present article focus on that aspect encompassing but not limited to different clinical studies. The randomized trials on MBC are sparse and most of the studies are retrospective in nature due to rarity of cases. MBC treatment line is derived from female breast cancer guidelines. MBC has a poorer prognosis than female breast cancer. MBC patients in India present in advanced stage and surgery remains challenging due to paucity of breast tissue. Post mastectomy radiation is indicated on the same lines as of female breast cancer and it decreases locoregional recurrence. Adjuvant hormonal therapy decreases recurrence and improves survival. Further clinical trials are required including large number of patients to study different parameters in respect of prognosis and survival.

Key words: breast, cancer, male, mastectomy, radiation

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Introduction

Male breast carcinoma (MBC), which is a relatively isolated phenomenon occurring in fewer than 1% of breast cancer cases in males, has been on the rise over the past two to three decades. The incidence of MBC increases with age and the median age at presentation in India is 57 years [1]. Risk factors include *BRCA1* and *2* mutations, Klinefelter syndrome, chronic testicular and liver disease, obesity, and alcohol intake [1]. Literature about male breast cancer, including randomized trials or retrospective series, is sparse, particularly in developing countries like India. Moreover, awareness about MBC in the general population is also very poor. There is an urgent need for collaborative trials and reviews from oncologists of different kinds to provide an evidence base for the most effective combination therapies for men with breast cancer.

Management of MBC is wholly derived from data on female breast cancer although there are some differences between breast cancer in males and females (Tab. 1 [2]). Literature suggests that MBC has a poor prognosis in comparison to female breast cancer [3, 4]. The paucity of breast tissue in males contributes to surgically poor adequate margins. Moreover, in India, most patients present in a locally advanced stage, which makes it even more difficult to achieve negative surgical margins. Hence adjuvant post-mastectomy radiotherapy (PMRT) is indicated as per female breast cancer guidelines. Post-mastectomy radiotherapy decreases locoregional recurrence (LRR) [5]. Chemotherapy and hormonal therapy are also given as per female breast cancer guidelines. Hormonal therapy has benefits in terms of fewer chances of recurrence and increased survival rates [1]. This article provides an in-depth review of male breast cancer regarding etiopathogenesis, diagnosis, and management in the Indian setting.

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Table 1. Differences between male and female breast cancer

	Male breast cancer	Female breast cancer
Incidence	Less common	More common
History of familial cancer	More common	Less common
Site	Central region	Upper outer quadrant
Nipple involvement	More common	Less common
Breast tissue	Less	More
Ducts and lobules	Few	More
Lobular carcinoma	Less common	More common
Age at diagnosis	6^{th} to 7^{th} decade	5^{th} to 6^{th} decade
Stage at presentation	Advanced	Early
High grade	More common: 85% grade 3 [2]	Less common: 50% grade 3 [2]
ER/PR expression	More than 95%	Less (60–70%)
HER2-neu overexpression	Less (2–15%)	More (18–20%)
Prognosis	Poor	Good
Surgery	Poor adequate margins due to paucity of breast tissue	Adequate margins possible
BCS	Less common	More common
Screening	Less common	More common
Trials	Less	More

BCS — breast conservative surgery; ER/PR — estrogen receptor/ progesterone receptor; HER — human epidermal growth factor receptor

Incidence

The approximate numbers of new cases of MBC are 1 in 100 000 in the US and Europe, < 5 in Japan, and may be 15% of all breast carcinoma cases in some parts of Africa [6]. The age-standardized incidence rate (ASR) is 0.4 per 100 000 in Mumbai in India. The incidence increases with age till 80 years, and then it reaches a plateau [7].

Etiopathogenesis and risk factors

Heredity, more precisely a positive family history, is the prime factor in occurrence of MBC. Breast or related cancers (like ovarian cancers) in a first-degree relative, irrespective of their sex, increase the risk of breast cancer in men from 2 to 5-fold. Breast cancer predisposing genes, which are well-known for increasing the risk of breast cancer in women, also increase the risk of MBC. In this regard, the significance of the *BRCA 2* gene mutation is much higher than that of its counterpart *BRCA 1* in causing male breast cancer [4, 8, 9]. Other genes associated with MBC with proven penetrance are *CHEK2*, *PALB2*, *TP53*, *PIK3CA*, and *RAD51* [10, 11]. A history of familial cancer was seen in 4–15% of cases [1].

Aging is one of the major non-modifiable risk factors, as MBC is thought to be a counterpart of breast cancer in post-menopausal females. Breast cancer in men occurs mostly in their 6^{th} to 7^{th} decades of life, with a more advanced disease stage; however, male breast cancer has been reported in patients aged from 5 to 93 years [1, 12–14].

The discrepancy in the estrogen-to-androgen ratio (and the conditions causing this) also has a high impact on the development of breast carcinoma in males. Klinefelter syndrome, one of such conditions, increases the risk of breast cancer by 50-fold and accounts for 3–7% of all MBC cases [7, 9]. Other factors that induce hormonal imbalance and result in MBC are obesity, liver and endocrine disorder, exogenous estrogen administration, and testicular abnormalities such as cryptorchidism, orchiectomy, or viral orchitis [14, 15].

Other risk factors with a high probability of causing MBC are occupational exposure to polycyclic hydrocarbon, long-term exposure to high temperature, and chest radiation due to other causes (these are supposed to suppress testicular function). Other rare risk factors are head trauma, marijuana and amphetamine abuse, which raises prolactin levels in the body, which is a risk factor for MBC [14]. A small number of cases of synchronous breast cancer and axillary tubercular lymphadenitis have been reported, particularly in tuberculosis-endemic countries [16]. The Association of MBC with neurofibromatosis is also documented in the literature although it is not clear whether it is a causative factor or a co-incidence [17]. However, some known risk factors for other cancer, such as smoking and alcohol intake, have not been demonstrated to contribute to developing breast cancer in men [18].

Histopathological classification

Infiltrating ductal carcinomas (IDC) account for more than 90% of cases of malignant lesions in male breasts [4]. Other less common varieties include lobular, papillary, secretory, and mucinous lesions (8–10%). The remaining carcinomas are rare tumors like sarcomas, lymphomas, and metastatic tumors from other primary cancers. The rarity of lobular carcinoma in males in comparison with females is due to the lack of terminal lobules in male breasts. Although rare, still infinitesimal cases of primary breast sarcoma are found in male breasts [19]. A few cases of basal cell and Merkel cell carcinoma of male breasts were also reported [20, 21]. Primary breast lymphoma, a relatively rare tumor, is also found in male breasts, but there is very little evidence [22]. Very rare cases of metastasis from other primary tumors spreading to male breasts have been described in the literature. Among these case reports, primary sites were the prostate, thyroid, cutaneous melanoma, urinary bladder, and kidney [23].

Clinical features

Most patients present in an advanced stage, either because of the lack of awareness, ignorance, low socioeconomic status, or taking indigenous treatment [1]. The NCI-SEER data reported that the incidence of stages at the time of presentation was 10%, 29%, 38%, 7%, and 8% for stages 0, I, II, III, and IV, respectively [15]. Most men (approx. 85%) present with complaints about a painless subareolar lump, which is hard, fixed, and unilateral in most cases [13, 14, 24]. Nipple involvement in terms of retraction, ulceration, and/or bleeding is present in 50% of cases [9]. Other common features include axillary mass, ulceration over the breast, and sometimes symptoms resulting from distant metastasis such as pain in bones, dyspnea, and abdominal pain. An old male patient having breast cancer presented with features of carcinoma *en cuirasse*, a rare form of cutaneous breast cancer metastasis [25].

Another rare presentation mentioned in the literature was pituitary symptoms in neuroendocrine tumors of male breasts [26]. Chances of distant metastasis in MBC are around 7–9% [15]. The most common site of distant metastasis is bone followed by the lung; others are the liver and brain. Isolated single-site metastasis is more common than oligo- or multiple sites involvement. Involvement of the left-sided breast in males is somehow more prevalent (L: R = 1.07:1) [15]; bi-laterality was seen in around 1% of cases [13, 27]. Unlike upper-outer quadrant involvement in females, MBC occurs predominantly in the central retro-areolar portion of the breast [27, 28].

Diagnostic workup

The approach to a patient with MBC is similar to that of a female patient. Earlier diagnosis could make a life-saving difference, as MBC is most often diagnosed in an advanced stage. Males presenting with suspected breast lesions should undergo a thorough clinical examination of both breasts and bilateral axilla, followed by using relevant imaging modalities such as ultrasonography, mammography, and magnetic resonance imaging (MRI), whenever needed [4]. Mammography is abnormal in nearly 90% of MBC and easily differentiates it from gynecomastia, the most common yet benign breast lesion in men [4]. Any lesion suggestive of malignant pathology should be confirmed by tru-cut biopsy; a biopsy is always preferable as the immunohistochemistry (IHC) assay leading to simultaneous hormone receptor status evaluation. HER2 (human epidermal growth factor receptor), a proto-oncogene, expression is estimated by IHC or fluorescent in situ hybridization (FISH). HER2-neu overexpression is associated with poor prognosis [7]. Genetic testing, particularly of BRCA and PALB2, is indicated in male breast cancer patients [11]. This testing helps not only in counseling the offspring or other family members but also to consider particular targeted therapies such as PARP inhibitors [11].

Staging is done according to the American Joint Committee on Cancer (AJCC) 8th edition of the TNM cancer staging system for female breast cancer [29]. Associated investigations to evaluate metastatic lesions, for treatment purposes and to supplement previous findings, are also done in the majority of the patients. Routinely, chest roentgenography, abdominal sonography, electrocardiography (ECG) and echocardiography, and blood investigations are done; special imaging techniques like MRI or computed tomography (CT) scans of the chest and/or abdomen, bone scintigraphy, and positron emission tomography (PET) scans are also used upon indications.

Prognostic factors

Male breast carcinoma has poor 5-year overall survival in the range of 40–65% in comparison to 80% in females [15]. But, when matched for age, stage, and hormone receptor status; female and male breast cancers revealed similar survival patterns. Other prognostic factors include tumor size, nodal status, stage, and hormone receptor status [13, 15].

Treatment strategy

Due to the few epidemiological data available in the literature, treatment guidelines for MBC are not standardized. Clinical practice generally follows

a copy-paste approach to their female version. However, timely diagnosis and early treatment strategy allow for the prevention of major complications. The treatment strategy, based on experience from female breast carcinoma, adopts a multimodality approach and consists of local therapy (surgery and radiation therapy), systemic therapy (chemotherapy, endocrine therapy, and targeted agents), and obviously, addressing metastatic lesions.

Surgery

Mastectomy has been the standard surgical approach in MBC. Despite the fact, that most treatment decisions about MBC including surgical interventions are extrapolated from the guidelines on female patients; breast conservative surgery (BCS) has not become popular in MBC. However, in some small-size trials, BCS was compared in terms of recurrence rate and survival [30]. The scarcity of male breast tissue may be the most probable cause of avoiding BCS in MBC. Other factors that encourage the surgeon to favor mastectomy are the central location of the tumor, nipple involvement, more advanced-stage disease at presentation, and regional nodal metastasis. Yet, the sentinel lymph node (SLN) biopsy technique was evaluated in some studies with a very good detection rate (90–100%) [9]. It can be concluded that the BCS and SLN biopsy techniques followed by axillary clearance in positive cases can be used in selected patients with good results. This limited surgical approach has the benefit of fewer long-term complications such as lymphedema and restricted shoulder movement. Farrow et al. [15] demonstrated positive outcomes of orchiectomy in metastatic MBC.

Radiotherapy

Radiation therapy (RT) is part and parcel of breast cancer management in females to prevent a locoregional recurrence. Similarly, postoperative radiation therapy is also incorporated into MBC management [4]. Indications and recommendations for adjuvant RT in MBC are the same as that for (female breast cancer) FBC. Moreover, RT is much more needed in MBC given the advanced stage of presentation. Conventional fractionation RT is most often evaluated in the literature on MBC treatment. The role of hypo- and ultra-hypo fractionation RT, which already turned out beneficial in FBC, is yet to be verified in MBC. In some advanced metastatic cases, palliative RT is also considered and, in that scenario, hypo fractionated dose schedules are preferred.

Post-mastectomy radiotherapy significantly improves disease-free (DFS) and overall survival (OS) irrespective of the stage, margin, and nodal status [1]. Yu et al. [5] demonstrated LRR improvement (without OS improvement) with PMRT in high-risk MBC cases such as patients with an advanced stage, node-positive, and ≤ 2 mm or unknown margin MBC [5]. The LRR rate without RT is approximately 5–20% in low-risk patients and 20–40% in high-risk patients. The LRR rate with PMRT is 8% and the 5-year local recurrence-free survival rate was 55–69% [1].

Chemotherapy

Chemotherapy drug and dose schedules for males with breast carcinoma are similar to those recommended in females; a few retrospective studies and case reports support these with documentation of better outcomes in adjuvant settings [1, 31, 32]. However, in a neoadjuvant setting, no case series or retrospective studies show any proper benefit which should be validated in future studies. In metastatic hormone-positive breast cancer, chemotherapy can be considered after at least two lines of endocrine-based therapy [33]. Furthermore, chemotherapy is a preferred option, particularly if there is a sign of imminent organ failure [33]. Drugs used in MBC in various studies are anthracylines, taxanes, cyclophosphamide, 5-fluorouracil, and, to some extent, platinum compounds, especially in metastatic disease. Initially, a CMF regimen (cyclophosphamide, methotrexate, and 5-fluorouracil) was administered. The NCI MB-82 study showed that in nodal positive disease, 20-year survival is 42% after 12 cycles of CMF [34]. The MD Anderson Cancer Centre reported a reduced death risk with adriamycin-based chemotherapy [35]. Giordano et al. [35] reported 10-year OS with chemotherapy to be 43% in node-positive cases.

Endocrine therapy

Nearly 90% of men with breast cancer are found to be estrogen receptor (ER) positive, progesterone receptor (PR) positivity is also seen in around 95% of cases [9, 10, 36]. This high ER positivity and the role of hormonal imbalance in MBC causation define the significance of endocrine treatment as a cornerstone in MBC. MBC has been likened to post-menopausal FBC and so aromatase inhibitors (AI) should also be used as adjuvant treatment for MBC. However, most of the retrospective studies support the use of tamoxifen as the standard endocrine therapy in ER-positive male patients [7, 10, 31]. Although AIs were found to be effective in a few small case series, their use as first-line adjuvant hormonal treatment is not encouraged and is reserved for tamoxifen-failure cases and as dual hormonal therapy along with the GnRH agonist in metastatic breast cancer in males [32, 37]. The probable explanation for less guidance on AIs is their inability to prevent testicular estrogen synthesis, which corresponds to up to 20%

of endogenous estrogen in men. The current recommendation for adjuvant endocrine therapy in MBC is tamoxifen, and extended use of up to 10 years should be encouraged [38]. Notably, first-line hormonal therapy in metastatic MBC is again tamoxifen; and dual therapy, as mentioned earlier, is reserved for progressive cases [15].

Adverse effects of tamoxifen have been a topic of recent discussions. The side-effect profile of tamoxifen, obviously similar to that seen in female patients, is much more prominent in males. This causes poor compliance in male patients with breast carcinoma and affects treatment outcomes [39]. In fact, it shows that 10-year disease-free survival is more than double in compliant patients than in non-compliers. Poor compliance with tamoxifen in a lot of patients underscores the importance of alternative endocrine therapies. Options include luteinizing hormone-releasing hormone analogs, anabolic steroids, and bilateral orchiectomy in selected cases. These are even useful in metastatic hormone-positive breast cancers that progressed after tamoxifen therapy. However, sometimes tolerability of these drugs is poorer than tamoxifen despite their shown efficacy in different studies.

The role of neoadjuvant endocrine therapy in MBC has not been evaluated in any study to date; hence no recommendations are available. However, it can be a potentially useful strategy in selected patients due to the invariable hormone receptor-positive status of MBC. Hormonal therapy before surgery can shrink the tumor and may offer an opportunity for less extensive surgery. Moreover, short-term neoadjuvant hormonal therapy in receptor-positive patients can provide better patient compliance than long-term hormonal therapy, which has its own adverse effect. The recurrence rate is statistically significantly lower in patients who received both hormonal therapy and chemotherapy in comparison to chemotherapy alone [1].

Targeted agents

As mentioned earlier, the application of targeted agents in MBC is also based on observation of their benefits in FBC. However, given the rare HER2 positivity in MBC, the addition of trastuzumab (anti-HER2 agent) in a multimodality treatment approach to MBC is comparatively less frequent. Yet, in limited studies, benefits of adding trastuzumab, obviously in HER2-positive tumors and metastatic settings, turned out beneficial [40]. So, rational use of trastuzumab in HER2-positive metastatic breast cancer can be considered and more studies on this aspect are expected.

Among other targeted agents, the use of mTOR inhibitors (everolimus) and PARP inhibitors (olaparib) can be considered in MBC, provided these drugs have turned out to be efficacious in certain gene-positive FBC which are also found in MBC [11, 41]. Still, a lack of evidence and guidance for MBC has restricted their routine use by physicians. Another important class of drugs are CDK4/6 inhibitors such as abemaciclib and palbociclib. Benefits of these drugs in metastatic hormone-positive FBC were demonstrated in large randomized trials. Those famous trials also included a few male patients with breast cancer, and those patients were also found to have benefited from the treatment. So, it can be concluded that the use of these CDK4/6 inhibitors is preferred as 1st-line therapy in metastatic hormone-positive breast cancer – not after endocrine therapy or chemotherapy [41].

Indian setting of MBC

In India, the incidence rate of MBC was reported to be 0.4%, 0.5%, and 4.1% of all breast cancer cases as reported by Chikaraddi et al., Rai et al., and Shah et al., respectively [42–44] . A few retrospective studies on MBC have been reported from India (Tab. 2 [1, 12, 15, 19, 28, 42–48]). These studies are important to understand the current situation of MBC in different parts of India. Some other rare case presentations on MBC were also reported in the literature from India (Tab. 3 [3, 4, 9, 13, 24, 27, 32, 36, 49–51]).

These retrospective studies depict approximately similar presentations and course of the disease. In the majority of the studies, more than 80% of patients had IDC and most were hormone receptor positive [15]. The MBC cases constituted from 1.03% to 2.5% of total breast cancer patients [12, 45]. The median age at diagnosis was from 54.2 to 67 years (Tab. 2). Half of the studies reported the median age as 55 years, which is somewhat less than the age that is reported in the literature [12]. The other half had a median age of around 62 years (Tab. 2). Surprisingly, the involvement of the right breast is more frequent (74%) [12]. Most of the patients presented in an advanced stage (III or IV) and many of them underwent mastectomy [15, 45]. The late presentation was caused by the lack of awareness, ignorance, low socioeconomic status, or taking indigenous treatment [1].

Most patients (60%) presented with distant metastasis, mostly bone involvement alone or in combination with visceral metastasis. All the patients had good general condition despite having metastatic disease; non-metastatic patients underwent primary surgical intervention [45]. Adjuvant chemo- and radiation therapy was given according to indications, and tamoxifen was administered for all hormone-positive patients [15, 45].

In a retrospective study on primary breast sarcoma by Ahuja et al. [52], 3 of 5 patients with breast sarcoma were male, which constituted 0.2% of all

Table 2. Summary of case series/research reports on male breast cancer in India

Study	Shukla et al. [19]	Rai et al. [43]	Mitra et al. [46]	Shah et al. [44]	Chikaraddi et al. [42]	Shah et al. [15]	Mukherjee et al. [47]	Sundriyal et al [45]	Gogia et al. [48]	Ram et al [28]	Pothamsetty et al. [12]	Yadav et al. [1]
Year	1996	2005	2007	2009	2012	2012	2014	2015	2015	2017	2017	2018
No. of patient	41	30	79	32	26	42	33	18	27	27	23	81
Median age [years]	54.2	56	67	55	57	56	60	60	62.6	62.6	56	57
Early disease	–	–	–	–	–	40%	–	11%	59%	85%	–	37%
Locally advanced disease	41%	43.3%	90% (stages 3 and 4	56.2%	50%	43%	57.6%	28%	–	15%	87%	42%
Metastatic disease	–	–	–	–	–	17%	–	61%	–	–	22%	21%
Mastectomy	–	–	–	–	–	86%	–	39%	–	100%	–	86%
Node positive	–	–	–	–	–	60%	–	28%	–	33%	–	59%
ER/PR +ve	43%	–	83%	62.5%	81%	27%/62%	54.5%	89%	78%	78%	56.5%	42%/26.5%
HER 2 +ve	–	–	–	–	–	–	–	11%	–	7.4%	4%	3%
PMRT	–	–	–	–	–	67%	–	–	–	22.2%	–	80%
Chemo	–	–	–	–	–	67%	–	–	–	70.4%	–	55%
Tamoxifen	–	–	–	–	–	90%	–	–	–	77.8%	–	70%
Median follow-up [months]	–	–	–	–	–	17 months to 136 months	–	–	–	–	24	60
LRR	–	–	–	–	–	14%	–	–	–	–	4%	12.5%
Distant metastasis	–	–	–	–	–	12.5%	–	–	–	–	22%	34%
DFS	–	40% (5 yr)	47–78% (5 yr)	–	–	46% (5 yrs)	–	–	–	76.3% (5 yr)	43%	42% (10 yrs)
OS	91.4% (4 yr)	–	–	–	–	–	–	–	80% (3 yr)	92.3% (5 yr)	74%	53% (10 yrs)

DFS — disease-free survival; ER/PR — estrogen receptor/progesterone receptor; HER — human epidermal growth factor receptor; LRR — loco-regional recurrence; OS — overall survival; PMRT — post-mastectomy radiotherapy

Table 3. Summary of case reports on male breast cancer in India

Study	Age	Laterality	Surgery	No of positive LN	Stage	HR status	HER2 status	CT given	HT given	RT given	Metastasis
Sarma et al. (2013) [36]	58	Right	Yes	1	IIA	ER + ve PR + ve	NK	Yes	Yes (T)	No	Nil; synchronous base of tongue cancer
Hariprasad et al. (2013) [24]	50	Left	Yes	Nil	II	ER + ve PR + ve	NK	No	No	No	Nil
Jagtap et al. (2014) [13]	70	Bilateral	Yes	2/10 (L) 0 (R)	IIIB (L) IIA (R)	ER + ve PR + ve	-ve	Yes	NK	NK	Nil
Gupta et al. (2015) [3]	73	Right	Yes	Nil	IIB	ER + ve PR + ve	equivocal	No	Yes	Yes	Nil
Agrawal et al. (2015) [49]	65	Right	Yes	5/16	IIB	ER + ve PR +ve	-ve	Yes	Yes (T, AI)	Yes	Multiple
Samanta et al. (2015) [50]	60	Right (chest wall)	No	NA	NA	ER + ve PR + ve	-ve	Yes	No	No	Nil; Ectopic breast cancer in the right chest wall
Uthamalingam et al. (2016) [32]	51	Left	Yes	1	IIIB	NK	NK	No	No	No	Nil; Paget's disease of the ipsilateral nipple
Mishra et al. (2018) [9]	62	Left	Yes	Multiple	recurrent	ER + ve PR + ve	-ve	Yes	Yes (T)	Yes	Multiple
Garg et al. (2018) [51]	64	Left	Yes	2	IIIB	ER + ve PR + ve	NK	Yes	Yes	Yes	Nil; synchronous basal cell carcinoma of left eyelid
Hazarika et al. (2019) [4]	63	Left	Yes	Multiple	IIIA	ER + ve PR + ve	NK	Yes	Yes (T)	Yes	NK
Kadam et al. (2020) [27]	60	Bilateral	Yes	Nil	IIA (R) IIB (L)	ER + ve PR + ve	-ve	Yes	Yes (T)	Yes	Nil

AI — aromatase inhibitor; CT — chemotherapy; ER — estrogen receptor; HER — human epidermal growth factor receptor; HR — hormonal receptor; HT — hormonal therapy; L — left; LN — lymph node; NK — not known; PR — progesterone receptor; R — right; RT — radiotherapy; T — tamoxifen;

breast malignancies. The 3 male patients had either leiomyosarcoma, dermatofibrosarcoma protuberans, or malignant peripheral nerve sheath tumors [46]. Various other studies summarized in Tables 2 and 3, which were retrospective in nature, demonstrated that patients' age at diagnosis was the 6th to 7th decade, they presented in a locally advanced stage, more than three-fourths were hormonal receptor-positive, and surgery and radiation were the mainstay of treatment and prognosis, which is a somewhat lower value than that in the case of female counterparts.

Limitations of those studies are small sample size, retrospective nature, and single-center experience. It can be recommended that male BC patients should be routinely included in all breast cancer trials unless there is a strong biological reason to exclude them. This will help researchers to achieve a better systematic characterization of MBC patients, including genetic mutations and tumor subtypes.

Conclusions

Breast cancer in males is still an unaddressed issue, especially in countries like ours where the doctor-to-patient ratio is very low and there are relatively few cancer awareness programs. More knowledge regarding such a life-threatening condition, in both doctors as well as the general population, would surely help in early diagnosis, proper treatment, and distant-site metastasis prevention. The importance of awareness of breast cancer in men should be highlighted, as lack of knowledge

contributes to delayed diagnoses established in advanced stages. The role of adjuvant systemic therapy deserves more research as well.

Author contributions

A.S.: conceptualization, methodology, formal analysis, original manuscript writing; D.P.: conceptualization, review of literature, original manuscript writing; P.K.: review of literature, final manuscript editing; A.C.: supervision, final manuscript editing; V.K.: supervision, final manuscript editing; M.V.: software, review of literature.

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Conflict of interest

Authors declare no conflict of interest.

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