

## Male breast cancer – how to treat?

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**Abstract** Treatment principles of breast cancer in males are derived from studies performed among females, while the low incidence in males has so far precluded such studies. The therapy recommendations for males therefore lack the solid evidence, frequently present for females with breast cancer. The primary breast cancer diagnosis in males is not infrequently in stage III/IV and at higher age, thereby requiring multiprofessional and multimodal management including preoperative therapy and adjuvant therapies based on the tumour's biological characteristics and the clinical circumstances. The majority of male breast cancer tumours are oestrogen-receptor positive and adjuvant/neoadjuvant tamoxifen is therefore recommended, surgery is frequently radical mastectomy and adjuvant radiotherapy should likely be used on wider indications. Chemotherapy should be considered both in the adjuvant and metastatic setting for receptor-negative cancers and for patients with biologically aggressive disease. Trastuzumab should be offered to patients with Her-2/neu-positive disease, while the use of aromatase inhibitors is more uncertain due to differences in the hormonal environment in males.

**Keywords:** Breast cancer; Male; Treatment

### Introduction

Male breast cancer (MBC) is a rare disease accounting for less than 1% of all breast cancer cases [1]. Due to the low incidence of the MBC, the aetiology and pathogenesis of the disease is not completely characterised and poorly understood compared with breast cancer in females (FBC). This fact is well documented by ongoing debate regarding similarity vs. emerging clear differences of the breast carcinoma in males and females [1–5]. The diagnostic and therapy procedures are not well

defined in MBCs. The probable reasons behind the frequent, late diagnoses presented at stages III or IV might be the low public awareness and neglected psychological aspect of the disease [6,7]. The rarity of the disease precludes large prospective randomised clinical trials. Therefore, the general treatment strategies for MBC extrapolates from clinical studies carried out in FBC and the optimal treatment principles remain to be established.

### Incidence and mortality

Unlike the continuously increasing incidence for FBC, the incidence for MBC has been reported to rise or be stable over the last decades. In a population-based study from USA, a 26% increase of incidence for MBC has been found, from 0.86 to 1.08/100 000 population during the time period 1973–1998 [3]. Stable age-adjusted incidence

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trends during the years 1973–2000 were revealed in an analysis of incidence data derived from surveillance, epidemiology and end-result (SEER) database [8]. In line with this, a recent report from Sweden demonstrates a stable incidence for MBC about 0.66/100 000 during the years 1971–2007 [6].

The median age at diagnosis for MBC is found to be higher as compared to FBC with a unimodal peak distribution. The incidence has been found to culminate in males between the ages of 63 and 71 years according to various reports [2,3,9].

Conflicting results have been published regarding prognostic factors and the clinical outcome of MBC as compared to FBC. The overall 5- and 10-years survival rates in MBC are 63% and 41%, respectively. Patients with MBC stage-by-stage fared statistically significantly worse compared to FBC [3]. However, these data are partly challenged by a recent study comparing 612 males and 2413 females from a veterans population with breast cancer, demonstrating a statistically significant worse outcome for MBC only in early-disease stages (stage I and II) [5]. Racial disparities with significantly shorter 5-year survival have been observed among black patients with MBC as compared to white patients with MBC (66% and 90%, respectively) [10].

### Risk factors for developing male breast cancer

Men with BCRA-2 mutations are predisposed to develop breast cancer. On the contrary, BCRA-1 mutation does not seem to be a risk factor, although it has been described in affected men [11,12]. Many of the risk factors for MBC involve abnormalities in oestrogen (excess) and androgen (deficiency) balance. Testicular dysfunctions caused by anatomic and/or physiologic aetiology gives consistent association with elevated breast cancer development in men. Individuals with Klinefelter's syndrome (karyotype 47XXY) have an up to 50-fold increased risk for MBC. Furthermore, lifestyle and environmental

factors such as alcohol, smoking, obesity, liver dysfunction, radiation to the breast and chronic exposure to heat have been found to correlate with increased risk for MBC [7]. Other reported factors are family history and Jewish ancestry (reviewed in [2], Table 1).

### Diagnosis, clinical and tumour characteristics

Approximately 75% of MBC cases clinically present with a painless subareolar lump in the breast tissue. In rare cases, pain associated with lump, nipple involvement, bleeding from the nipple, ulceration or axillary nodal metastasis without palpable breast lump could be the first sign of the disease [1].

Generally, males with breast cancer differ in presenting characteristics as compared to females such as higher age at the time of diagnosis, more advanced disease stage, larger tumour size and more frequent lymph node involvement [3].

The diagnosis of MBC should be based on the combination of clinical assessment, mammography/ultrasound and morphology verification (a fine-needle biopsy or a core biopsy for histopathology) [6,7,13].

The predominant histological type is invasive ductal carcinoma accounting for 90% of MBC cases [13]. Hormone receptor positivity is more frequent in MBC than in FBC. In a large population-based cohort comparing 680 males with 119 732 females, 90.6% of MBC were oestrogen-receptor (ER) positive and 81% progesterone (PR) positive, compared with 76% and 67% in females, respectively [3]. This is in line with another recent study describing a significantly higher ER and PR positivity in males (95% and 85%, respectively) than in females (82% and 79%) [5].

### Primary local and loco-regional therapies for male breast cancer

The first-choice treatment modality of MBC is surgery, either in the primary setting for early/localised

**Table 1.** A selection of risk factors in male breast cancer and the corresponding relative risk of increased risks for men.

Risk factor	Relative risk/increase	High-risk group
Family history	2,5 RR	MBC in first-degree relative
Klinefelter's syndrome	20–50-fold increase	People with Klinefelter's syndrome
Obesity	2,3 RR	Very overweight
Testicular abnormality	2–12-fold increase	Mumps in >20 years, cryptorchidism
Alcohol consumption	1,16 RR	16% increase with every daily drink (10g alcohol)
Liver cirrhosis	3–4-fold increase	
Radiotherapy to the breast	1,6–1,9 RR	Treated for gynaecomasty
Age		Elderly individuals with a peak incidence at 71 years

disease or following neoadjuvant therapy in locally advanced breast cancers. The modified radical mastectomy is the most commonly performed surgical procedure [1,11,14]. However, breast-conserving approaches with or without radiotherapy as well as more radical surgical procedures have also been used [7,13]. Surgical assessment of the axilla should be performed along with the primary surgery, either by sentinel node biopsy in clinically node-negative disease with small tumours ( $\leq 2$  cm) or by axillary node dissection in node-positive cases [13].

Radiation is given aiming to reduce loco-regional recurrence, thus improving long-term impact on survival [15]. Males with tumours larger than 1 cm and/or all males with node-positive disease should receive postoperative radiotherapy as well as cases operated with breast-conserving surgery [16]. Nevertheless, it is mandatory to deliver three-dimensionally planned radiotherapy aiming to minimise total heart doses [13].

### Neoadjuvant therapy

In males with inoperable breast cancer (tumour ulceration, tumour fixation to thorax or advanced lymph node status), neoadjuvant treatment should be considered. The neoadjuvant treatment should be based on the tumour's biological characteristics and proof of invasiveness needs to be present before starting treatment. In females, neoadjuvant treatment has so far demonstrated similar survival expectations compared with the corresponding therapy given in the adjuvant setting [17–19]. The superior advantage of neoadjuvant therapies in males is that the effect of selected therapy can be followed *in situ*. The neoadjuvant treatment usually includes chemotherapy, aromatase inhibitors (AI) [20,21] but trastuzumab may also be an option [22].

### Adjuvant therapy

Most information on adjuvant treatment of MBC comprises retrospective case series analyses, which give conflicting findings on the benefit of adjuvant chemotherapy and hormonal therapy in male patients [9,23–30].

### Hormonal treatment

A majority, 85%, of MBC is ER positive, and tamoxifen is generally considered as standard adjuvant therapy [1,31]. Due to scarcity of randomised trials evaluating tamoxifen in men, the relationship between ER positivity and survival benefit with tamoxifen is less clear in men than in women.

On searching in the literature, the number of men included in studies is low. In one study, which included 57 men, significant increased disease-free survival ( $P = 0.0368$ ) and overall survival ( $P = 0.04$ ) was found [9]. Similar results were found in another series with significant improvement in 5-year survival with 39% and 61% with and without 1–2 year tamoxifen use, respectively [30]. The side-effects from tamoxifen are as for females: hot flushes, depression, weight gain, impotence and thromboembolic accidents [32].

### Aromatase inhibitors

The AI anastrozole [33] and letrozole [34] have recently shown to be effective in the adjuvant setting among postmenopausal females giving prolonged disease-free survival compared to tamoxifen in large multicentre trials. Switching treatment to exemestane after 2–3 years treatment with tamoxifen also improves disease-free survival [35]. Anastrozole given to young men (16 years) reduced the estradiol values by 50% and increased testosterone values by 41–61% [36], and letrozole (CGS 20267) reduced the estradiol values with 80% in males; thus, these drugs might be considered as potential therapeutic tools. The AI may be more efficient if the testicular function is down regulated, by either a surgical or medical orchidectomy [37]. The combined therapy with gonadal ablation by gonadotropin-releasing hormone (GnRH) analogue such as gosereline and AI may give complete suppression of oestrogens but unfortunately also impairing quality of life due to reduced libido. However, there is no such data in the literature at present.

### Chemotherapy

In males, there is an increased risk of higher toxicity from conventional chemotherapy and it is more common with medical contraindications due to higher mean age at breast cancer diagnosis [3].

Non-randomised, earlier and recent studies show that males with breast cancer and lymph node involvement will have a better prognosis if systemic adjuvant therapy is offered [24,28,29,38–40]. Different types of regimens have been used [41] including cyclophosphamide-methotrexate-5-fluorouracil (CMF) or anthracycline-based regimens, predominantly being 5-fluorouracil-adriamycin-cyclophosphamide (FAC). In addition, taxanes have more recently been used, but conclusive data are lacking in MBC [1]. In one prospective study with CMF, 24 patients with stage II disease, was the 5-year survival rate projected by actuarial means of

80% (95% confidence interval: 74–100%) [38]. In a recent prospective study with a 20-year follow up of 31 patients treated with CMF, the overall survival at 10 years was 64.5%, at 15 years 51.6% and at 20 years 42.4% [40]. In a retrospective study of 156 men, 51 men received systemic therapy of which 72% ( $n = 23$ ) were treated with anthracycline-based regimes. The hazards ratio (HR) for time to recurrence was 0.7 (CI: 0.42–1.17) and the HR for overall survival was 0.57 (CI: 0.34–0.95) compared with those who did not receive any systemic therapy [39].

Although the reported studies are small and inconclusive, males with breast cancer and lymph node involvement and patients with endocrine unresponsive tumours should be offered adjuvant chemotherapy.

### Her-2/neu

Her-2/neu overexpression in men with breast cancer varies from 9% to 29% in three main series, and one of the groups demonstrated a higher frequency of Her-2/neu-positive breast cancers in males compared with the findings in females [42–44]. Among 77 male patients, primary tumour in 29% were Her-2/neu positive as assessed by immunohistochemistry [44]. The high degree of positivity is likely due to the advanced tumour stage [45]. Based on the data from females, males with Her-2/neu-amplified breast cancers should be offered therapy with trastuzumab in both the adjuvant and metastatic setting based on the criteria established for females [46–48].

### Metastatic disease treatment

The sites of metastases in men are similar to those in women and include bone, lung, liver, brain and others. The approach to the treatment of metastatic breast cancer is similar in male and female patients with breast cancer. Historically, a male with metastases from breast cancer was treated with different ablative surgical procedures: adrenalectomy, hypophysectomy and orchidectomy, which in historical series showed a 55–80% response rate [49]. These surgical procedures are rarely used today and have been replaced by additive hormonal therapies. There are data from females with breast cancer that primary tumours can be hormonal receptor negative and the relapse turns out to be negative and vice versa [50]. Similar data are reported in the Her-2/neu with inconsistency of Her-2/neu amplification in the primary tumour compared with the corresponding metastases [51]. Accordingly, it is recommended that

at least one metastatic lesion should be biopsied to estimate Her-2/neu status, hormonal receptor status and proliferation. This procedure gives the opportunity to tailor the metastatic treatment therapy based on the tumour's biological characteristics in the relapse rather than in the primary tumour.

The first approach in palliative therapy in men with oestrogen receptor-positive tumours is hormonal therapy with tamoxifen with an approximate 50% response rate [49]. Use of AI is still doubtful in men, but in one report three out of five male patients had stable disease after treatment with anastrozole [52]. Benefit of letrozole in recurrent metastatic disease has also been reported [53].

AI, when treating males, should probably better be used in combination with a GnRH analogue [52]. Fulvestrant, a pure anti-oestrogen, has been reported to have effect in two cases of MBC [7]. Chemotherapy for metastatic disease should of course be offered at first relapse to males with a receptor-negative disease and/or for those with biologically aggressive disease and can provide significant palliation. Patients who have developed a hormone-resistant metastatic disease should also be offered systemic chemotherapy and trastuzumab in Her-2/neu-positive cases could be considered.

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