

# Endocrine Therapy for Male Breast Cancer

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## Abstract

More than 90% of male breast cancers (MBC) are estrogen receptor positive but unfortunately over 40% are either stage III or stage IV at the time of presentation. This means that for a substantial proportion of patients, endocrine therapy will be used in a palliative role in the management of MBC. Tamoxifen is the main first line agent that is given for both adjuvant treatment and control of advanced disease. Although effective it can be more toxic in men than in women so that a significant proportion of males will become non-compliant. It is important that non-adherence is recognised and whenever possible second line therapy is instituted with either aromatase inhibitors or LHRH analogues. International collaboration in randomised trials will be necessary to determine the future endocrine therapies for MBC.

**Keywords:** Male breast cancer; Immunohistochemistry; Estrogen receptor; Progesterone receptor

## Introduction

Male breast cancer (MBC) is a rare disease comprising <1% of total cases. As such, single institutions have been unable to amass sufficient patients for inclusion in prospective randomised trials so that clinical practice has been largely determined by experience with female breast cancer. In order to develop rational therapies it is important to understand the similarities and differences between breast cancers in women and men.

## Risk Factors

Data on risk factors for male breast cancer has been largely derived from retrospective studies which can be biased by selective recall. To overcome this problem Brinton et al. studied 324 920 male participants in the prospective National Institutes of Health -AARP Diet and Health Study [1]. Of this cohort, 121 were subsequently diagnosed with MBC. Obesity was positively associated with risk (RR=1.79) as was a prior history of bone fracture, (RR=2.20). The authors postulated that risk factors in men may result from unique mechanisms associated with the ratio of androgens and bioavailable estrogens.

In subsequent work Brinton et al. [2] accessed 26 million hospital discharge records on the US Veterans Affairs database for the period 1969-1996. From 4,501,578 men aged 18-100 years, 642 MBC cases were identified. Several diseases were associated with increased risk including diabetes (RR=1.30), obesity (RR+1.98), orchitis/epididymitis (RR=1.84), and Klinefelter syndrome (RR=29.64).

## Prognosis

Anderson et al. [3] examined the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program for male and female breast cancers diagnosed between 1973 and 2005. They reported that deaths from breast cancer declined over time. Comparing 1976-85 with 1986-2005, for women cause-specific hazard rates reduced by 42% compared with only 28% in men.

Gnerlich et al. [4] conducted a retrospective cohort study to investigate breast cancer-specific and all-cause mortality between males (1,541) and females (244,518) using 1988-2003 SEER Program data. Males were more likely to be older, have more advanced cancers, but have tumours of lower grade which were mostly estrogen/progesterone receptor positive. After adjustment, men had higher breast cancer specific mortality only if diagnosed with stage I disease.

In a large international study, Miao et al. [5] analysed data from Denmark, Finland, Geneva, Norway, Singapore, and Sweden which included 459,846 women and 2,665 men with breast cancer. Standardised incidence rates were 66.7 per 105 person-years in women and 0.40 in men. Median ages at diagnosis were 61.7 and 69.6 years respectively. Although males had a worse 5-year relative survival ratio (0.72 v 0.78) after adjustment for age, stage, and treatment, they had a significantly better relative survival.

Another gender comparison from the Veterans Affairs (VA) Central Cancer Registry (VACCR), examined survival of 612 patients with MBC and 2413 with FBC [6]. Mean ages at diagnosis were 67 and 57 years respectively. Males had higher stage of disease and greater likelihood of nodal involvement. Median overall survivals were 7 and 9.8 years respectively. In contrast, for those with stage I/II disease the median survivals differed significantly. Node-negative males had a median survival of 6.1 years whereas for females it was 14.6 years. Median survival was similar in lymph node-positive patients of both genders. In multivariate analysis age, sex, stage, and nodal status were independent prognostic factors but tumour type and grade were not.

## Male Breast Tumour Molecular Profiling

Molecular subtyping by gene expression in female breast cancer has been extensively investigated, with more recently data on MBC becoming available and these are summarised in Table 1. Ge et al. [7] used immunohistochemistry (IHC) for estrogen receptor (ER), progesterone receptor (PR), cytokeratin 5/6 (CK5/6), EGFR, and NF-κB, Human epidermal growth factor receptor 2 (HER2) expression to subtype 42 MBC tumours. The luminal A subtype was the most common subtype (83%, 35/42), followed by luminal B subtype (17%, 7/42). There were no basal-like and HER2+/ER subtypes identified. All tumours were ER+ve and 67% were PR+. High nuclear grades represented 71% of the luminal B subtype and 34% of luminal A subtype (34%, 12/35).

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Author	N	ER +ve	PR +ve	HER2 +ve	Luminal A	Luminal B	Basal-type
Ge et al. [7]	42	100%	67%	17%	83%	17%	0
Sánchez-Muñoz et al. [9]	43	93%	84%	0	44%	51%	5%
Deb et al. [10]	60	90%	77%	9%	89%	9%	2%
Johansson et al. [11]	286	88%	73%	8%	M1 70 M2 30%		
Kornegoor et al. [12]	134	94%	68%	3%	76%	21%	
Nilsson et al. [13]	197	93%	77%	11%	81%	11%	1%

Table 1: Molecular subtyping of MBC.

This suggests that both pathology and aetiology are different in males and females.

In a multi-centre study, Shaaban et al. compared 251 male and 263 female breast cancers, matched for grade, age, and lymph node status. Tissue microarrays were immunostained for ER $\alpha$ , ER $\beta$ 1, -2, -5, PR, PRA [8]. In both sexes luminal A was the commonest phenotype with luminal B and HER2 not seen in males and basal phenotype was infrequent in both. AR-positive luminal A male breast cancer had improved overall survival over female breast cancer at 5 but not 10 years. In a relatively small Spanish series Sanchez-Munoz reported that 6-year survival in men with luminal A and luminal B tumours was similar [9].

Deb et al. [10] studied 60 cases of familial MBC of whom 3 were BRCA1 and 25 BRCA2 mutation carriers. In contrast to FBC there was greater proportion of BRCA2 tumours (42% versus 8%, and fewer BRCA1 tumours (5.0% versus 14%). The histological subtypes seen in familial MBC were more similar to those seen in sporadic MBC with 77% being invasive ductal carcinoma of no special type (IDC-NST). Most tumours were of the luminal phenotype (89%), a few were HER2 (9%) and rarely basal (2%).

Using unsupervised hierarchical clustering (HCL) Johansson et al. studied gene expression in 66 frozen MBC specimens and separated them into two subtypes, luminal M1 and luminal M2 [11]. This separation was recapitulated in a validation set of 220 archival MBCs. M1 tumours, although ER +ve, expressed fewer genes associated with ER signalling and had a more aggressive phenotype and a worse prognosis. M2 tumours had higher expression of both immune response genes and ER signalling genes.

Of the most differentially expressed genes, class 1 human leukocyte antigen (HLA) and the metabolizing gene N-acetyltransferase-1 (NAT1), there was significantly better survival associated with high expression of both. On multivariate analysis, NAT1 retained significance suggesting that it is a prognostic marker in MBC.

Kornegoor et al. studied 134 MBC using immunohistochemistry stained on tissue microarrays for expression of multiple markers including ER, PR, AR, HER2, p53, Ki67, and EGFR [12]. In unsupervised HCL, four groups were delineated that associated with particular clinicopathological features. The groups were: A1, hormone-negative; A2, ER-positive high grade; B1, ER-positive intermediate grade; B2, ER-positive low grade. Of the individual prognostic markers PR and p53 were the most promising.

Nilsson et al. [13] reviewed paraffin-embedded tumour tissue from 197 MBC patients and used tissue microarrays and grading of H and E stained slides. Of the tumours, 93% were ER+VE and 77% PR +ve, with 41% being grade III and 11% HER2+ve. Using IHC markers 81% were luminal A and 11% luminal B. There were 2 basal-like cancers and no HER2-like tumours. There was no difference in breast cancer mortality between the luminal subgroups. Androgen receptor positivity has been reported in 39-95% of MBC specimens but no association with

clinicopathological features or prognosis has been reported [14,15]. All of these disparate results clearly indicate that MBC is a predominantly estrogen dependent disease.

Until now the only molecular targeting for male breast cancer has been either endocrine therapies in those with ER +ve cancers and herceptin or lapatanib for the few with tumours over-expressing HER2 [16]. As molecular profiling moves from a research tool to a prognostic system so it is hoped that specifically targeted regimens for specific groups can be tested.

## Historical Endocrine Treatments for MBC

Over 40% of MBC present with stage III/IV disease so that treatment is often palliative rather than curative [17]. After Beatson had shown that oophorectomy could achieve remissions in advanced breast cancer [18] so orchidectomy became first line treatment for MBC. Before the discovery of estrogen receptors a response rate of approximately 30% was seen in men with advanced disease [19]. Although orchidectomy could be effective in palliation it was not an option that was acceptable to many with MBC.

In 1978, Cantwell et al. [20] reported a series of three cases of MBC that had been treated with the selective estrogen receptor modulator (SERM) tamoxifen. All three patients went into remission, two of them for more than a year. Subsequently Kantarjian et al. [19] showed that first line tamoxifen was as effective tamoxifen after orchidectomy so that men could be spared the psychological distress of castration. Furthermore tamoxifen could be used as an adjuvant treatment as well as a palliative therapy for advanced disease.

## Adjuvant Therapy for MBC

The rarity of MBC has meant that randomised trials of adjuvant endocrine therapy for MBC have not been conducted. Assumptions have been made concerning treatments for MBC based on extrapolation from results of trials conducted for women with breast cancer. The first reported study of adjuvant tamoxifen for MBC was that of Ribeiro and Swindell who treated 39 men [21]. Tamoxifen was originally given for 1 year and subsequently extended to 2 years. All cases had clinical axillary nodal involvement and surgery was either a radical mastectomy or simple mastectomy with radiotherapy. The 5 year disease-free survival was 61% compared with 44% in historical controls. No serious side-effects were recorded. The authors concluded that significant improvement in disease-free survival could be achieved with minimal toxicity. Outline results from non-randomised studies of adjuvant tamoxifen for MBC are shown in Table 2.

In a US series of 42 men with non-metastatic breast cancer (all ER/PR+ve); 21 received tamoxifen (50%), 18 had chemotherapy (43%), and 11 were irradiated [22]. After a median follow-of 8 years, the 10-year overall survival was 100% in patients in those given tamoxifen and radiation, compared with 65% for tamoxifen alone and 83% for radiation alone. Adjuvant chemotherapy in combination with Tamoxifen or used alone did not significantly improve overall survival.

Author	N	Duration	Result
Ribeiro et al. [21]	39	1-2yr	61% 5yr DFS
Zhou et al. [25]	32	5yr	100% 10yr OS
Fogh et al. [22]	42	5yr	100
Xu et al. [27]	20	5yr	80% 10yr
	99	<5yr	50% 10 yr

DFS = Disease-free survival OS = Overall survival

Table 2: Results of adjuvant treatment of MBC by tamoxifen.

Goss et al. [23] reported a significant increase in both disease-free and overall survival in a series involving 229 MBCs treated in Toronto over a 40-year period. Patients in both these studies had received Tamoxifen for only 1 or 2 years and given that optimal results in women are achieved after 5 years of therapy, it is likely that the results for men are underestimated [24]. In a study from China Zhou et al. [25] reported a series of 72 MBC of whom 32 (44%) received tamoxifen [25]. The 5 year survival of this group was 100%.

Between 1999 and 2009, 126 MBC cases were treated at the MD Anderson Hospital and of these, 64 were stage I-III, treated with tamoxifen and had at least one follow visit after tamoxifen was started [26]. A descriptive analysis of toxic effects was carried out on these 64 patients. Median age at diagnosis was 61 years and median follow-up after starting tamoxifen was 3.9 years (range 0.3-19.4 years). Side effects were reported by 34 (53%) patients. These included weight gain (22%) and sexual dysfunction (22%). Treatment with tamoxifen was discontinued because of toxicity by 13 men (20%). Problems included ocular symptoms, leg cramps, neurocognitive deficits, bone pain, sexual dysfunction, and thromboembolic events (4/64, 6%).

Recently, Xu et al. [27] assessed tamoxifen adherence in relations to mortality in MBC patients. Of a cohort of 116 men diagnosed with ER+ve disease and had been prescribed tamoxifen, only 65% were taking the agent 1 year later, reducing to 29% after 3 years and to 18% in the final year. In a multivariate analysis, significant factors for stopping tamoxifen were low social support (Hazard ratio 2.45), age (HR = 1.10), and toxicity (HR = 2.19). For compliant patients the 10 year overall survival was 80% compared with 50% in the non-adherent group. This illustrates the urgent need to identify and deal with tamoxifen non-adherence in men.

## Aromatase Inhibitors

Harris et al. used the combination of the aromatase inhibitor aminoglutethimide and hydrocortisone to treat 5 men with advanced breast cancer [28]. There was no response in the men with intact testes whereas the previously orchidectomised patient responded for 14 months. Although estrone and estradiol levels were suppressed in all patients, this was a smaller effect from that achieved by orchidectomy.

After anastrozole had been demonstrated to be superior to tamoxifen as an adjuvant therapy for postmenopausal women with ER+ve metastatic breast cancer [29,30]. Giordano et al. [31] used that aromatase inhibitor (AI) to treat 5 men with advanced disease. No clinical responses were reported: 3 patients had static disease for 4-9 months and 2 had progressive disease. As a result the MD Anderson group treated a further 2 cases of advanced MBC with a combination of letrozole and the GnRH analogue leuprolide [32]. Both cases responded to the combination whereas one had not responded to either as a single agent. Based on these encouraging results the Southwestern Oncology Group (SWOG) have started a trial S0511 in which males with metastatic ER+ve MBC are receiving anastrozole and goserelin (another LHRH analogue).

Doyen et al. [33] treated 15 men who had metastatic MBC with various aromatase inhibitors (letrozole 5, anastrozole 5, exemestane 5). Two (13%) complete responses were reported, 4 (27%) had partial responses, two patients (13%) had stable disease and progression occurred in 7 (47%) had progressive disease. E2 levels in all assessable patients (n=6) undetectable during AI treatment. Among them, three had partial response, one had stable disease and two had progressive disease. There was a surge in follicle-stimulating hormone, luteinising hormone and estradiol levels in one responding patient at the time of progression.

To examine toxicity of endocrine treatment for MBC, Visram et al. conducted a review of 59 male patients treated at The Ottawa Hospital Cancer Centre between 1981 and 2003 [34]. The median age was 68.0 years. Thirty eight (64%) received tamoxifen. 8(14%) were given anastrozole to 8, and 5 (8.5%) were treated with letrozole. Adjuvant chemotherapy was given to 10 (25%).

Of the 38 men given tamoxifen, 50% reported toxicity of which hot flushes were the most frequent problem (18%). Five reported decreased libido, weight gain, and malaise (13.2%). Two complained of a rash and erectile dysfunction (7.9%). Rarer side effects included elevated liver enzymes, pulmonary embolism, superficial thrombophlebitis, myalgia, depression, visual blurring, and passage of loose stools. Nine patients (24%) stopped tamoxifen because of toxicity.

Among those treated with anastrozole, 3 (37.5%) reported side effects including decreased libido, leg oedema, and depression (12.5%) but none of them stopped taking anastrozole. Two patients taking letrozole reported peripheral oedema, and another had hot flushes but no patient stopped taking letrozole.

Eggemann et al. [35] studied 257 MBC patients with ER+ve disease from several German cancer registries of whom 207 were treated with tamoxifen and 50 with aromatase inhibitors. With a median follow-up of 42.2 months and after adjustment for the age, tumour size, nodal status, and grade. Treatment with an aromatase inhibitor was associated with a 1.5-fold increase in risk of mortality compared with tamoxifen.

## LHRH Analogues

As an alternative to surgical castration luteinising hormone releasing hormone (LHRH) analogues have been used in various ways for treatment of advanced MBC. Vorobiof and Falkson reported a case of MBC with pulmonary metastases successfully treated with buserelin, as an intranasal spray [36]. There was complete remission of the lung metastases but minimal toxicity.

In a larger series of 10 men with advanced breast cancer Doberauer et al. [37] administered buserelin, alone or together with flutamide (an antiandrogen). Of the 5 given buserelin alone, one had a partial remission for 12 months, extending over a further 24 months after starting flutamide. Three men had stable disease for a median of 6 months and 1 had progressive disease. For those 5 given buserelin and flutamide, 4 patients had a partial remission (median of 15 months) and one had stable disease for 12 months. Side effects included hot flushes, loss of libido, and impotence.

## Cyproterone Acetate

Cyproterone acetate, a synthetic derivative of 17-hydroxyprogesterone, is an androgen receptor antagonist and also a weak progesterone receptor agonist. Lopez et al. [38] reported a 43% response rate in 11 patients with disseminated MBC given cyproterone acetate. This

compared with 3 of 7 given tamoxifen, 2/5 receiving estrogens, 2/5 given aminoglutethimide, and 0/3 treated with high-dose medroxyprogesterone acetate, and 1 of 3 undergoing orchidectomy. The median overall response duration was 10 months.

In a subsequent study, Lopez combined cyproterone with the LHRH analogue buserelin to treat 11 men with recurrent or progressive MBC by total androgen blockade. They received buserelin 1500 µg subcutaneously daily for one week and 600µg daily subsequently together with cyproterone acetate (CPA) 100 mg twice daily, starting 24 hours before the first buserelin injection.

There was an objective responses in 7/11 (64%) with a median duration of 11.5 months. Stable disease for 5 months was reported in 3 patients and the median survival was 18.5 months. The main side effects were decreased or absent libido, impotence, and hot flushes. Unfortunately other groups have not explored this option for treatment of metastatic MBC.

## Fulvestrant

Fulvestrant is a synthetic estrogen receptor (ER) antagonist acting as a selective ER down-regulator. Unlike tamoxifen and the aromatase inhibitors, fulvestrant binds competitively to estrogen receptors in breast cancer cells. de la Haba Rodríguez reported a single case of metastatic MBC, heavily pre-treated with chemotherapy who had a partial response after 4 months of fulvestrant with symptomatic improvement [39]. Masci et al. [40] evaluated fulvestrant in 5 MBC patients with progressive metastatic disease and recorded one partial response, stable disease in two and progressive disease in two.

Zagouri et al. [41] treated 14 cases of metastatic MBC with fulvestrant, giving a loading dose of 500 mg on day 1, then 250 mg on day 14 and monthly thereafter. All the men had received prior endocrine therapy, fulvestrant was second-line treatment in 6, third-line agent in 7 and fourth line in one. There were no complete response and a partial response in 3 (21%) patients, with stable disease in 7 (50%), and progressive disease in 4 (29%) patients. Median time to progression was 5 months with the median overall survival being 61.5 months

## Conclusions

After a multidisciplinary international meeting held at Bethesda, Maryland in September 4, 2008 it was agreed that the mainstay of systemic therapy for hormone receptor-positive MBC is hormonal therapy [42]. As has been discussed, tamoxifen is the most extensively used and studied first line therapy for both adjuvant treatment and palliation of advanced disease.

Second-line therapies include LHRH agonists, orchidectomy, estrogens, and progestins but any of these may produce psychological or physical side-effects. The role of aromatase inhibitors with or without concurrent LHRH for treatment of MBC remains undefined. There is a pressing need for large international studies with defined molecular subtyping and testing of new endocrine approaches by controlled randomised trials.

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