Prognostic Factors for Male Breast Cancer: Similarity to Female Counterparts

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Abstract. *Aim: To assess whether prognostic factors in male (MBC) and female (FBC) breast cancer have similar impact on survival. Patients and Methods: Charts for men and women diagnosed with breast cancer referred to the London Regional Cancer Program (LRCP) were reviewed. Patients with distant metastatic diseases were excluded. Data on prognostic factors including age, nodal status, resection margin, use of hormonal therapy, chemotherapy with/without hormone and radiation therapy (RT), overall survival (OS), cancer-specific survival (CSS), and disease-free survival (DFS) were analyzed. Survival estimates were obtained using the Kaplan-Meier methodology. The Cox regression interaction was used to compare male and female differences in prognostic factors. Results: From 1963-2006 there were 75 cases of MBC and 1,313 of FBC totaling in 1,388 breast cancer cases. The median age of the cohort was 53 (range=23-90) years. The median follow-up was 90 (range=0.4-339) months. Of the prognostic factors considered, nodal status had a significant Cox regression interaction. For OS, p=0.001 with hazard ratios of 0.83 (95% confidence interval CI=0.42-1.64) and 2.88 (95% CI=2.36-3.52) for males and females, respectively. For CSS p=0.041 with hazard ratios of 1.22 (95% CI=0.45-3.27) and 3.52 (95% CI=2.76-4.48) for males and females, respectively. For node-positive cases, distant disease recurrence-free survival was worse for MBC (log rank, p<0.001). Conclusion: This large series showed that the nodal status influences survival differently in MBC and FBC. The findings of this study need confirmation from a more complete prospective database and further investigations on improving high-risk node-positive MBC management are warranted.*

Male breast cancer (MBC) makes up fewer than 1% of all cancer cases in men and fewer than 1% of all breast cancer in the United States (1). In 2012, 2,190 new cases were diagnosed in the United States and approximately 410 men died from this disease (2). Because of its rarity, little is known about its etiology, and there have been no randomized control trials of MBC. The management of MBC is primarily extrapolated from female breast cancer (FBC) trials and clinical data. Although prognostic factors, including anatomic factors, have been reported to be possibly responsible for poor survival outcome for MBC (3), the controversy of whether MBC has poorer or equal prognosis compared to FBC has not been completely resolved (4-10).

The objective of the present study was to investigate prognostic factors and their impact on survival and distant disease control in MBC compared to FBC.

Patients and Methods

Adult male and female patients with diagnosis of invasive mammary carcinoma of the breast referred to London Regional Cancer Program (LRCP) in the past 40 years were reviewed. Patient characteristics, pathological data, treatment and outcome information were collected. The patients were staged using the Seventh American Joint Committee on Cancer (AJCC) criteria for breast cancer (11). Patients with stage IV (M1) disease were excluded. All patients underwent surgery consisting of lumpectomy or simple mastectomy and axillary dissection or modified radical

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Table I. *Patients' demographics.*

Patient characteristic		MBC N=75	FBC N=1313	*p*-Value
Age	<60 years	22 (29%)	685 (52%)	0.001[a]
	≥60 years	53 (71%)	628 (48%)	
Tumor size	T1	27 (36%)	693 (53%)	
	T2	37 (49%)	490 (37%)	0.100[b]
	T3	2 (3%)	73 (6%)	
	T4	9 (12%)	57 (4%)	
Tumor grade	Low	28 (37%)	268 (20%)	0.004[b]
	Intermediate	24 (32%)	429 (33%)	
	High	13 (17%)	448 (43%)	
	Unknown	10 (14%)	168 (13%)	
Nodal status	Negative	37 (49%)	582 (44%)	0.300[a]
	Positive	38 (51%)	731 (56%)	
Resection margin	>2 mm	49 (65%)	1115 (85%)	0.290[b]
	≤2 mm	11 (15%)	105 (8%)	
	Unknown	15 (20%)	93 (7%)	
Hormonal therapy	No	36 (48%)	1093 (83%)	0.001[a]
	Yes	39 (52%)	220 (17%)	
Chemotherapy+/– hormonal	No	63 (84%)	713 (54%)	0.001[a]
	Yes	12 (16%)	600 (46%)	
Radiation therapy	No	29 (39%)	381 (29%)	0.100[a]
	Yes	46 (61%)	922 (71%)	

[a]χ^2 test; [b]unpaired *t*-test; +/–, with/without.bv.

Table II. *The effect of prognostic factors on overall survival in male breast cancer (MBC) and female breast cancer (FBC).*

Prognostic factor	Hazard ratio (95% CI)		*p*-Value
	MBC	FBC	
Age ≥60 years *vs.* <60 years	1.95 (0.84-4.53)	1.20 (1.01-1.43)	0.333
Tumor size			0.146
T2	1.42 (0.61-3.31)	2.15 (1.78-2.59)	
T3 & T4	1.97 (0.45-8.67)	3.39 (2.43-4.73)	
Tumor grade, High vs. inter/low	2.08 (0.55-7.83)	1.76 (1.37-2.28)	0.612
Nodal status, Pos vs. neg	0.83 (0.42-1.64))	2.88 (2.36-3.52)	0.001[†]
Resection margin Close/positive (<2 mm) *vs.* neg	2.90 (0.79-10.60)	0.97 (0.70-1.35)	0.585
Hormonal therapy	1.01 (0.50-2.01)	1.27 (0.99-1.62)	0.263
Chemotherapy+/– hormonal	1.03 (0.36-2.95)	1.96 (1.63-2.36)	0.140
Radiation therapy	1.06 (0.52-2.13)	0.95 (0.77-1.17)	0.932

CI: Confidence interval; Pos, positive; neg, negative; inter, intermediate; +/– with/without; [†]Cox regression.

mastectomy (MRM). Adjuvant radiation therapy was given in the postoperative setting for high-risk patients with close/positive resection margins, or tumor positive nodes (12). Radiation dose ranged from 40 Gy in 15 fractions to 50 Gy in 25 daily fractions to the breast or chest wall with or without supraclavicular axillary and internal mammary regions. A boost dose of 10 Gy in five fractions with electrons was generally given to patients with resection margin involvement. Radiation treatment was given after completion of chemotherapy using cobalt 60 or 4 MV linear accelerator.

Chemotherapy and tamoxifen were given in the adjuvant setting for high-risk patients with nodal involvement. The chemotherapy regime was cyclophosphamide, methotrexate, and 5-fluorouracil (CMF), or cyclophosphamide, epirubicin, and 5-fluorouracil (CEF) and tamoxifen was offered for estrogen receptor (ER) positive cases. Aromatase inhibitors were not offered as common practice in MBC.

The primary endpoints for our review were overall survival (OS) and cancer-specific survival (CSS). The secondary endpoints were disease-free-survival (DFS) and distant failure. Distant failure was defined as the recurrence of disease beyond the locoregional area of breast/chest wall or supraclavicular or axillary regions. DFS was defined as the duration from diagnosis to first recurrence. CSS was defined as time duration from pathological diagnosis to death or last follow-up, with breast cancer death defined as an event. OS was defined as the duration from pathological diagnosis to death, or last follow-up if still alive, with any death defined as an event. Chi-square and unpaired *t*-test were employed to compare demographic and disease characteristics of MBC and FBC. Survival estimates were obtained using Kaplan-Meier methodology. Cox regression interaction terms were used to evaluate male to female difference.

Results

From Jan 1963-Dec 2006, a total of 1,388 breast cancer patient charts were reviewed; 75 were MBC and 1,313 FBC. Patients were treated during similar time periods. Cases of MBC were from 1979-2006 and FBC were from 1963-1992. The median age of the cohort was 63 years (range=23-90 years). The median follow-up time was 90 months and ranged from 0.4-339 months.

Patients' characteristics are shown in Table I. For males, the median age was 65 years, (range=35-83 years) and for females was 60 years (range=23-90 years). Cases of MBC were significantly older at diagnosis (p=0.001), and had more low- and intermediate-grade tumors (p=0.004). More MBC tumors were ER-positive (83% *vs.* 57%) and were more often treated with hormonal therapy only (p=0.001), and less often with chemotherapy-based treatment (p=0.001), compared to FBC. Chemotherapy for MBC was CMF-based. Out of the prognostic factors analyzed, nodal status is the only factor with a significant Cox regression interaction in OS (p=0.001), and CSS (p=0.041). For OS, the hazard ratios were 0.83 (95% CI=0.42-1.64) and 2.88 (95% CI=2.36-3.52 for males and females, respectively (Table II). For CSS, the hazard ratios were 1.22 (95% CI=0.45-3.27) and 3.52 (95% CI=2.76-4.48) for males and females, respectively. For DFS,

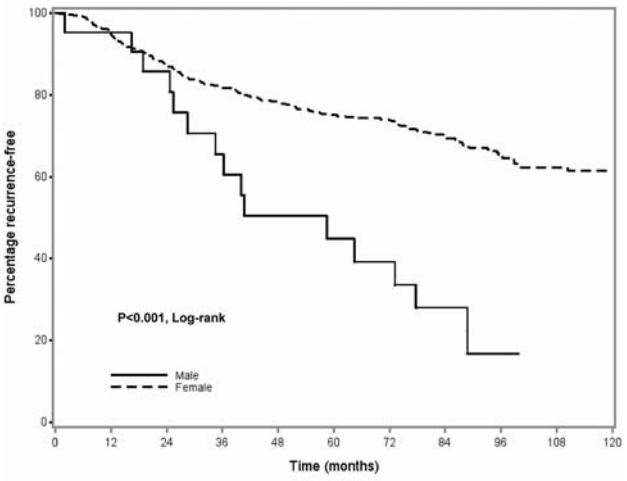

Figure 1. *Distant disease recurrence-free survival for node positive male breast cancer (MBC) versus female breast cancer (FBC).*

the hazard ratios were 2.36 (95% CI=1.04-5.37) and 2.64 (95% CI=2.21-3.15) for males and females, respectively, and non-significant (p=0.891).

Further analysis of the node-positive subgroup in MBC and FBC showed that the all-cause mortality rate was higher in MBC (at 10 years 67% for MBC *vs*. 52% for FBC), MBC cases with tumor-positive nodes were older (p<0.001), and MBC had poorer distance disease recurrence-free survival (log rank p<0.001) compared to their FBC counterparts (Figure 1).

The 5-year and 10-year OS rates for patients with node-positive disease were 75.0% and 33.1% for MBC and 66.6% and 48.6% for FBC, respectively; for node-negative cases the rates were 68.2% and 38.3% for MBC and 89.3% and 77.2% for FBC, respectively. The 5-year and 10-year CSS rates for node-positive cases were 79.3% and 55.2% for MBC, and 71.6% and 56.0% for FBC, respectively; for node-negative cases the rates were 91.5% and 69.2% for MBC, and 92.0% and 84.6% for FBC, respectively (Table III).

Table III. *Summary of overall survival and cancer specific survival.*

Survival	Node-negative				Node-positive			
	5-year		10-year		5-year		10-year	
	MBC	FBC	MBC	FBC	MBC	FBC	MBC	FBC
OS	68.2%	89.3%	38.3%	77.2%	75.0%	66.6%	33.1%	48.6%
CSS	91.5%	92.0%	69.2%	84.6%	79.3%	71.6%	55.2%	56.0%

Discussion

Our results showed that interaction of nodal status on patient outcome is different in MBC compared to FBC. Nodal status is a known prognostic indicator for both MBC (13, 14) and FBC (15-17). Our results show that more high-risk MBC patients with nodal involvement experience distant disease recurrence than their female counterparts.

Consistent with the literature, our MBC cases were diagnosed at an older age, had tumor pathology of often low and intermediate grade, more ER-positive tumors, often received tamoxifen over systemic therapy and had higher all-cause mortality. Chemotherapy for MBC in our center was CMF-based.

The reason for the higher rate of distant disease recurrence for MBC is not entirely clear. Although the descriptive patterns show the biology of MBC resembles the late-onset and ER-positive type of FBC, controversy is that MBC is similar to the late-onset type of FBC has increased over the past century (18). A large-scale population-based study reported that the mortality and survival rates for MBC have lagged behind the progress in FBC (19). The declining FBC mortality rates are probably attributed to adjuvant systemic therapy, screening mammography, and reduction in usage of hormone replacement therapy (20, 21). Evidence-based guidelines for adjuvant systemic therapy in FBC are rapidly implemented into community practice (22), but the same may not be true for men. Any declines in MBC mortality rates would likely reflect the impact of adjuvant systemic treatments since men receive neither screening mammography nor hormone replacement therapy.

Bouchardy and co-workers reported an experience of 407 patients with FBC aged greater than 80 years; half of their patient cohort were under-treated, with strongly reduced specific survival as a consequence (23). Naito and co-workers also reported an experience of 280 highly-elderly (75 years or older) patients with FBC with substantial under-treatment (24). Those included underwent significantly (p<0.001) less chemotherapy, with chemotherapy of less frequent anthracycline and taxane, and mainly 5-fluorouracil-based single-agent therapy. Chemotherapy was often omitted because of age.

Although many elderly cases of MBC received endocrine therapy as monotherapy for adjuvant cancer management, there have been no population-based studies confirming the efficacy of tamoxifen among men. Tamoxifen for MBC may also be limited by poor compliance because it is associated with high rates of treatment-limited side-effects (25), including decreased libido, weight gain, hot flashes, and deep venous thrombosis.

Oncologists are often concerned about the substantial high risk of toxicity in cancer treatment for the elderly. This can result in fit elderly patients suffering from potential undertreatment, with consequent lower relative survival (26).

Besides further investigation on suitable adjuvant systemic therapy and adjuvant endocrine therapy for high risk MBC, specific geriatric screening tools may be useful to identify fit patients with MBC who would be able to receive more aggressive treatment to improve their outcome (27).

We acknowledge the limitation in our study, including being a single-center retrospective study, lacking patient co-morbidity information, no pair-matching with FBC, and the patient cohort not being treated at the exact same period of time; however, our study is the first, to our knowledge, to report that node-positive MBC differs from node-positive FBC in regard to survival. A significantly higher proportion of MBC cases have distant recurrence when compared to their female counterparts. Adjuvant therapy for high-risk node-positive MBC needs to be revisited. Further investigations on the development of a safer and more efficacious treatment strategy in MBC are warranted.

Conclusion

Nodal status in MBC and FBC does not influence survival in a similar fashion. Nodal status has significant interaction in OS and CSS for MBC compared to FBC, with MBC having significantly lower distant recurrence-free survival. The findings of this study need confirmation from a prospective database with a more complete dataset, and further investigations on improving high-risk node-positive MBC management are warranted

Conflicts of Interest

There are no conflicts of interest for the Authors.

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