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ORIGINAL ARTICLE

Male Breast Cancer in Hong Kong: 15-Year Experience from a Tertiary Institution

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ABSTRACT

Objective: *Male breast cancer (MBC) is a rare disease entity and few data are available for the Chinese population. This study aimed to report MBC data from a single institution in Hong Kong to supplement existing evidence of this disease in our local population.*

Methods: *Patients with histologically confirmed MBC treated between July 1997 and February 2012 were retrospectively identified from an institutional patient database. Clinical, pathological, treatment, and survival data were collected and subsequently analysed.*

Results: *Within the captioned period, 52 cases of MBC were identified. The median age was 63 years, with evenly distributed tumour laterality. The majority of patients had invasive ductal carcinoma (84.6%), most of which were histologically grade II (50.0%). Almost all patients demonstrated hormone receptor positivity (oestrogen receptor–positive 98.0%, progesterone receptor–positive 96.0%), and HER2 amplification rate was 25.0%. Patients tended to present at an early stage of disease: approximately 85% presented as a T1 or T2 tumour, and 56.1% had axillary nodal involvement. Surgery with curative intent was performed in 48 patients, with 13 (27.1%) received adjuvant chemotherapy, and 35 (72.9%) underwent adjuvant radiotherapy. Almost all hormone receptor–positive patients received adjuvant tamoxifen. The median time to tamoxifen discontinuation was 60 months (range, 2-61 months). Discontinuation rate before 60 months was 15.9%. For those who underwent radical surgery, none developed loco-regional recurrence, and 5- and 10-year disease-free survival was 89.6% and 85.1%, respectively. The median overall survival for the entire population was 14.3 years.*

Conclusion: *Our single-institutional data indicate that a good long-term survival outcome can be achieved in MBC following a treatment protocol similar to that established for females with breast cancer. Prospective data will be helpful to further evaluate optimal treatment strategies as well as treatment tolerance for MBC in the Asian population.*

Key Words: *Breast neoplasms, male; Prognosis; Tamoxifen; Therapeutics*

中文摘要

香港的男性乳腺癌：一所提供第三層醫療服務的醫院的15年經驗

周重行、顏繼昌

目的：男性乳腺癌是一種罕見的疾病，華籍人口中有關男性乳腺癌的數據廖廖可數。本研究通過報導本港一所醫療機構中男性乳腺癌的數據，旨在加深瞭解本地人口中此症的現況。

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方法：回顧研究數據資料庫中於1997年7月至2012年2月期間經組織學證實患有乳腺癌的男性病例。收集和分析患者的臨床、病理、治療和生存數據。

結果：研究期間共有52例男性乳腺癌。患者平均年齡63歲，左右兩邊的腫瘤病例數量相若。大多數病例為浸潤性導管癌（84.6%），其中又以組織學II級居多（50.0%）。幾乎所有患者屬激素受體陽性（ER+ 98.0%，PR+ 96.0%），HER2擴增率為25.0%。患者多在疾病早期階段接受治療：約85%的病例屬T1或T2腫瘤，56.1%的患者腋窩淋巴結受累。48例接受了根治性手術，13例（27.1%）接受了輔助化療，35例（72.9%）接受了輔助放療。幾乎所有激素受體陽性的患者接受了他莫昔芬輔助治療。他莫昔芬停藥時間的中位時間為60個月（介乎2-61個月）。60個月前停藥的比率為15.9%。接受根治性手術的患者中無局部復發的病例，其5年和10年無病生存率分別為89.6%和85.1%。所有患者的總生存中位時間為14.3年。

結論：這單一機構的數據表明，根據針對女性乳腺癌的類似治療方案來處理男性乳腺癌能得到良好的長期生存結果。前瞻性數據將有助進一步評估亞洲男性乳腺癌的最佳治療策略及耐受性。

INTRODUCTION

Male breast cancer (MBC) is a rare malignant disease. The annual incidence of MBC in Hong Kong is approximately 0.4 per 100,000 men,[1] which is 140-fold less common than breast cancer in the female population. Despite the increasing incidence worldwide,[2] MBC remains rare. Most published data are retrospective, and many current treatment strategies are derived from experience with female breast cancer. Strong evidence to guide clinical decisions is lacking.

A recent retrospective review of the population-based MBC statistics in Hong Kong was carried out for the years 1997-2006, and a matched comparison was made with a corresponding female cohort.[3] This was the largest local report of the clinical, pathological, treatment, and outcome data for MBC. Results demonstrated that Chinese patients with MBC tend to have better breast cancer–specific survival than females.[3] In this study, we aimed to report our institutional experience of MBC across a 15-year period, and to further supplement current existing data on MBC in this locality.

METHODS

This was a single-institutional retrospective analysis of the clinicopathological characteristics and treatment outcomes of MBC. All consecutive MBC patients treated between July 1997 and February 2012 at our centre were identified from an institutional breast cancer database. Demographic, clinical, and pathological data were reviewed retrospectively from patients' case records. All cases were restaged using 2010 American Joint Committee on Cancer (7th ed) staging criteria; if surgery was not performed, clinical staging was applied.

Because there has been a lack of consistent reporting of the intensity and definition of hormone (oestrogen and progesterone) receptor positivity from different laboratories, a binary (positive or negative) approach was used for data analysis. Human epidermal growth factor receptor 2 (HER2) positivity was defined as either score 3 by immunohistochemical criteria, or a positive in-situ hybridisation test. Follow-up and survival data were calculated from the first date of histological diagnosis until time of data collection (25 January 2015).

Descriptive analyses were used for patient demographics and clinicopathological characteristics. Statistical analyses were conducted using the Statistical Package for the Social Sciences (Windows version 22.0; SPSS Inc, Chicago [IL], US). The Kaplan-Meier method was used to obtain overall and disease-free survival results, as well as tamoxifen discontinuation rate.

RESULTS

Demographics and Staging

Between July 1997 and February 2012, 52 cases of pathologically confirmed MBC were identified (Table 1). All patients were Chinese. The median age at diagnosis was 63 (range, 31-87) years and 23.1% (12/52) were aged <50 years. Tumour laterality was even between right and left side (51.9% and 48.1%, respectively). Overall stage at presentation was 0 (5.8%), I (25.0%), II (48.1%), and III (19.2%) respectively, and one patient

Table 1. Demographics, and clinical and pathological characteristics (n=52).

Characteristic	No. (%) of patients*
Age (years)	
<50	12 (23.1)
≥50	40 (76.9)
Laterality	
Right	27 (51.9)
Left	25 (48.1)
Stage	
0	3 (5.8)
I	13 (25.0)
II	25 (48.1)
III	10 (19.2)
IV	1 (1.9)
T-stage	
Tis	3 (5.8)
T1	22 (42.3)
T2	22 (42.3)
T3	1 (1.9)
T4	4 (7.7)
N-stage	
N0	29 (55.8)
N1	17 (32.7)
N2	5 (9.6)
N3	1 (1.9)
M-stage	
M0	51 (98.1)
M1	1 (1.9)
Histology	
IDC +/- DCIS	44 (84.6)
DCIS (only)	3 (5.8)
Papillary carcinoma	3 (5.8)
Papillary carcinoma + IDC	1 (1.9)
Mucinous carcinoma	1 (1.9)
Grade	
I	12 (28.6)
II	21 (50.0)
III	9 (21.4)
Unknown	10
ER	
Positive	49 (98.0)
Negative	1 (2.0)
Unknown	2
PR	
Positive	48 (96.0)
Negative	2 (4.0)
Unknown	2
HER2 amplification	
Positive	7 (25.0)
Negative	21 (75.0)
Unknown	24
Margin	
Clear	45 (97.8)
Involved	1 (2.2)
Not applicable (axillary dissection only)	2

Abbreviations: DCIS = ductal carcinoma in-situ; ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; IDC = invasive ductal carcinoma; PR = progesterone receptor.
* Percentages were calculated based on no. of known status.

(1.9%) presented with distant metastases to bone. Most patients in our series presented with a T1 (42.3%) or T2 (42.3%) tumour, and four (7.7%) presented with locally advanced T4b disease with skin involvement. Of those who underwent surgical axillary assessment, 56.1% (23/41) had axillary nodal metastases. Among the 11 patients with unknown pathological nodal status, three refused definitive surgery, one presented with metastatic disease, and seven underwent surgery to the primary tumour only; all of these 11 patients were clinically node negative. While no known *BRCA* mutation testing was performed in any of our patients, two patients in our cohort reported a positive family history of female breast cancer. One patient had known Klinefelter's syndrome, a well-established risk factor for MBC.[4] Apart from one patient who had concomitant liver cirrhosis, there was no other associated medical illness that could alter the androgen-to-oestrogen ratio, including primary testicular conditions.

Pathological Characteristics

Invasive ductal carcinoma (IDC) with or without a ductal carcinoma in-situ (DCIS) component was present in 44 (84.6%) of 52 cases, three (5.8%) were DCIS only, three (5.8%) were papillary carcinoma, one (1.9%) was mucinous carcinoma, and one (1.9%) showed a dual component of IDC and papillary carcinoma. The most common histological grade was II (50.0%), followed by grade I (28.6%) and grade III (21.4%). Among those with surgery performed for primary tumour, all except one patient had a clear resection margin. Most patients had a hormone-positive status, with 98.0% and 96.0% being ER+ and PR+, respectively. HER2 amplification status was evaluated in 28 patients, of whom seven (25.0%) were positive (Table 1).

Treatment

Surgery with curative intent was performed in 48 (92.3%) patients, of whom 37 (77.0%) had modified radical mastectomy, two (4.2%) had simple mastectomy with sentinel lymph node biopsy, four (8.3%) had simple mastectomy only, and three (6.3%) had wide local excision of tumour only (Table 2). Two patients in our series presented with malignant axillary lymphadenopathies with pathological findings suggestive of breast primary. Neither of them had an identifiable breast tumour, and both underwent axillary dissection without surgical intervention to the breast.

Adjuvant chemotherapy was administered to 13 (27.1%) of 48 patients, in most cases anthracycline- or taxane-

based. None of the patients in this series received neo-adjuvant chemotherapy. Adjuvant radiotherapy was administered to 35 (72.9%) of 48 patients, with radiotherapy being delivered to the chest wall in 16 and both chest wall / supraclavicular fossa in 19. The prescribed radiotherapy doses were: 50 Gy in 25 Fr (n=24), 50 Gy in 20 Fr (n=4), 39 Gy in 13 Fr (n=3), 42.56 Gy in 16 Fr (n=3), and 45 Gy in 18 Fr (n=1). An additional tumour bed boost, mostly due to close or involved resection margins, was received by 12 of 35 patients. Boost dose prescribed was: 12 Gy in 6 Fr (n=9), 7.5 Gy in 3 Fr (n=2), and 9 Gy in 3 Fr (n=1). Overall, with more advanced pathological stages, a larger proportion of patients received adjuvant chemotherapy and radiotherapy (Table 3).

Among the 46 patients who had a hormone receptor–positive tumour and who underwent curative intent surgery, 42 (91.3%) received adjuvant tamoxifen. The median time to tamoxifen discontinuation was 60 (range, 2-61) months. Overall discontinuation rate before 60 months was 15.9% (Figure 1). Extended tamoxifen therapy for a planned duration of 10 years was prescribed for one patient. In our series, although seven patients tested positive for HER2 amplification, none received adjuvant trastuzumab.

Among all patients, 10 received palliative treatment within the follow-up period. Tamoxifen was used in all but one patient who had a history of atrial fibrillation and was prescribed an anticoagulant; six received palliative aromatase inhibitors; five received palliative chemotherapy; and seven had palliative radiotherapy.

Table 2. Surgery and adjuvant treatments.

Treatment	No. (%) of patients*
Underwent surgery	
MRM	37 (77.0%)
WLE	3 (6.3%)
SM only	4 (8.3%)
SM + SLNB	2 (4.2%)
AD only	2 (4.2%)
Adjuvant chemotherapy	
Yes	13 (27.1%)
No	35 (72.9%)
Adjuvant radiotherapy	
Yes	35 (72.9%)
No	13 (27.1%)
Adjuvant tamoxifen	
Yes	42 (89.4%)
No	5 (10.6%)

Abbreviations: AD = axillary dissection; MRM = modified radical mastectomy; SLNB = sentinel lymph node biopsy; SM = simple mastectomy; WLE = wide local excision.
* Percentages were calculated based on no. of known status.

Table 3. Proportion of patients received adjuvant chemotherapy and radiotherapy by stage.

		Adjuvant chemotherapy	Adjuvant radiotherapy	Total No. of patients
Stage 0	Yes	0 (0%)	1 (33%)	3
	No	3 (100%)	2 (67%)	
Stage I	Yes	2 (17%)	8 (67%)	12
	No	10 (83%)	4 (33%)	
Stage II	Yes	6 (24%)	19 (76%)	25
	No	19 (76%)	6 (24%)	
Stage III	Yes	5 (63%)	7 (88%)	8
	No	3 (37%)	1 (12%)	

Treatment Outcomes

In the 48 patients who underwent surgery, the 5-year and 10-year disease-free survival was 89.6% and 85.1% respectively (Figure 2a). At the time of data collection, six patients had documented disease recurrence. First relapse sites were variable: one patient had distant neck node recurrence, one patient was noted to have bone metastases, and the remaining four had visceral involvement. None of the relapsed patients had local or regional recurrence. Median time to relapse was 3.3 (range, 0.3-6.5) years. Response to palliative chemotherapies varied, and the duration of disease control for each regimen was less than 6 months in all cases.

Overall, 15 patients had died at the time of data collection. The median overall survival of the entire

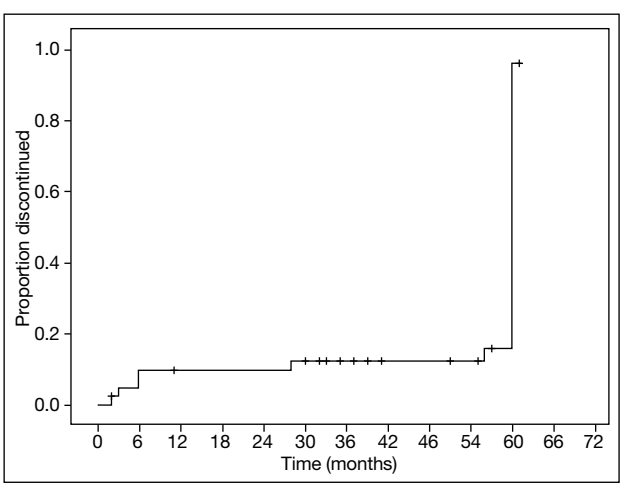

Figure 1. Time to tamoxifen discontinuation.

series was 14.3 (range, 0.9-17.6) years, with a 5-year and 10-year overall survival rate of 80.7% and 74.8% respectively (Figure 2b). Of the 15 deaths, six were breast cancer–related.

DISCUSSION

MBC is an uncommon disease entity. Locally, and in accordance with other reported series, our data suggest that MBC tends to be diagnosed at an older age.[2,3,5] Nonetheless, although most data suggest that men tend to have a later disease stage at presentation, in our series approximately 80% of patients presented with an early stage 0 to stage II disease, in whom curative surgery with clear resection margins was possible. Similar to other reported data, the majority of our cases were IDC: none was noted to have lobular carcinoma, which is most likely due to the lack of breast lobules in normal male breast tissue.[5]

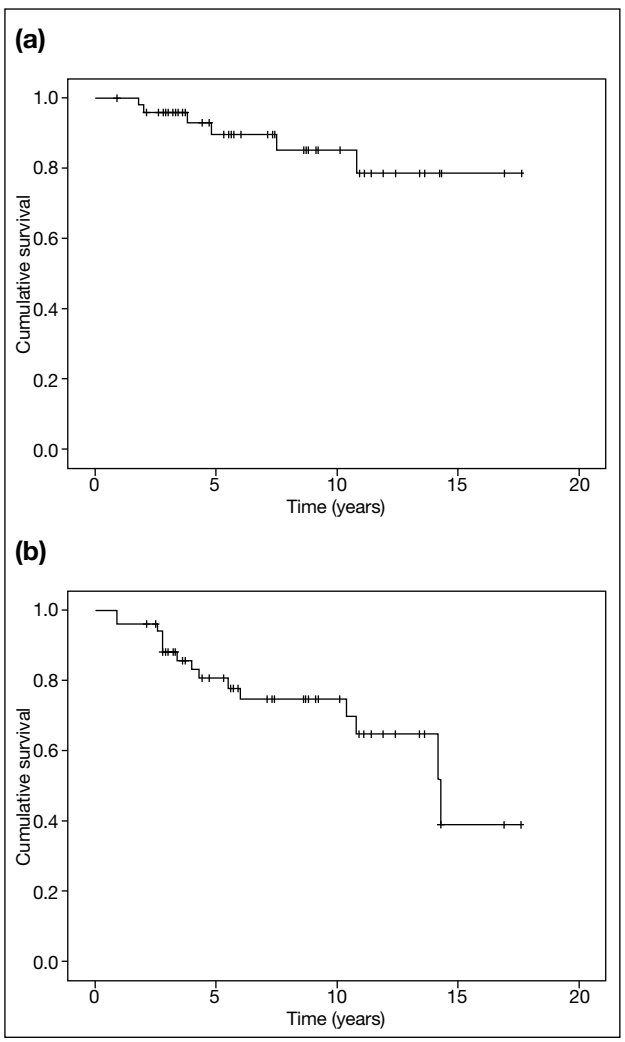

Figure 2. (a) Disease-free and (b) overall survival.

Despite a lack of uniform consensus on definition, over 95% of the tumours in our series were hormone receptor–positive. This finding is in agreement with the published literature where male patients are consistently reported to have a higher rate of hormone receptor positivity.[2,3,6] It is conceivable that with such a high receptor positive rate, as shown in our series, almost all patients with ER- or PR-positive disease received tamoxifen, in an adjuvant or palliative context. Despite the lack of prospective data, retrospective analyses have demonstrated improved survival outcome with the use of adjuvant tamoxifen in MBC.[7,8] In one report, men with node-positive MBC who received adjuvant tamoxifen had better 5-year disease-free survival than those who did not (56% vs. 28%).[9] Although one of our patients was prescribed extended tamoxifen therapy, its effectiveness in MBC remains unclear, and its use was mainly extrapolated from data in female breast cancer patients.[10]

As evidenced by existing reports, men tend to experience more treatment-related side-effects from tamoxifen, with a higher incidence of sexual dysfunction, weight gain, and hot flashes. In a US retrospective analysis of tamoxifen-related side-effects in MBC, there was up to 20% discontinuation rate due to toxicity, with an overall discontinuation rate of more than 50% before 60 months.[11] On the contrary, in our series only 15.9% patients discontinued therapy before 5 years, and most were able to complete a 60-month course of adjuvant treatment. Unfortunately, detailed documentation of treatment-related toxicities and the reason for discontinuation were not available. Further study in an Asian population will be useful to determine a possible ethnic discrepancy in tamoxifen treatment tolerance. Detailed survey of the impact of tamoxifen on quality of life in younger patients with MBC will also help to further assess patient acceptance and compliance, since 23% of patients in our series were younger than 50 years.

The use of aromatase inhibitors, which have been shown to be superior to tamoxifen in post-menopausal women,[12,13] has not been shown to improve survival in men as an adjuvant agent. In fact, a large retrospective analysis that evaluated adjuvant aromatase inhibitors versus adjuvant tamoxifen in MBC demonstrated an inferior overall survival.[14] This can be partially explained by the fundamental biological difference

between men and women: one-fifth of circulating oestrogen in men is produced directly from the testes,[15] rendering blockade of aromatase relatively ineffective.

HER2 status was available in 54% of our cases, and among those reported, seven were HER2 amplification test–positive. Nevertheless, none of these seven patients received adjuvant or palliative HER2-directed therapy during the follow-up period. This may reflect the fact that trastuzumab was a relatively new agent in the management of breast cancer, and that its use has become widespread only in the last 10 years. Current evidence for a benefit of HER2-directed therapies in MBC remains limited, and the exact functionality of the HER2 amplification pathway in MBC carcinogenesis is yet to be clarified.

In our series, among the 48 patients who completed radical surgery, adjuvant chemotherapy and radiotherapy were given in 27.1% and 72.9% respectively, largely following the treatment protocol for female patients. Together with the use of adjuvant tamoxifen in hormone receptor–positive patients, satisfactory treatment outcomes were achieved. None of the 48 patients had evidence of loco-regional recurrence within the follow-up period, and the 10-year disease-free survival was 85.1%. As mirrored in a retrospective review of MBC in a Chinese population, which reported a similar 10-year disease-free survival of 89.7%,[2] our satisfactory survival outcome may be attributed to an overall earlier stage at diagnosis, hence a high chance of disease eradication following radical treatment. The apparently higher tamoxifen compliance rate might have also played a role.

CONCLUSION

MBC is a rare disease in the Hong Kong Chinese population. Our series suggests that, with the majority of patients having early disease stage at presentation, excellent long-term survival outcome can be achieved following treatment strategies established for female breast cancer. More comprehensive local prospective data will help refine treatment strategies for MBC, as well as help evaluate the tolerance of our patients to various adjuvant therapies.

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