ORIGINAL ARTICLE

Royal Australasian College of Surgeons

Male breast cancer: a Singapore perspective

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Key words
breast cancer, male, Singapore.

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Accepted for publication 7 April 2022.

doi: 10.1111/ans.17737

Abstract

Introduction: Male breast cancer (MBC) is rare, representing <1% of all breast cancers. Treatment recommendations have been extrapolated from trial data of female breast cancer patients. This study aims to report our institutional experience of MBC across a 20 year period, analyse the survival outcome and prognosis of this group against female breast cancer patients treated at the same centre.

Methods: Clinical, histopathological, treatment and survival data of male and female breast cancer patients treated between Jan 1999 and July 2019 at Singapore General Hospital and National Cancer Centre Singapore were identified and analysed.

Results: Fifty-seven male patients were identified. The median age at diagnosis was 63 years. Majority had invasive ductal carcinoma (86%) and presented at an early disease stage: 70.2% presented as Tis/T1/T2 and 49.1% had no axillary nodal involvement. 84.2% had a simple mastectomy with either a sentinel lymph node biopsy or axillary clearance. The median follow up was 5.69 years for males and 5.83 years for females. The median survival was 11.86 years for males and 16.3 years for females. At 5 years, overall survival (OS) was 69.9% (52.3–82.1%) and disease free survival (DFS) was 62.9% (44.9–76.5%) for males compared with OS 83.8% (83.21–84.39%) and DFS 74.5% (73.91–75.09%) for females.

Conclusion: MBC remains understudied. Our institutional data indicates that good long term survival in South-East Asian patients can be achieved with treatment protocols that are similar to female breast cancer. More prospective studies are required.

Introduction

Male breast cancer (MBC) is rare, accounting for less than 1% of all cancers in men and less than 1% of all breast cancers,[1] but the incidence has been rising from 0.86 to 1.06 per 100 000 population over the last 26 years.[2] Due to its low incidence, most treatment recommendations have been extrapolated from data based on postmenopausal female patients.[1] To date, there is no standard of care for MBC. This study aims to report our institutional experience of MBC across a 20 year period, analyse the survival outcome and prognosis of this group against female breast cancer patients treated at the same centre.

Table 1 Demographics and clinical characteristics of male and female breast cancer patients

		Male	Female
		N(%) (*N* = 57)	*N*(%) (*N* = 20 408)
Laterality	Left	22 (38.6%)	10 048 (49.2%)
	Right	35 (61.4%)	9738 (47.7%)
	Bilateral	NA	512 (2.5%)
	Unknown	NA	110 (0.5%)
Ethnicity	Chinese	39 (68.4%)	15 150 (74.2%)
	Malay	3 (5.3%)	1557 (7.6%)
	Indian	4 (7%)	1044 (5.1%)
	Others	11 (19.3%)	2657 (13.0%)
Breast surgery	Mastectomy	48 (84.2%)	9916 (48.6%)
	Breast conservation	1 (1.7%)	5883 (28.8%)
	Excision biopsy	2 (3.5%)	NA
	No surgery	5 (8.8%)	3787 (18.6%)
	Unknown	1 (1.7%)	822 (4.0%)
Reconstruction	No	55 (96.5%)	13 031 (63.9%)
	Yes	2 (3.5%)	1603 (7.9%)
	Unknown	NA	5774 (28.3%)
Axillary clearance	Yes	31 (54.4%)	8845 (43.3%)
		−5 from positive SLNB	
		−26 upfront	
	No	19 (33.3%)	4977 (24.4%)
	Axillary sampling	NA	797 (3.9%)
	No surgery	5 (8.7%)	NA
	Unknown	2 (3.5%)	5789 (28.3%)
T Stage	Tis	2 (3.5%)	2254 (11.0%)
	T0	NA	288 (1.4%)
	T1	18 (31.6%)	6818 (33.4%)
	T2	28 (49.1%)	6271 (30.7%)
	T3	1 (1.7%)	995 (4.9%)
	T4	4 (7.0%)	650 (3.2%)
	Unknown	4 (7.0%)	3132 (15.3%)
N Stage	N0	28 (49.1%)	10 835 (53.1%)
	N1	15 (26.3%)	3931 (19.3%)
	N2	4 (7%)	1477 (7.2%)
	N3	6 (10.5%)	996 (4.9%)
	Unknown	4 (7%)	3169 (15.5%)
M Stage	M0	50 (87.7%)	17 712 (86.8%)
	M1	5 (8.8%)	1804 (8.8%)
	Mx	2 (3.5)	892 (4.4%)
AJCC8 Anatomic Staging	Stage 0	2 (3.5%)	2331 (11.4%)
	Stage 1	11 (19.3%)	5386 (26.4%)
	Stage 2	27 (47.4%)	6535 (32.0%)
	Stage 3	9 (15.8%)	3460 (17.0%)
	Stage 4	5 (8.8%)	1804 (8.8%)
	Unknown	3 (5.3%)	892 (4.4%)
Tumour grade	Grade 1	6 (10.5%)	2513 (12.3%)
	Grade 2	25 (43.9%)	6952 (34.1%)
	Grade 3	16 (28.1%)	7836 (38.4%)
	Unknown	10 (17.5%)	3107 (15.2%)
Histology	Infiltrative ductal carcinoma (IDC)	49 (86%)	14 728 (72.2%)
	Invasive papillary carcinoma	5 (8.8%)	104 (0.5%)
	Intra-ductal (DCIS/LCIS)	2 (3.5%)	2293 (11.2%)
	Adenoid cystic carcinoma	1 (1.7%)	NA
	Infiltrative lobular carcinoma	NA	888 (4.4%)
	Mixed ductal lobular carcinoma	NA	273 (1.3%)
	Mucinous carcinoma	NA	463 (2.3%)
	Medullary carcinoma	NA	118 (0.6%)
	Metaplastic carcinoma	NA	102 (0.5%)
	Others	NA	974 (4.8%)
	Unknown	NA	465 (2.3%)
ER status	Positive	49 (86%)	12 687 (62.2%)
	Negative	4 (7%)	4583 (22.5%)
	Unknown	4 (7%)	3138 (15.4%)
PR status	Positive	42 (73.7%)	10 679 (52.3%)
	Negative	11 (19.3%)	6467 (31.7%)
	Unknown	4 (7%)	3262 (16/0%)
HER2 status	Positive	8 (14%)	4396 (21.5%)
	Negative	40 (70.2%)	10 368 (50.8%)
	Equivocal	1 (1.8%)	1025 (5.0%)
	Unknown	8 (14%)	4619 (22.6%)

Table 1 Continued

		Male	Female
Hormone therapy	Yes	41 (71.9%)	11 637 (57.0%)
	No	3 (5.3%)	8199 (40.2%)
	Unknown	13 (22.8%)	572 (2.8%)
Chemotherapy	Yes	27 (47.4%)	8770 (43.0%)
	No	23 (40.4%)	11 635 (57.0%)
	Unknown	7 (12.3%)	3 (0.0%)
Radiotherapy	Yes	22 (38.6%)	10 082 (49.4%)
	No	29 (50.9%)	5400 (26.5%)
	Unknown	6 (10.5%)	4926 (24.1%)

Methods

This study was approved by SingHealth's Centralised Institutional Review Board under the protocol title 'Outcomes research in breast cancer care' (Ref 2019/2419). All male and female breast cancer patients treated between Jan 1999 and July 2019 at the Singapore General Hospital and National Cancer Centre Singapore were identified prospectively from an institutional database, the Joint Breast Cancer Registry. There were 20 465 patients – 57 male (0.28%) and 20 408 (99.72%) female. The clinical, histopathological, treatment and survival data were retrospectively reviewed and analysed. The focus was on the male group and all results refer to the male group unless otherwise stated.

Staging was done according to the AJCC eighth edition anatomic staging. Tumour, node, metastases (TNM) staging was recorded based on pathological staging post-surgery. If they did not undergo surgery, clinical TNM staging was used. Survival data were calculated from the date of histological diagnosis to the date of death or till the last follow up date for survivors.

Statistical analysis was conducted using R (version 3.6.3). Overall survival and disease-free survival analysis was done using the Kaplan–Meier method. Overall survival is defined as time from date of initial diagnosis to date of death or date of last follow-up for surviving patients. Patients who were still alive at their last follow up date would be censored at their last follow up date. Univariate analysis evaluating factors correlating with survival was done using log-rank test. Follow-up time was estimated using the reverse Kaplan–Meier method. A *P*-value of <0.05 was considered to be statistically significant.

Results

There were 57 male cases identified over a 21-year period from 1999 to 2019 as compared with 20 408 female cases. The median age at diagnosis for males was 63 years (range 28–82 years) while that of females was 53 years (range 16–104 years). Majority of cases for both genders were Chinese (ethnicity breakdown illustrated in Table 1 below). MBC exhibited a right sided predominance: 35 (61.4%) were on the right and 22 (38.6%) on the left while female breast cancer exhibited a left sided predominance: 10048 (49.2%) were on the left and 9738 (47.7%) were on the right. Majority of MBC presented with a unilateral breast mass. Other symptoms included bloody nipple discharge, pain and axillary lymphadenopathy. The duration of symptoms for males ranged from 1 week to 120 months. Only five males reported a positive family history of female breast/ovarian cancer in a first-degree relative.

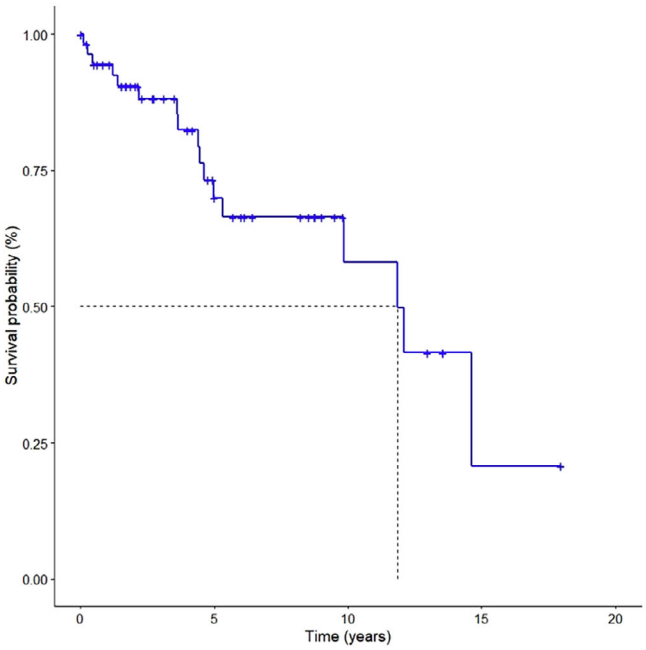

Fig. 1. Overall survival of MBC patients.

Of the 57 male cases, 48 (84.2%) underwent a simple mastectomy with either a sentinel lymph node biopsy (SLNB) ($n = 25$) or axillary clearance ($n = 31$). One (1.7%) underwent breast conservation surgery (BCS), two (3.5%) underwent an excision biopsy and five (8.8%) declined surgery. Of those who underwent a mastectomy, one required a chest wall reconstruction and the other underwent a delayed fat injection to his depressed scar.

The BCS patient underwent BCS with axillary clearance, adjuvant chemotherapy, radiotherapy and hormonal therapy but passed away from non-breast cancer related cause. Of the two excision biopsy patients, one underwent an excision biopsy and axillary clearance, adjuvant chemotherapy and radiotherapy but passed away from metastatic breast cancer. Another presented with metastatic gastric cancer with an incidental left breast nodule seen on staging scans and underwent an excision biopsy for diagnostic purposes to guide adjuvant therapy. He passed away from non-breast

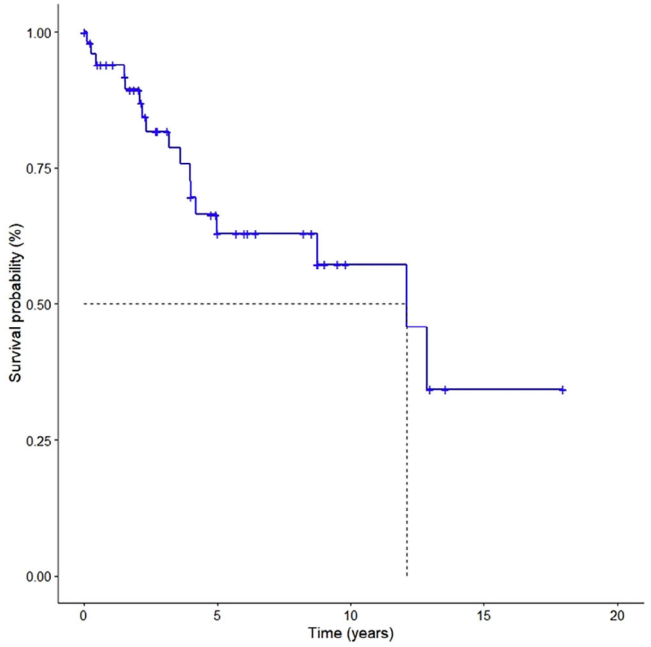

Fig. 2. Disease-free survival of MBC patients.

cancer related cause. Of the five who had no surgery, four were metastatic at the time of diagnosis and have since passed away due to metastatic breast cancer. One who was diagnosed in June 2017 declined surgery in view of his elderly age and was started on hormonal therapy. Recent staging scans show disease progression in the skin, axillary nodes and lungs and he remains alive at the time of writing.

Twenty-five male cases underwent a SLNB, of which five were positive. These five proceeded to have an axillary clearance. Twenty-six patients underwent an upfront axillary clearance, of which the majority was before the year 2007 – when our institution adopted SLNB as the standard of care for breast cancer patients.

Twenty-seven male patients (47.4%) underwent adjuvant chemotherapy, in most cases anthracycline- or taxane-based. 22 (38.6%) received radiotherapy and 41 (71.9%) received hormonal therapy, of which the majority ($n = 32$) was tamoxifen. Only five patients reported side effects – four were minor (alopecia, fatigue, arthralgia, mood changes) and one was major (deep vein thrombosis and pulmonary embolism). The patient who suffered the major side effect eventually stopped tamoxifen.

The histopathological characteristics of the patient cohort are shown in Table 1. The majority of the cancers were infiltrative ductal carcinoma, ER and PR positive and HER2 negative. The molecular subtyping is as follows: 37 ER positive/Her2 negative, 2 triple negative, 8 Her2 positive and 10 unclassified.

The median follow up was 5.69 years (IQR 2.16 years; 9.50 years) for males and 5.83 years (IQR 2.5 years; 11.17 years) for females. At time of analysis, the median survival was 11.86 years for males and 16.3 years for females. The median disease-free survival was 12.08 years (male) and 14.75 years (female). At 5 years, overall survival (OS) was 69.9% (52.3–82.1%) and disease free survival (DFS) was 62.9% (44.9–76.5%) at 95% confidence interval for males and 83.8% (83.21–84.39%) at 95% confidence interval and DFS was 74.5% (73.91–75.09%) at 95% CI.

Thirty-five male patients (61.4%) had no evidence of recurrent disease. Five who had metastatic disease upon diagnosis had passed away. Nine patients (15.8%) had a recurrence after initial curative surgery. Seven of them presented with both visceral and bone metastases at a median of 36 months (range 18–104 months), one presented with local recurrence (at 46 months) and one presented with bone metastasis at 24 months. Five (8.8%) of these nine recurrences have since passed away. One passed away while undergoing adjuvant chemotherapy post completion mastectomy. One (alluded to earlier) who refused surgery due to his elderly age and was only treated with hormonal therapy was alive with metastatic disease. Six (10.5%) had passed away from non-breast cancer related causes – two from lung cancer, one from lymphoma, one from gastric cancer, two from trauma. Figures 1 and 2 shows the Kaplan–Meier survival curves for overall and disease-free survival in our study.

Within this cohort of 57 male patients, only five patients underwent genetic testing but none of them tested positive. Univariate analysis comparing the effect of age, grade, stage, hormone receptor status and treatment type was done but no statistically significant differences were seen for both OS and DFS (data not shown).

Discussion

MBC is rare in Singapore with only 57 cases compared with 20 408 new female breast cancer cases diagnosed and treated at our institution over a 21-year period. The incidence of MBC in the Asian population is lower compared with that the non-Asian population, in keeping with current literature.[3,4]

Men tend to be diagnosed at a later age than women,[5] with median age at diagnosis of 63 and 53 years, respectively, in keeping with the current literature (67 vs. 61 years).[1] Most men present with a painless retroareolar mass. Other signs can include nipple retraction, nipple discharge and axillary lymphadenopathy. Only 5 (8.8%) reported a positive family history, similar to a Hong Kong study (3.8%)[6] although Western studies have shown that ~15–20% of men with breast cancer report a positive family history[1] which could be due to different genetics and lifestyle. In contrast to a previous local study on MBC which showed that 47.6% of patients presented with advanced disease[5] (Stage III/IV), 70.2% of our patients had early disease (Stage 0/I/II). Two other Hong Kong and Korean studies also showed that 86.3% and 66.5% presented with early disease (Stage I/II), respectively.[6,7] This may reflect better health awareness in our male population over the years since it is now comparable to early disease in our female population (69.8% in Table 1). Generally though, men are more likely to present with advanced stage disease (larger tumours and nodal metastasis) than women due to the absence of screening programmes, possible stigmata and low disease awareness.[8]

Interestingly, there was a preponderance of male right sided tumours and female left sided tumours in our study, although its significance is yet to be understood and appreciated. There is conflicting evidence in the literature regarding laterality in MBC. Weiss *et al.*[9] reported an overall 5% excess of left-sided disease in women but none in men. However, Ekbom *et al.*[10] found that

overall incidence of cancer was higher in the left than in the right breast among both women and men. Multiple theories put forth to explain the higher likelihood of left breast cancer in women such as handedness, nursing behaviour and breast size are mostly not applicable to men. It has been suggested that the same molecules causing left–right asymmetry in embryonic development before and during gastrulation might contribute to the development of cancer[11] and hence its laterality.

The most common male histological subtype was invasive ductal carcinoma not otherwise specified (86%), consistent with previous studies[2] followed by papillary (8.8%), DCIS (3.5%) and adenoid cystic carcinoma (1.7%). In contrast, in females, ductal carcinoma accounts for 72.2% of all female breast cancer cases followed by invasive lobular (8%), ductal/lobular carcinoma *in situ* (7%), mucinous (2.4%), tubular (1.5%), medullary (1.2%) and papillary (1%).[12] There were no cases of lobular carcinoma in our study, in keeping with the rarity in the literature since male breast tissue is rudimentary and does not usually differentiate to undergo lobule formation unless exposed to increased oestrogen concentration. Less common histological subtypes include papillary cancers. The majority were ER (86%) and PR (73.7%) positive and HER2 negative (70.2%), in keeping with other published data in the literature,[13] similar to older, menopausal women.

Treatment for MBC has been extrapolated from studies on treatment of female breast cancer. Women with breast cancer can undergo breast-conserving therapy (with whole breast radiation). For MBC, conventional treatment has been simple mastectomy with axillary clearance for node positive patients or SLNB.

In our study, only one patient underwent breast-conserving therapy with postoperative adjuvant irradiation. While uncommon, breast-conserving therapy has been associated with survival rates equivalent to those associated with mastectomy in observational studies, suggesting that data from women may be extrapolated to males.[14–16] However, the cosmetic benefits of breast conserving surgery may be limited in males due to the small volume of male breast tissue and nipple involvement at presentation for many cases.[17]

Cardoso *et al*. found that 40% of men presented with node positive disease[18] which was concordant with previous studies showing higher stage disease in men than women.[19] In our study, 43.9% of men had nodal positive disease at presentation versus 31.4% of women. SLNB seems to be both feasible and accurate in men with breast cancer[20] despite a larger proportion of male patients having nodal disease.

Endocrine therapy plays an important role in cancer management since most MBC cases are positive for oestrogen and progesterone receptors. Despite the lack of prospective data, it has been shown that adjuvant endocrine therapy (most commonly tamoxifen) may improve DFS and OS in MBC patients in retrospective studies.[21–23] The standard adjuvant endocrine therapy for male patients with hormone receptor positive breast cancer is 5 to 10 years of tamoxifen.[13] In our study, five patients (12.2%) reported side effects but only one (2.4%) was severe enough (thromboembolism) to result in changing to an aromatase inhibitor. Visram *et al*.[24] reported 50% of patients on tamoxifen suffered toxicity resulting in 23.7% of them discontinuing treatment. Although our study had less patients suffering from toxicity, it might be premature to conclude as 13 patients (31.7%) are currently still on hormone therapy. The side effects of endocrine therapy (commonly hot flashes and decreased libido for tamoxifen) remain understudied.[25] Further studies in an Asian population will be useful to detect any ethnic differences in tamoxifen toxicity. For males who have contraindications to tamoxifen or are unable to tolerate the side effects, aromatase inhibitors with a gonadotropin-releasing hormone analogue are an alternative although studies have shown that men treated with adjuvant aromatase inhibitors compared with tamoxifen have inferior survival rates.[26,27] There is also a paucity in the literature about the psychosocial consequences of MBC. France *et al*.[28] found seven major issues in a qualitative study: delay in diagnosis, shock, stigma, body image, casual factors, provision of information and emotional support which might delay men from seeking professional help early.

There was no correlation between age, stage, grade, hormone receptor status or treatment (chemotherapy/surgery/hormone) with overall survival or disease-free recurrence in our data. Choi *et al*.[7] showed that in multivariate analysis, age and tumour size were prognostic factors of OS. It is likely that our data set was too small to make a meaningful comparison and show a statistically significant difference.

Within our study, the median survival and OS for male patients was shorter than that of female patients at 11.86 versus 16.3 years and 69.9% versus 83.8%. Possible factors contributing to the lower OS compared with females would include older age at diagnosis and an average shorter life expectancy for men compared with women (2020 statistics: 81.5 years *vs*. 86.1 years). Miao *et al*.[29] showed that male patients had a poorer 5-year relative survival ratio than females (0.72 *vs*. 0.78) but better relative survival than female patients after adjustment for demographic characteristics, disease stage and treatment. However, adjustment for such factors was unable to be performed in our study due to the small male numbers.

Our male OS was shorter than that of studies in Hong Kong[6] (69.9% *vs*. 80.7% at 5 years) and Korea[7] (69.9% *vs*. 85.9% at 5 years). Chow *et al*.[6] reported a 5 year DFS of 89.6% which was significantly higher than that in our study (62.9%). Compared with the Hong Kong study, the median age of our patients was the same (63 years) and a majority presented at an early stage but our study had a lower proportion of hormone receptor positive patients (86% *vs*. 98% for ER; 73.7% *vs*. 96% for PR). We hypothesize that the increased percentage of hormone receptor positive patients who respond more favourably to endocrine therapy and the different patient profile (1/3 of our patients were non-Chinese versus 100% Chinese in the Hong Kong study) contributed to this. Moreover, as our overall numbers are small, 35.3% of the deaths were due to a non-breast cancer cause which affected the OS.

Pritzlaff *et al*.[30] reported that multi-gene panel testing (16 genes) of MBC patients revealed a 18.1% carrier detection rate. Pathogenic variants were most commonly found in the *BRCA2* (11.0%) and *CHEK2* (4.1%) genes. Within our local cohort, only 5 of 57 patients (8.8%) underwent genetic testing and none tested positive. The low uptake of genetic testing may be attributed to social reasons, lack of genetic awareness[31] and high out-of-pocket costs of genetic testing.[32] Multi-gene panel testing within our institution's cancer

genetics service (CGS) routinely offers breast cancer genetic testing to male and female patients who meet clinical testing criteria, of which demand and uptake of testing in females far exceeds males. Regardless, the identification of male carriers predisposed to breast cancer may be useful in guiding treatment for PARP inhibitors and cascade testing for at-risk family to understand cancer risk and management options. Within our institution, there are on-going efforts to understand the motivators and barriers of genetic testing in males with the intention to promote greater uptake of genetic testing in males.

We acknowledge several limitations of this study. As a retrospective study, information bias, loss to follow up bias and incomplete data are inevitable. The treatments administered over the years were not protocolized and as such not standardized. Other limitations include the lack of individual risk factors like smoking or drinking which might affect the OS and limited data on systemic therapy in metastatic disease due to the small numbers. However, this study's strength is that it includes all consecutive local MBC patients seen and followed closely in a single practice which offers a more realistic representation in general.

Conclusion

MBC is rare locally and remains understudied. Patients tend to present at an advanced age but at an earlier stage of disease. Community education is essential to break down the twin barriers of disease awareness and stigmata to ensure early presentation of disease. Our institutional data indicates that a good long-term survival in MBC patients can be achieved with treatment protocols that are similar to female breast cancer. More prospective studies are required to evaluate optimal treatment strategies and treatment toxicity for Asian MBC especially the side effects of endocrine therapy. The qualitative aspect of MBC should also be further explored.

Acknowledgement

The authors would like to thank the Joint Breast Cancer Registry co-investigators, Phyu Nitar and Zhou Siqin for their invaluable help in writing this article.

Conflict of interest

None declared.

Author contributions

Joshua S. H. Lim: Conceptualization, data curation, formal analysis, investigation, methodology, writing – original draft, writing – review & editing. **Yirong Sim:** Conceptualization; data curation; formal analysis; investigation; methodology; supervision; validation; writing – original draft; writing – review and editing. **Joanne Ngeow:** Conceptualization; data curation; formal analysis; supervision; writing – original draft; writing – review and editing. **Jeanette Yuen:** Formal analysis; investigation; writing – original draft; writing – review and editing. **Benita Kiat Tee Tan:** Conceptualization; data curation; formal analysis; investigation; supervision; writing – review and editing. **Veronique K. M. Tan:** Conceptualization; data curation; investigation; supervision; writing – review and editing. **Wei-Sean Yong:** Conceptualization; supervision; writing – review and editing. **Chow Yin Wong:** Conceptualization; supervision; writing – review and editing. **Sue Zann Lim:** Conceptualization; supervision; writing – review and editing. **Julie Liana B. Hamzah:** Conceptualization; supervision; writing – review and editing. **Si Ying Tan:** Conceptualization; supervision; writing – review and editing. **Fuh Yong Wong:** Conceptualization; data curation; supervision; writing – review and editing. **Preetha Madhukumar:** Conceptualization; data curation; formal analysis; investigation; methodology; supervision; validation; writing – original draft; writing – review and editing.

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