

Male Breast Cancer: The Philippine General Hospital Experience

Kristine A. Paguirigan, MD, DPBS; Mark Richard C. Kho MD, FPCS; Gemma Leonora B. Uy MD, FPCS and Rodney B. Dofitas, MD, FPCS

Division of Surgical Oncology, Head & Neck, Breast, Skin & Soft Tissue, and Esophagogastric Surgery, Department of Surgery, Philippine General Hospital, University of the Philippines Manila

Rationale/Objective: Breast cancer among males is often diagnosed at a later age and at an advanced stage. The study aimed to present the epidemiology, associated risk factors, clinical and pathological characteristics, treatment patterns and outcomes of male breast cancer patients treated at the Philippine General Hospital from January 2008- December 2017. Information from this study can provide for better understanding of the disease and basis for creating guidelines toward better outcomes.

Methods: Retrospective study of medical records involving male breast cancer patients who underwent surgery and treatment at the Philippine General Hospital from January 2008- December 2017.

Results: Male breast cancer accounted for 15 (0.26%) of 5,777 resected breast specimens for breast cancer patients with a 1:384 male to female ratio. The mean age of presentation was 60 years. The most common presentation was a retro-areolar mass, with 33% of patients presenting post-excision. Sixty-seven percent were at Stage II and 20% at Stage III. About 94% of patients have invasive ductal carcinoma, while the only other histology is papillary carcinoma at 13%. Majority of those tested were both estrogen receptor and progesterone receptor (ER/PR) positive (33% versus 1%), and Her2neu negative. All patients underwent modified radical mastectomy. Only two patients were documented to have received adjuvant chemotherapy while one patient received neoadjuvant chemotherapy.

Conclusion: Breast cancer remains to be a rare disease among males, is often diagnosed at a later age and at an advanced stage. Because of its rarity, awareness is necessary not only in the community but also among healthcare providers to identify and treat the problem earlier. Further investigation and prospective studies are recommended.

Key words: male breast cancer, ductal carcinoma, retrospective study, surgery, chemotherapy, hormonal therapy, radiotherapy, recurrence, survival

Male breast cancer is a relatively uncommon disease that accounts for less than one percent of all breast cancers.¹ There is only a certain population among Jewish men² as

well as some Africans in Tanzania where the incidence is relatively higher at about 6 percent.^{3,4,6} In sub-Saharan Africa, the similarity in the occurrence of endemic hepatic disease and male breast cancer has led to the suggestion of hyperestrogenism as a possible cause.^{3,4,6} The incidence increases with age and usually peaks during the sixth decade of life.⁵ Because of its rarity, management is generally based on small institutional studies or trials done involving female breast cancer, wherein hormonal, environmental and genetic factors interplay in the pathogenesis of the disease for both groups. However, despite the similarities, differences exist such that male breast cancer usually has a lower incidence and appears at a later onset.^{1,2}

The most commonly identified factors attributed to poor outcomes are the relatively small size of the male breast, lack of awareness that males can also have breast cancer, poor health seeking behavior, lack of diagnostic and treatment algorithms, absence of screening programs, and associated comorbidities due to advanced age upon diagnosis.^{2,3,4,5} A strong family predisposition has been linked to the disease^{5,6}, with recommendation for testing for breast cancer mutations (BRCA2) for the high risk population.² Men who tested positive for BRCA2 are said to carry six percent of absolute lifetime risk.⁶ In the absence of terminal lobules for the male breast, the identified pathology is said to be of the ductal type, with hormone-receptor positivity and rarely with Human Epidermal Growth Factor (HER-2) neu positivity.² Males with a first-degree relative affected with breast cancer were found to have two-to-three times increased risk for the disease, and have also been associated with Cowden

disease as well as Hereditary non-polyposis colorectal cancer (HNPCC) syndrome. There is also a susceptibility to develop a second primary cancer (16% risk) and a thirty-fold increased risk to develop contralateral breast cancer compared to two to four times in females.⁵ Other gene related irregularities (CHEK2, AR, CYP17 gene) have also been studied in the pathogenesis of male breast cancer but the supporting evidence is insufficient.

Exposure to carcinogens was found to contribute to the pathogenesis of the disease. One specific occupation (truck driving) was cited to have a strong association, increasing the risk for male carriers of BRCA1/2 mutations in one study.⁵ Other environmental conditions linked to male breast cancer include exposure to ionizing radiation, heat and electromagnetic radiation (possibly causing testicular failures), polycyclic aromatic hydrocarbons (PAH), alcoholic beverages (six-fold increase if more than 90 grams per day has been consumed), and consumption of red meat.⁵

Similar to females, hormonal imbalance, particularly a surplus of estrogen and scarcity of testosterone has also been associated with increased risk of the disease. Certain conditions such as testicular abnormalities from cryptorchidism, congenital inguinal hernia, orchitis, orchiectomy, and testicular injury as well as liver diseases (cirrhosis) are said to contribute to hyperestrogenism. Obesity is another factor that causes hyperestrogenism due to increased peripheral conversion of androgens, thereby doubling the risk for breast cancer in males.⁵ Other conditions that are associated with male breast cancer are: Klinefelter's syndrome (a condition characterized by a 47XXY karyotype involving testicular dysgenesis, gynecomastia, hypotestosteronism and hypergonadotrophinism, increasing the risk to 20-50x), exogenous intake of estrogen by transsexuals, as well as those undergoing treatment for prostate cancer (anti-androgen intake).⁵

There is no available published data regarding the incidence and outcome of breast cancer among Filipino men. This study reviewed the data on male breast cancer patients treated at the Philippine General Hospital from 2008-2017. Information gained from this study can provide for better understanding of the disease, thereby offering a basis for creating clinical guidelines or algorithms with the hope of achieving better outcomes.

Methods

This study presented data on male breast cancer patients seen at the Philippine General Hospital—Breast Care Center from January 2008- December 2017. More specifically, with the objectives of presenting the epidemiology, presence of possible risk factors (such as obesity, testicular disease, liver cirrhosis, trauma, radiation history, intake of drugs or exogenous estrogens, gynecomastia, smoking, alcoholism, and family history of cancer), clinical and pathological characteristics of the disease (tumor, node, metastasis) stage, nuclear grade, lympho-vascular invasion, hormone receptor and human epidermal growth receptor (HER2neu) status, treatment patterns in terms of applicability and types of surgery, chemotherapy, radiation, hormonal and targeted therapy as well as outcomes (remission, recurrence, survival or death) of male patients treated for breast cancer from January 2008- December 2017.

A retrospective review of medical records of male breast cancer patients seen at the Philippine General Hospital Breast Care Center from January 2008 to December 2017 was done. Male patients who underwent surgery for breast cancer were identified through the Integrated Surgical Information System (ISIS) database of the Department of Surgery-Philippine General Hospital.

Inclusion criteria: All male breast cancer patients—regardless of age, who underwent surgery, ± chemotherapy, and ±radiotherapy. Patients who eventually expired (whether as a consequence of the disease or from other conditions) were still included using the information available in the chart.

Exclusion criteria: Patients diagnosed with chest wall sarcoma, and those with metastatic disease.

Results

From January 2008-December 2017, fifteen cases of male breast cancer treated at the Philippine General Hospital were identified. Over the 10-year period, male breast cancer accounted for 15 (0.26%) of all 5,777 resected

breast specimens for breast cancer patients, with a 1:384 male to female ratio. This did not include patients who did not undergo surgery due to the presence of unresectable breast cancers or metastatic lesions.

The mean age of presentation was at 60 years (range, 36 to 94 years). Of the fifteen cases, only one patient (7%) was documented to have a positive family history of breast cancer. Eight patients had a history of smoking (27%) and/or alcoholism (20%), and one patient reported use of illicit drugs (7%). Four patients had comorbidities such as hypertension (20%) and diabetes (7%) (Table 1).

Table 1. Risk factors and comorbidities associated with male breast cancer (N=15).

Family history of breast cancer	1 (7%)
Smoking	4 (27%)
Alcoholism	3 (20%)
Use of illicit drugs (e.g. marijuana)	1 (7%)
Gynecomastia	1 (7%)
Hypertension	3 (20%)
Diabetes	1 (7%)

The most common presentation was a retro-areolar mass, ranging from a pea-sized lesion up to seven centimeters in greatest dimension, with some manifesting with skin changes and/or nipple discharge (Table 2). Thirty-three percent of patients have already undergone excision biopsy.

Majority of the patients (67%) already have Stage II disease upon consultation, with the predominant histopathology of an invasive ductal carcinoma in 94% (Tables 3 & 4).

The breast cancer subtypes of some of these patients based on hormonal and human epidermal growth receptor (Her2neu) status are summarized in Table 5. Majority of the patients were not able to test for these due to the high cost of these examinations. Of the patients tested, five (33%) were ER/PR positive and 3 (20%) were HER2neu negative. None of these patients were tested for BRCA 1 or 2.

All fifteen patients underwent a modified radical mastectomy, with none undergoing breast conservation surgery. As mentioned previously, a number of these

Table 2. Characteristics of mass (N=15)

Initial presentation	
Fungating or with skin changes	2 (13%)
Nipple discharge	1 (7%)
Breast mass, enlarging	12 (80%)
Size	
≤ 2 cm	6 (40%)
2-5 cm	8 (53%)
>5 cm	1 (7%)
Laterality	
Right	8 (53%)
Left	7 (47%)
Location	
Central/retroareolar	5 (33%)
Upper outer	2 (13%)
Undocumented	8 (53%)

Table 3. Stage upon consult (N=15)

Stage I	2 (13%)
Stage II	10 (67%)
Stage III	3 (20%)
Stage IV	0

Table 4. Histopathology (N=15)

Invasive ductal carcinoma	13 (87%)
with ductal carcinoma in situ component	1 (7%)
Papillary carcinoma	2 (13%)

Table 5. Hormonal and Her2neu status of patients

	Positive	Negative	Undetermined
ER	5 (33%)	1 (7%)	9 (60%)
PR	5 (33%)	1 (7%)	9 (60%)
Her2neu	0	3 (20%)	12 (80%)

patients (33%) have already undergone excision biopsy on their initial consult and proceeded with mastectomy. There were only two patients (13%) who presented with nodal positivity, one with lympho-vascular invasion (7%) and with about 53% having nuclear grade 2. The histopathologic features of the resected specimen are summarized in Table 6.

Table 6. Histopathologic features (N=15)

Lymphovascular invasion	
Positive	1 (7%)
Negative	6 (40%)
Undetermined	8 (53%)
Nuclear Grade	
I	1 (7%)
II	8 (53%)
III	6 (40%)
Axillary node metastasis	
Positive	2 (13%)
Negative	12 (80%)
Undetermined	1 (7%)

There was only one patient who received neoadjuvant chemotherapy with four cycles of Doxorubicin and Cyclophosphamide. This patient initially presented with a T4 lesion and had his last four doses of Taxane (Docetaxel) given after his mastectomy. The patient subsequently underwent radiation and hormonal therapy. This along with another patient were the only two cases (13%) documented to have received adjuvant chemotherapy and hormonal therapy. Both cases were recurrence-free up to at least 17 months post-mastectomy. Statistics were limited as these were the only information gathered from the charts that were available from the medical records section. As such, disease-free and overall survival could not be inferred from the data set gathered from this series.

Discussion

Male breast cancer in the Philippines still remains to be a rare disease and is consistent with other studies

accounting for less than one percent of all breast cancer cases. Despite reports of increasing trend for both sexes^{2,5}, the figures are still low as compared to female breast cancer, and differs primarily on the later onset of presentation for males. Unlike in other territories where male breast cancer was seen to be more prevalent—Northern America, Europe, Africa, as well as in Jewish men regardless of their residence, present findings remain consistent with a lower incidence for Asians, for example, Japan with 5 per 1,000,000 cases of breast cancers.^{2,3,5} Several theories could account for the high rates of male breast cancers in these countries—genetic predisposition for the Jewish population, and a state of hyperestrogenism for the African population, which was probably brought about by chronic liver damage from endemic infectious diseases such as hepatitis or schistosomiasis.⁵

Several risk factors for male breast cancer have been reported in literature. However, many of these factors were not identified in this study, as they were not routinely asked and were therefore not reported in their charts. Hence, this aspect should be included for future investigation and should be routinely documented during a patient's initial consult to give a better picture of the disease. These risk factors are primarily from interactions of genetic predisposition (by inheritance or mutation), hormonal irregularities and imbalances, and environmental or occupational contacts.⁵ Hormonal imbalance pertains to excessive estrogen and testosterone deficiency which can be found in cases of testicular abnormalities (cryptorchidism, orchitis, chronic hernia, etc.), liver diseases (cirrhosis), obesity and intake of exogenous estrogens (as in those with prostate cancer)—all of which are conditions leading to hyperestrogenism that increases the risk for breast cancers in male. Other conditions such as Klinefelter's syndrome and gynecomastia were also identified as risk factors. Gynecomastia, which was reported in only one of the patients of the present study, has contrasting results and does not seem to be identified as a strong risk factor.⁵ Intake of alcoholic beverages was identified in 20% of patients. The amount was not documented in the present study but strong consumption of alcohol (>90g/day) presented with a 6-fold increase in the development of male breast cancer in some reports. As for familial

predisposition, only one patient in this series was documented to have a strong family history. The presence of breast cancer among first-degree relatives confers a 2-3 fold increase in risk for breast cancer for either sex.⁵ Investigation for breast cancer should extend to other first-degree members of his family. The authors were unable to confirm the presence of germ-line mutations as expressed in BRCA1/2 gene due to the high cost and unavailability of the examination in this hospital. BRCA2 mutations have higher frequency (60-76%) among male breast cancer patients than BRCA1 (10-16%)^{4,5}, hence the presence of which should be tested ideally for high risk male populations. There are no exact guidelines on who should be tested for BRCA mutations, but the following general criteria should apply to males as in females: family history of breast or ovarian cancer in first or second degree relatives diagnosed before age 50 for males without cancer, males diagnosed with breast cancer regardless of family history, males with prostate cancer if with family history of breast or ovarian cancer in first or second degree relatives diagnosed before age 50, and presence of Jewish descent.⁵

The mean age of diagnosis was similar to international data (60 vs 63-67 years old).^{3,5} Its onset at a later age or advanced stage at presentation may be partly attributable to poor health seeking behavior as well as the behavior of the tumor itself. As it is a rare disease among males, establishing an effective routine screening program may still not be feasible. Hence, it is imperative to investigate any mass in the breast—the most common location for males being at the retroareolar region. These patients should undergo mammography with ultrasonography (for both breasts and axillae) and a tissue biopsy should be obtained.

The most common pathology in this series was of the invasive ductal type (87%)^{2,3,5}, followed by the papillary type—present in 13% (vs 2% in literature) and mucinous type—which was not found in this study. The lobular histology type, which was the least common and also not found in this series, has only been identified in cases of excessive exposure to estrogen and in association with Klinefelter's syndrome.⁵ For patients who were able to have their hormonal status examined, the majority came out to be estrogen (ER) and progesterone (PR) positive (33% vs 7%), consistent with previous reports of hormone positivity for about 80-90% of patients.^{2,5}

This information on predominant hormone positivity is essential especially for those who initially tested negative for hormone receptors and as such, results should be reviewed so as not to overlook the opportunity to initiate hormonal treatment.⁵ In contrast to hormonal receptor status, Her2neu positivity, although not determined for most of the patients in the present study, was found to be rare based on published literature compared to females (5% vs 15%). It should be noted that there are suggestions that Her2neu status of metastatic lesions are not the same as the original primary tumor and as such, entails further research.⁵

The surgical treatment of choice for all patients in this study was a modified radical mastectomy. Breast conservation for selected patients with smaller tumors has been proposed as in female breast cancer, but the technicalities of the procedure especially with the location of tumor along with the scantiness of male breast parenchyma may preclude adequate partial resection. There were only a few select situations as in those with gynecomastia for which breast conservation was deemed acceptable, but further studies are still needed to support its application.⁵ Experience regarding the use of sentinel lymph node biopsy for male breast cancer was also limited² and the situation is the same locally. However, there were some larger centers that actually recommended its use for males with tumors <2.5cm and clinically negative axillary nodes. Such a procedure which has become their standard was said to have a detection rate of almost 100%.⁵

Adjuvant therapy for male breast cancer is usually administered using the same guidelines as in female patients. Documentation of subsequent follow-ups for the patients in the present study was lacking such that there were only two reported patients who underwent adjuvant chemotherapy and radiotherapy. Chemotherapy given was mostly anthracycline-based, followed by taxanes. Systemic chemotherapy was recommended for hormone receptor negative cases or in those with suspicion of hormonal receptivity. Taxanes were recommended in the presence of axillary nodal metastasis.⁵

Previous studies suggested that males were less likely to receive radiotherapy as compared to female patients, unless presenting in more advanced stages. The standard dose of 50 Gy in 25 fractions is usually given. The most common sites of recurrence were in

the chest wall and supraclavicular chains.¹ Radiation of the upper axillary nodes and internal mammary nodes were generally indicated for those with higher risk of axillary involvement, recurrence or failure. Retrospective studies suggested five-year disease free survival and local control rate of around 73% and 96%⁵, or a five-year recurrence rate of 3-20%.¹ Although radiation seems to reduce local recurrence, its impact on survival could not be clearly established due to the lack of statistical power for most studies.⁵

The role of aromatase inhibitors is still controversial in male breast cancer, and Tamoxifen remains the mainstay of hormonal adjuvant treatment for male breast cancer. Although not covered in this paper, Tamoxifen is also the treatment of choice in palliative settings.^{1,2,5} The long term effects or tolerance to Tamoxifen in males are still to be established, side effects reported include deep vein thrombosis, impotence, decreased libido, hot flashes and mood changes.⁵

The five-year overall survival for male breast cancer was reported at 87% in some studies.² However, due to the institution's limitations with record keeping and data retrieval, the outcomes of these patients could not be adequately assessed based on their charts alone.

Cases in this series may be enrolled prospectively in future studies and be recorded in a unified local, if not a national tumor registry.⁵ Metastatic breast cancer should also be included in future studies to provide a better data on male breast cancer population. Given an efficient tumor registry, it becomes possible to generate more reliable results and significant statistics from where investigators could corroborate and tailor better treatment options for the male breast cancer population. Knowing the burden of the disease would lead to improved awareness in the community, establishment of treatment guidelines including screening of high risk populations, so patients can be diagnosed earlier and outcomes will be better.

Conclusion

Breast cancer remains to be a rare disease among males, often diagnosed at a later stage and at an advanced stage. This study showed a 1:384 male to female ratio, mean age

of presentation at 60 years and majority at Stage II with invasive ductal histology, as well as ER/PR positivity for those few tested. Risk factors identified include family history of breast cancer, alcoholism, and smoking. All patients underwent modified radical mastectomy and received neo-adjuvant chemotherapy along with adjuvant radiation and hormonal therapy.

Due to the rarity of the disease, awareness is key not only in the community but also among healthcare providers to identify and treat the problem earlier. Further investigation and prospective studies are recommended.

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