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ORIGINAL ARTICLE

Case Series Analysis of Male Breast Cancer

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Abstract
Male breast cancer is a rare disease, accounting for less than 1% of all cases of breast cancer. However, the incidence of male breast cancer is increasing. In this study, we systematically analyzed the cases of male breast cancer and evaluated the management of operable male breast cancer in daily clinical practice according to the international clinical guidelines. Data of male breast cancer characteristics and management were recorded from our electronic database. We present a case series of male breast cancer patients treated at our institution between 2013 and 2021 and summarize the recommendations on management of male patients with breast cancer. Twenty-six patients met the search criteria. The majority of tumors were hormone-receptor positive and human epidermal growth factor receptor 2 negative. Two tumors were derived from axillary accessory breast. All patients underwent mastectomy. Fifteen patients received adjuvant chemotherapy containing anthracycline or taxane. Ten patients received adjuvant radiotherapy for lymph node metastasis. Twenty-five patients received adjuvant endocrine therapy. None of patients received anti-human epidermal growth factor receptor 2 therapy. During the median follow-up period of 37 months, one patient died of previous lung cancer recurrence and one patient developed lung metastases 2 years after breast surgery. No recurrence or distant metastasis occurred in the other twenty-four patients. The incidence of male breast cancer is low. In this study, we present twenty-six cases of male patients with operable breast cancer in our department. All of them received surgery and adjuvant treatment. Early diagnosis and combined therapy benefit male patients with breast cancer. Surgery together with adjuvant treatment can bring a good prognosis.

Keywords Male breast cancer · Surgery · Case series · Chemotherapy · Endocrine therapy · Radiotherapy

Introduction

Breast cancer is the most common malignancy among women worldwide [1]. Compared to female breast cancer, the incidence of male breast cancer is low, accounting for less than 1% of all cases of breast cancer [2]. The incidence of male breast cancer is also low in all male malignancies. However, the incidence of male breast cancer is increasing with growing rate of male gynecomastia [2]. With the low incidence, there were no large-scale prospective randomized clinical trials conducted to determine effective therapy for male patients. Diagnostic and treatment evidence for male breast cancer is limited. Currently, male breast cancer is treated similar to female breast cancer [3, 4]. For the different pathogenesis of male breast cancer and lack of knowledge about male breast cancer, the prognosis of male patients with breast cancer is worse than that of female patients [5, 6, 7]. In the present paper, we present a case series of male patients diagnosed with breast cancer treated at Department of Breast Surgery, Hwa Mei Hospital, University of Chinese Academy of Sciences, between 2013 and 2021. We systematically analyzed the cases of male breast cancer and evaluated the management of operable male breast cancer according to the international clinical guidelines.

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Patients and Methods

Operable male patients with breast cancer were selected from electronic database by using the search criteria of "breast cancer" and "male" between January 1, 2013, and December 31, 2021. Patients with distant metastasis were excluded. Patients and tumor characteristics, treatment, and follow-ups were collected. Data were analyzed applying descriptive statistics. The study was approved by the ethics committee of Hwa Mei Hospital, University of Chinese Academy of Sciences.

Result

Twenty-six patients matched the search criteria in the period between January 1, 2013, and December 31, 2021. The average age of the patients was 60 (from 37 to 82) years. About 58% of the patients were elderly men over 60 years old. Twenty-four cases of breast cancer were derived from breast, and the other two cases were derived from axillary accessory breast. Twenty-four cases underwent mastectomy, and two cases underwent accessory mastectomy. Fourteen patients received axillary lymph nodes dissection for metastasis or suspected metastasis of axillary lymph nodes, among whom two patients did not develop axillary lymph nodes metastasis. Pathology of twenty-one cases was invasive ductal carcinoma with three cases of ductal carcinoma in situ and two cases of mucinous carcinoma. Twenty-five cases were luminal type breast cancer with ten cases of luminal A and fifteen cases of luminal B. Only one case was triple negative breast cancer. In staging, there were three cases in stage 0, eight cases in stage I, ten cases in stage II, and five cases in stage III.

Fifteen patients received adjuvant chemotherapy. Nine patients received eight cycles of chemotherapy containing anthracycline and taxane, and the other six patients received four cycles of chemotherapy containing taxane. Ten patients received adjuvant radiotherapy for lymph nodes metastasis. Twenty-five patients received adjuvant endocrine therapy, including tamoxifen for twenty-one patients and gonadotropin-releasing hormone agonist (GnRHa) combined with aromatase inhibitor (AI) for four patients. All cases were human epidermal growth factor receptor 2 (HER2) negative breast cancer. None of patients received anti-HER2 therapy. During the median follow-up period of 37 months, one patient died of previous lung cancer recurrence (he received lung cancer surgery 2 years before breast cancer surgery. Lung cancer and breast cancer were both primary cancer), and one patient developed lung metastases 2 years after breast surgery. No recurrence or distant metastasis occurred in the other twenty-four patients. The survival time of the death case after breast surgery was 26 months. Details were listed in Table 1.

Discussion

The incidence of male breast cancer is low, accounting for less than 1% of all cases of breast cancer. However, the incidence of male breast cancer is increasing with growing rate of male gynecomastia in recent years [2]. Most male breast cancer occurs in elderly men [2, 4, 6]. Here, we describe the diagnosis and treatment of male breast cancer based on clinical guidelines and our case series.

The diagnosis of male breast cancer is similar to that of female breast cancer. Pathology is the gold standard [8]. Physical examination, ultrasound, mammography, and magnetic resonance help make clinic diagnosis. Physical examination included palpation of breast masses and axillary lymph nodes. The size, consistency, boundary, and mobility of tumor should be assessed. Male breast cancer is usually a hard mass with ill defined margins and poor mobility [9]. Ultrasound and mammography are routine preoperative examinations for breast diseases. Under breast ultrasound, male breast cancer is usually a mass with unclear boundaries, incomplete capsule, and abundant vascular supplication [10]. Mammography is difficult to carry out in male patients. Experienced mammography technicians are required to operate on account of a certain amount of breast tissue. Breast cancer in mammography is characterized by high density mass, unclear boundaries, and burrs [11]. For most patients, enhanced magnetic resonance is less available than ultrasound and mammography. It costs more and takes more time to receive enhanced magnetic resonance. In enhanced magnetic resonance, male breast cancer is characterized by irregular shape and enhanced signal of lesion [12]. Based on the above examination, we make the diagnosis of male breast cancer in clinic. Histopathological examination is required to make the final diagnosis.

Surgery

Surgery is the main treatment for early operable male breast cancer [13]. Mastectomy is the most common surgery for

Table 1 Characteristics of case series of male breast cancer

Characteristic	Number of patients	Percentages of the patients
Age		
≥ 60	15	58%
< 60	11	42%
Type of BC surgery		
Mastectomy + SLNB	12	46%
Mastectomy + SLNB + ALND	1	4%
Mastectomy + ALND	11	42%
Accessory mastectomy + ALND	1	4%
Accessory mastectomy + SLNB + ALND	1	4%
Histological type		
DCIS	3	11%
IDC	21	81%
MC	2	8%
T stage		
Tis	3	11%
T1	17	65%
T2	6	23%
T3	0	
N stage		
N0	13	50%
N1	8	31%
N2	2	8%
N3	3	11%
Stage		
0	3	11%
I	8	31%
II	10	38%
III	5	19%
ER/PR status		
ER and/or PR positive	25	96%
ER negative and PR negative	1	4%
HER2 status		
Positive	0	0%
Negative	26	100%
Chemotherapy		
None	11	42%
TC*4	6	23%
EC*4-T*4	9	35%
Radiotherapy		
None	16	62%
Received	10	38%
Endocrine therapy		
None	1	4%
TAM	21	81%
GnRHa + AI	4	15%
Events		
None	24	92%
Recurrence	1*	4%
Death	1**	4%

BC breast cancer, *SLNB* sentinel lymph node biopsy, *ALND* axillary lymph node dissection, *DCIS* ductal carcinoma in situ, *IDC* invasive ductal carcinoma, *MC* mucinous carcinoma, *ER* estrogen-receptor, *PR* progesterone-receptor, *HER2* human epidermal growth factor receptor 2, *TC* taxane and cyclophosphamide, *EC* epirubicin and cyclophosphamide, *TAM* tamoxifen, *GnRHa* gonadotropin-releasing hormone agonist, *AI* aromatase inhibitor

*One patient got lung metastasis 2 years after initial breast surgery

**One patient died of previous lung cancer 26 months after breast surgery

male patients with breast cancer. Sentinel lymph node biopsy can be applied for patients whose axillary lymph nodes are considered negative clinically. If the sentinel lymph nodes are negative, axillary lymph nodes dissection could be avoided. If the sentinel lymph nodes are positive, the surgeon may continue axillary lymph node dissection [14, 15]. Modified radical mastectomy (mastectomy + axillary lymph nodes dissection) is used for patients with suspected metastasis of axillary lymph nodes. Evidence shows that breast conserving surgery for male patients with breast cancer is feasible under the condition that the margin is negative and patients have the desire to receive breast conserving surgery [16, 17, 18]. However, in clinical practice, most of the male patients with breast cancer have limited breast tissue concentrated under nipple and areola, leading to breast mass located near the nipple. Those patients lose the chance of breast conserving surgery. Also, majority of male patients with breast cancer do not have a strong desire to undergo a breast conserving surgery in our experience. All patients in our case series received mastectomy or accessory mastectomy.

Chemotherapy

The application of chemotherapy in male patients with breast cancer is similar to that of female patients. The prognosis of male breast cancer is worse than that of female breast cancer. Male sex is a risk factor of prognosis [2, 13]. In our experience, chemotherapy is an important therapy for male patients

with breast cancer. We should make a careful consideration before avoiding chemotherapy for male patients with breast cancer except for ductal carcinoma in situ or favorable histologic types such as pure tubular carcinoma and pure mucinous carcinoma. Between 1974 and 1988, a prospective study of adjuvant chemotherapy in male breast cancer was conducted by the American National Cancer Institute. Thirty-one male patients with breast cancer and lymph nodes metastasis were enrolled. The result showed that the 5-year, 10-year, and 20-year survival rates of patients undergoing adjuvant chemotherapy were 80%, 65%, and 42%, respectively, superior to historical control [19]. An observational cohort study showed that adjuvant chemotherapy for male patients with breast cancer could improve the prognosis [20]. Oncotype DX and other gene prognostic models could be applied to assess risk of distant recurrence and help clinician decide whether adjuvant chemotherapy is necessary for hormone receptor positive male breast cancer patients [21]. In our study, most patients (15 out of 21) with invasive ductal carcinoma received four to eight cycles of chemotherapy containing anthracycline or taxane. Most of them achieved good prognosis during the follow-up period.

Endocrine Therapy

In our retrospective study, 96% of male breast cancer is hormone receptor positive breast cancer. Tamoxifen is the gold standard of endocrine therapy for male patients with hormone receptor positive breast cancer [22, 23]. If tamoxifen is contraindicated, AI combined with gonadotropin-releasing hormone agonist could be a choice. AI monotherapy cannot be used in male patients with breast cancer. AI monotherapy plays an opposite role due to negative feedback regulation [24]. There is no evidence showing that GnRHa plus AI is superior to tamoxifen in male breast cancer [13]. As a selective estrogen receptor degrader, fulvestrant has been proved to be effective in the treatment of male breast cancer [25]. However, the guideline does not recommend use of fulvestrant as adjuvant therapy for male patients with breast cancer [26]. Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors also have not been recommended to be used in adjuvant therapy for male patients with breast cancer [26]. In our study, most male patients with breast cancer received tamoxifen monotherapy and achieved good results.

Table 2 Case series of male breast cancer published in the last decade

First author	N	ER		PR		HER2		Ki-67	
		ER+	ER-	PR+	PR-	HER2+	HER2-	> 20%	≤20%
Aggarwal A (2021) [28]	1528	59%	2%	52.8%	7.9%	NA	NA	NA	NA
Lomma C (2021) [29]	585	ER+ and/or PR+ 94%				7%	85%	NA	NA
		ER- and PR- 2%							
Johnson, A.E (2021) [30]	100	93%	NA	90%	NA	5%	91%	NA	NA
Pellini F (2020) [31]	69	96.6%	3.4%	94.6%	5.4%	52.4%	47.6%	37.3%	62.7%
Yetkin G (2019) [32]	15	93.3%	6.7%	86.7%	13.3%	13.3%	86.7%	NA	NA
M. K. Chhabra (2019) [3]	106	81%	NA	74%	NA	25%	75%	NA	NA
Oana Cristina V (2018) [33]	6	100%	0%	83.3%	16.7%	0%	100%	83.3%	16.7%
Wan BA (2018) [34]	161	78.3%	1.9%	70.2%	9.3%	9.9%	54.7%	NA	NA
Weir J (2018) [35]	23305	ER+ and/or PR+ 92.2%				11.6%	NA	NA	NA
McKinley N (2017) [36]	22	77.3%	0%	40.9%	0%	0%	36.4%	NA	NA
Rayne S (2017) [37]	23	96%	4%	87%	13%	13%	74%	NA	NA
Vermeulen MA (2017) [38]	1483	ER+ and/or PR+ 93%				7.3%	86.6%	NA	NA
		ER- and PR- 1%							
Madden NA (2016) [39]	1337	68%	5%	59%	13%	NA	NA	NA	NA
Masci G (2015) [40]	91	96.7%	3.3%	92.3%	7.7%	14.2%	79.2%	35.2%	57.1%
Bradley KL (2014) [41]	158	96%	3%	91%	8%	6%	62%	NA	NA
Iorfida M (2014) [42]	99	97%	3%	88%	12%	8%	90%	NA	NA
Rushton M (2014) [43]	72	81.4%	NA	72.2%	5.6%	5.6%	34.7%	NA	NA
Fogh S (2013) [44]	42	100%	0%	100%	0%	NA	NA	NA	NA
Nilsson C (2013) [45]	197	92.9%	4.6%	79.7%	19.3%	10.6%	83.2%	NA	NA
Yu XF (2013) [46]	68	ER+ and/or PR+ 85.3%				35.3%	64.7%	NA	NA
		ER- and PR- 14.7%							
Arslan UY (2012) [47]	118	82.9%	17.1%	75.8%	24.2%	23.4%	76.7%	NA	NA
Dabakuyo TS (2012) [48]	75	72%	12%	65.3%	14.6%	NA	NA	NA	NA
Müller AC (2012) [49]	40	65%	17.5%	60%	17.5%	15%	20%	NA	NA
Yu E (2012) [50]	81	82.7%	1.3%	70.7%	10.7%	NA	NA	NA	NA

ER estrogen-receptor, *PR* progesterone-receptor, *HER2* human epidermal growth factor receptor 2, *NA* not available

Radiotherapy

The adjuvant radiotherapy applied to male breast cancer is similar to that used for female patients with breast cancer. Adjuvant radiotherapy is recommended for patients with axillary lymph node metastasis or undergoing breast conserving surgery. Postoperative radiotherapy is also recommended for patients with tumors larger than 5 cm [13, 26]. Those patients need to receive chest wall and related lymph node drainage area radiotherapy. An observational study showed that male patients with breast cancer and lymph nodes metastasis benefited from radiotherapy [27]. In our study, almost all the patients with lymph nodes metastasis received radiotherapy except for 3 patients with poor tolerance (2 patients were over 80 years old and 1 patient had psychiatric illness).

Targeted therapy

For HER2 positive male patients, adjuvant targeted therapy combining trastuzumab is required. Similar to female breast cancer, clinician recommends trastuzumab for lymph node negative HER2 positive patients and trastuzumab plus pertuzumab for lymph nodes positive HER2 positive patients. Male patients with other high risk of recurrence (such as $T > 5$ cm, age < 35) could be recommended trastuzumab plus pertuzumab [3, 5, 13, 14]. However, the rate of HER2 overexpression in male breast cancer is low. In our study, none of the 26 male patients got HER2 positive breast cancer, and none of them received anti-HER2 therapy.

We have searched the PubMed for case series of male breast cancer published in the last decade. Twenty-four retrospective studies are found [3, 28-50]. Some data was collected from last four decades with missing or not available information. Male breast cancer is rare. Most case series from single center contained less than twenty patients. Data of large-scale studies come from multicenter or national database. Like our study, most studies showed male patients with breast cancer have ER or PR positive and HER2 negative disease. One study showed 52.4% HER2 positive disease in 69 patients [31]. It is interesting for such high percentage of HER2 positive disease. More attention should be paid to find the reasons. Ki-67 value was reported in five studies with different cut-off values (20% in three studies and 14% in two studies) [31, 33, 40, 42, 45]. We select 20% as Ki-67 cut-off value to build Table 2. Our study showed 17/26 patients had lower Ki-67 value ($\leq 20\%$), while two of five studies showed more patients had higher Ki-67 values [33, 42]. It showed male patients with breast cancer did not mean high Ki-67 values. Details are listed in Table 2.

Conclusion

The incidence of male breast cancer is low. In this study, we present twenty-six cases of male patients with operable breast cancer in our department. All of them received surgery and adjuvant treatment. During the median follow-up period of 37 months, most patients do not have recurrence or distant metastasis disease. Early diagnosis and combined therapy benefit male patients with breast cancer. Surgery together with adjuvant treatment can bring a good prognosis.

Abbreviations GnRHa: Gonadotropin-releasing hormone agonist; AI: Aromatase inhibitor; HER2: Human epidermal growth factor receptor 2; ER: Estrogen-receptor; PR: Progesterone-receptor; FISH: Fluorescence in situ hybridization; NA: Not available

Data Availability The datasets generated and analyzed during the current study are not publicly available for our institutional electronic database is not open to the public but are available from the corresponding author on reasonable request.

Declarations

Ethics Approval and Consent to Participate The studies involving human participants were reviewed and approved by the ethics committee of Hwa Mei Hospital, University of Chinese Academy of Sciences. The patients/participants provided their written informed consent to participate in this study.

Conflict of Interests The authors declare no competing interests.

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