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Male Breast Cancer: Management and Follow-up Recommendations

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■ **Abstract:** National Comprehensive Cancer Network (NCCN) guidelines for female breast cancer treatment and surveillance are well established, but similar guidelines on male breast cancers are less recognized. As an NCCN institution, our objective was to examine practice patterns and follow-up for male breast cancer compared to established guidelines for female patients. After Institutional Review Board approval, a prospective breast database from 1990 to 2009 was queried for male patients. Medical records were examined for clinico-pathological factors and follow-up. The 5-year survival rates with 95% confidence intervals were estimated using Kaplan–Meier method and Greenwood formula. Of the 19,084 patients in the database, 73 (0.4%) were male patients; 62 had complete data. One patient had bilateral synchronous breast cancer. The median age was 68.8 years (range 29–85 years). The mean/median invasive tumor size was 2.2/1.6 cm (range 0.0–10.0 cm). All cases had mastectomy (29 with axillary node dissection, 23 with sentinel lymph node biopsy only, 11 with sentinel node biopsy followed by completion axillary dissection). Lymph node involvement occurred in 25/63 (39.7%). Based on NCCN guidelines, chemotherapy, hormonal therapy, and radiation are indicated in 34 cases, 62 cases, and 14 cases, respectively. Only 20/34 (59%) received chemotherapy, 51/62 (82%) received hormonal therapy, and 10/14 (71%) received post-mastectomy radiation. Median follow-up was 26.2 months (range: 1.6–230.9 months). The 5-year survival estimates for node positive and negative diseases were 68.5% and 87.5%, respectively (p = 0.3). Despite the rarity of male breast cancer, treatment options based on current female breast tumors produce comparable results to female breast cancer. Increased awareness and a national registry for patients could help improve outcomes and tailor treatment recommendations to the male variant. ■

Key Word: male breast cancer

According to the American Cancer Society, there will be an estimated 1,910 new cases of male breast cancer diagnosed in 2009 (1). This number comprises less than 1% of total cases for breast cancer. Although guidelines for the screening, management, and surveillance of female breast cancer are well established by organizations such as the National Comprehensive Cancer Network (NCCN), guidelines for the male variant are less defined, as there have been no prospective trials due to the low incidence (2). Larger series of male breast cancers involve single institution retrospective data collection spanning decades due to the paucity of cases (3–7).

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Treatment of male breast cancer traditionally mirrors the management of female breast cancer with regard to surgery, adjuvant therapy, and radiation, but with a time lag. Thus, evolution of male breast cancer treatment has been similar in that sentinel nodes have replaced axillary dissections, molecular evaluation of tumors play an integral role in adjuvant chemotherapy decisions, and the use of genetic testing has increased. These treatment plans seem to provide equal survival for male patients when matched for multiple variables, including stage, to a female cohort (8).

The role of screening and post-cancer surveillance creates further uncertainty for the clinician due to the low incidence of male breast cancer. With an age-standardized incidence rate of 1 per 100,000 person-years, the lifetime risk of male breast cancer is less than 1/1000 (9–11). Due to this low lifetime risk, screening mammography is impractical for the general population.

On the other hand, for certain high risk groups such as a personal history of breast cancer, there may be a role for surveillance imaging of the contralateral breast.

The main purpose of this study is to evaluate our single institution's experience with male breast cancer over the past 20 years. In addition, as a participating NCCN institution, we wished to examine practice patterns of male breast cancer in relationship to current (2009) NCCN guidelines for female breast cancer. Compliance of greater than 80% with each of the guidelines is required of an individual institution to maintain active status with the NCCN. Significant changes in general recommendations for chemotherapy, hormone therapy, and radiation have not occurred with respect to prior versions with the exceptions of (a) treatment of HER-2 positive disease; (b) use of Onco*type* Dx™ assay; and (c) consideration of chest wall radiation for 1–3 positive nodes. Furthermore, we examined the surveillance patterns of these patients after the treatment of their primary cancer to better delineate the best practice of monitoring survivors of this rare entity.

MATERIALS AND METHODS

An Institutional Review Board (IRB)-approved Health Insurance Portability and Accountability Act (HIPPA)—compliant breast cancer database and electronic health record prospectively accrued 19,084 patients between 1990 and 2009. Under separate IRB approval, this database was queried for male patients with breast cancer.

Seventy three patients (0.4%) were identified but only 62 had complete data available for review. Patients' demographic, clinical, and treatment variables were recorded. Recommendations for use of adjuvant chemotherapy, hormone therapy, and radiation therapy were based on the 2009 version 1 of the NCCN guidelines for female breast cancer. Follow-up data were obtained from the breast cancer database and chart review. The 5-year survival rates with 95% confidence intervals were estimated using Kaplan–Meier method and Greenwood formula. A log-rank test was used to compare nodal status for significant difference (12).

RESULTS

Of the 62 patients with complete medical records, the median age was 68.8 years (range 29–85 years). One patient had bilateral synchronous breast cancer at the age of 72 years; therefore 63 total cancer cases. Fifty-nine cases (90.1%) initially presented with a palpable mass in the breast, five cases presented with a lump combined with nipple discharge (7.9%), two cases presented with nipple discharge alone (3.2%), and two cases presented with changes to the nipple (3.2%). Imaging work up revealed ipsilateral gynecomastia in 9/63 cases (14.3%) in addition to cancer and 6/63 cases (9.5%) also had contralateral gynecomastia on mammography. Familial history of breast, ovarian or colon cancer was seen in 18/62 patients (29.0%). Seven patients (11.3%) had a personal history of previous prostate cancer and five patients (8.1%) had other synchronous cancers (three papillary thyroid cancers, two lung cancers).

The mean/median invasive tumor size was 2.2/1.6 cm (range 0.2–10.0 cm). Histology of the 63 breast cancer cases consisted of invasive ductal (n = 58), ductal carcinoma in situ (n = 1), invasive lobular (n = 1), invasive papillary (n = 1), invasive mucinous (n = 1), and invasive cribiform (n = 1). The grade of invasive tumor was high grade in 18 cases (29%), intermediate grade in 28 cases (45%), low grade in nine cases (15%), and unknown in seven cases (11%). All cases were surgically treated with mastectomy. Sentinel node biopsy for male breast cancer started at our institution in 1998 and has been performed in 34 (55%) cases with an average of 3.38 nodes removed (range 1–10). Ten of 34 cases (29.4%) had positive sentinel nodes and all 10 patients subsequently underwent axillary nodal dissection. Axillary dissection without lymphatic mapping was performed in 29 patients. In total, positive lymph nodes were involved in 25/63 (39.7%) cases of male breast cancer. All 63 cases were estrogen receptor positive and 7 of 55 cases (12.7%) were HER-2 neu positive tumors (HER-2 neu testing only became available at our institution in 1998).

The NCCN guidelines based on tumor size and nodal status were reviewed with regard to chemotherapy, hormonal therapy, and radiation. The 2009 version 1 NCCN guidelines were used for all patients in the study period to evaluate outcomes of current treatment plans. These recommendations were compared to our institutional recommendations as well as patient treatment choices (Tables 1 and 2). The reasons for the decisions made by clinicians and patients were not always available in the medical chart.

According to NCCN guidelines, chemotherapy was indicated in 34 cases of these cases. Of the 34 men,

Table 1. Adjuvant Chemotherapy and Hormonal Therapy of Male Breast Cancer Cases by Stage

Stage	Number of cases	NCCN chemotherapy recommendation	Recommended chemotherapy	Received chemotherapy	NCCN hormonal recommendation	Recommended hormonal therapy	Received hormonal therapy
0	1 cases-T0is	No	0/1	0/1	Consider	0/1	0/1
I	28 cases-T1,N0	No for T1a-b Consider for T1c	T1a-b: 2/12 T1c: 4/16	T1a-b: 1/12 T1c: 3/16	Yes for ER+	28/28	26/28
IIA	8 cases-T1,N1 7 cases-T2,N0	Yes	10/15	6/15	Yes for ER+	12/15	10/15
IIB	5 cases-T2,N1 1 case-T3,N0	Yes	4/6	4/6	Yes for ER+	6/6	5/6
IIIA	5 cases-T1-2,N2 1 cases-T3,N1-2	Yes	6/6	4/6	Yes for ER+	4/6	4/6
IIIB	2 cases-T4	Yes	2/2	2/2	Yes for ER+	2/2	2/2
IV	5 cases-M1	Yes	5/5	4/5	Yes for ER+	5/5	4/5
Total cases	63	Yes Consider No	27/34 (79%) 4/16 (25%) 2/13 (15%)	20/34 (59%) 3/16 (19%) 1/13 (8%)	Yes for ER+ Consider No	57/62 (92%) 0/1 (0%) 0/0 (0%)	51/62 (82%) 0/1 (0%) 0/0 (0%)

27 (79%) were recommended to undergo chemotherapy at our institution; 20 of 27 (59%) agreed to these recommendations and completed treatment. By the guidelines, 62 cases would be recommended by the NCCN to receive hormonal therapy. Ninety-two percent of cases (57/62) were offered to have hormonal treatment by their clinician and 51 (82%) agreed to treatment. Forty-five patients received tamoxifen, four patients received an aromatase inhibitor, and two patients started on tamoxifen and were subsequently switched to an aromatase inhibitor. Chest wall radiation would be recommended by the NCCN guidelines for 14 cases. Ten of these 14 cases (71%) were offered post-mastectomy radiation and all patients completed radiation therapy.

Table 2. Adjuvant Radiation Therapy of Male Breast Cancer Cases by Stage

Stage	Number of cases	NCCN radiation recommendation	Recommended radiation	Received radiation
0	1 cases-T0is	No	0/1	0/1
I	28 cases-T1,N0	No	1/28	1/28
IIa	8 cases-T1, N1	Consider for N1	N1: 0/8	N1: 0/8
	7 cases-T2, N0	No for N0	N0: 1/7	N0: 1/7
IIB	5 cases-T2,N1	Consider for N1	T2N1: 3/5	T2N1: 3/5
	1 case-T3,N0	Yes for T3	T3: 1/1	T3: 1/1
IIIA	5 cases-T1-2,N2 1 cases-T3,N1-2	Yes	4/6	4/6
IIIB	2 cases-T4	Yes	2/2	2/2
IV	5 cases-M1	Yes	3/5	3/5
Total cases	63	Yes	10/14 (71%)	10/14 (71%)
		Consider	3/13 (23%)	3/13 (23%)
		No	2/36 (6%)	2/36 (6%)

Recently, three patients were eligible and underwent Onco*type* Dx™ breast cancer assay testing following mastectomy. Our institution follows current NCCN guidelines for selecting patients to receive Onco*type* Dx™ testing. Two patients had intermediate risk recurrence scores and were both subsequently recommended to undergo adjuvant chemotherapy based on these results. One patient had a low risk recurrence score and went on to receive hormonal therapy alone.

After the surgical treatment of their breast cancer, follow-up annual mammograms of the unaffected breast were obtained in 27/62 patients (43.5%); all subsequent mammograms were either a BIRADS 1 or 2 score including those with gynecomastia. No mammograms of the contralateral side were done in 28/62 patients (45.2%) and follow-up imaging for the remaining seven patients (11.3%) is unknown.

There was limited follow-up with a median follow-up of 26.2 months (range: 1.6–230.9 months). Fourteen patients (22.5%) had follow-up less than a year. The 5-year survival estimates for node positive and negative diseases were 68.5% and 87.5%, respectively (Fig. 1) ($p = 0.3$). Six patients (9.7%) died of

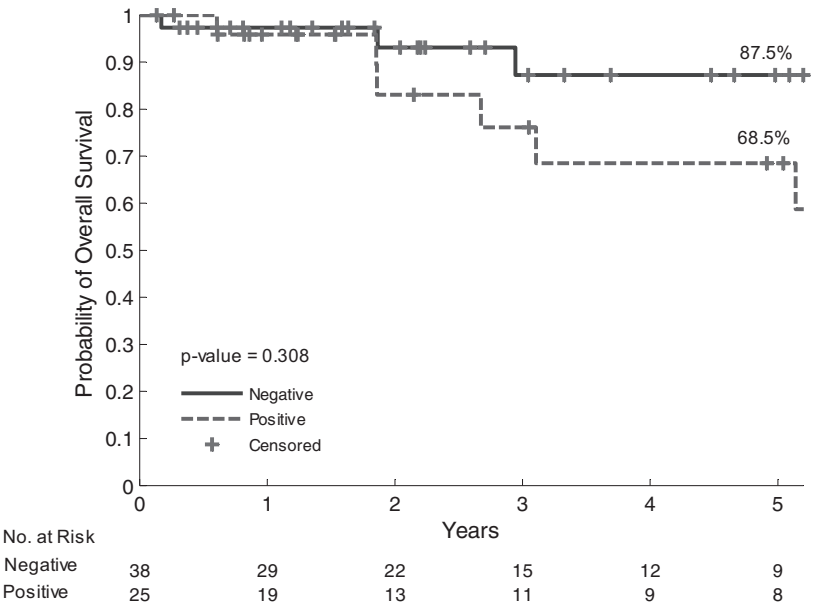

Figure 1. Survival of male breast cancer patients by nodal status.

metastatic disease, five patients (8.1%) are alive with distant disease, and 51 patients (82.8%) had no evidence of disease at last follow-up. Six patients (9.7%) have died with no evidence of distant disease at last follow-up. There were two men (3.2%) with local recurrences on the chest wall after mastectomy with chest wall radiation. Both of these patients were found to have distant disease at time of their local recurrence.

DISCUSSION

The NCCN is a compilation of 21 cancer centers that meet on a regular basis to develop and continually update multidisciplinary guidelines in the management of various tumor types. Decisions towards these algorithms in patient care are driven by evidence-based literature. As male breast cancer is relatively rare compared to its female variant, guidelines in the management of this condition are not well established. As such, current treatment strategies for surgery, adjuvant therapy, and hormonal therapy are quite similar regardless of the sex of patient with the caveat that most data supporting these decisions are based on female breast cancer.

In reviewing our institutional experience with male breast cancer, we found that adjuvant therapy with chemotherapy, hormonal therapy, and radiation were recommended according to the current female breast cancer guidelines in 79%, 92%, and 71% of patients, respectively. A lower percentage of each group agreed to the recommendations and received treatment (59% received chemotherapy, 82% received hormonal therapy, and 71% received post-mastectomy radiation). Unfortunately, we cannot draw any firm conclusions from the treatment decisions of these patients due to a low number of patients in this study with limited follow-up. On the other hand, this demonstrates the need to develop a national registry of male breast cancer patients to formulate treatment guidelines that may or may not differ from female breast cancer.

The management of male breast cancer at our institution is summarized in the algorithm (Fig. 2) and the reasons supporting these decisions are described below.

Surgery

Due to the subareolar position of most tumors and the smaller size of the overall breast, most male patients proceed with a mastectomy over concerns of skin and nipple involvement (4,13). Although breast conservation therapy with a lumpectomy and radiation is feasible (14), it is a less common choice for the male patient. Mastectomy provides local control by removing the tumor and potentially eliminating the need for postoperative radiation. Reconstruction has been offered to some patients to compensate for a mastectomy defect in cases where the original breast also had pseudogynecomastia. Transverse rectus abdominus myocutaneous (TRAM) flaps offer the advantage of replacing hair to the chest (15–17). In addition, tattooing a nipple-areolar disk is available

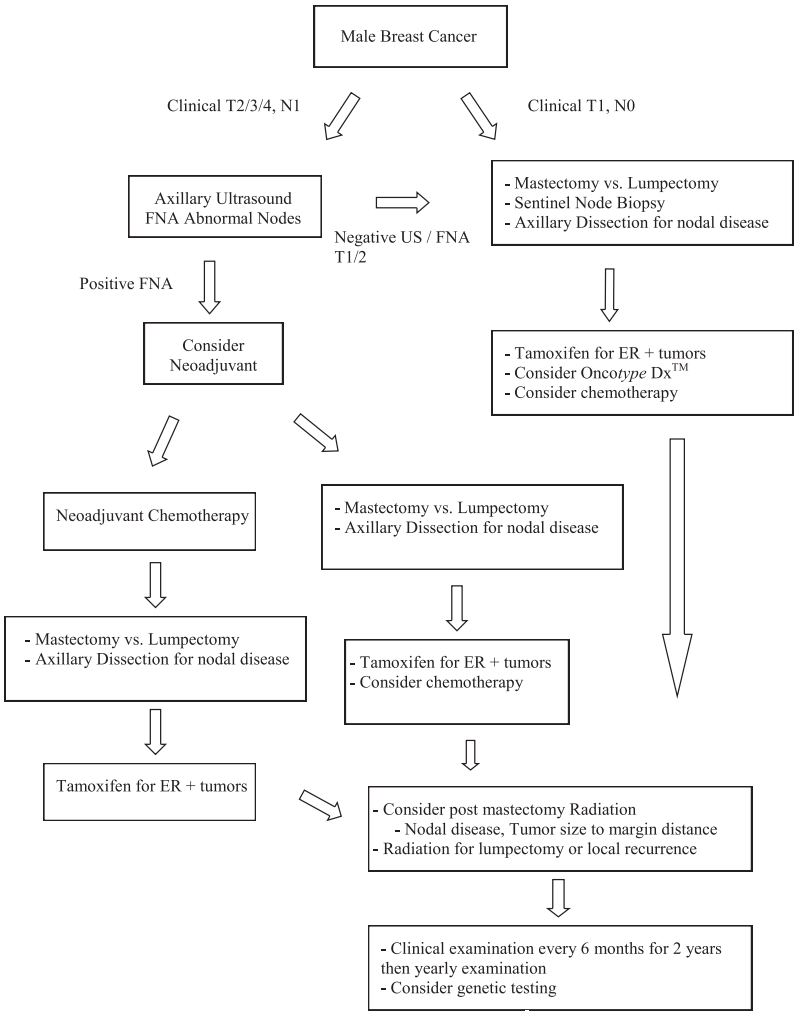

Figure 2. Algorithm on treatment of male breast cancer.

if the man so desires. Most men, however, opt out of reconstruction.

Axillary nodal evaluation provides important staging information for both clinician and patient while maximizing local control. Sentinel node biopsy has been well documented to be a reliable choice of nodal assessment with decreased morbidity in male breast cancer (18–20). Preoperative evaluation of axillary nodes through an axillary ultrasound with fine needle aspiration of any abnormal nodes should be offered for clinically suspicious nodal involvement prior to surgery (21). Axillary nodal dissection of levels one and two is performed for positive nodal disease.

Chemotherapy and Hormonal Therapy

The vast majority of male breast cancers are hormone receptor positive and hormonal therapy is the most commonly used adjuvant treatment. The role of tamoxifen has been clearly established to improve survival and decrease recurrences in female breast patients but there are limited retrospective data in males (5,11). Cutuli et al. recently demonstrated that tamoxifen decreased the development of metastatic disease in 243 node positive men from 62% to 28% ($p = 0.0001$). However, these findings were not shared in 223 node negative patients who took tamoxifen (15.2% to 9.6%, $p = 0.21$) (4). The role of aromatase inhibitors has yet to be determined in male patients. There are concerns that decreasing estrogen levels in males will lead to an increase in testosterone that may be converted into estrogen. Therefore, a combination of an aromatase inhibitor with an androgen suppressor such as goserelin or leuprolide may achieve best results (15,22,23).

Since most male breast cancer is estrogen sensitive, Oncotype Dx™ provides a potential evaluation modality for long-term recurrence risk. In addition, this 21-gene breast cancer assay helps identify more aggressive

tumors and patients who would therefore benefit from chemotherapy in addition to hormonal therapy (24,25). We do incorporate this testing for our male population, although the data for this are limited. As Onco*type* Dx™ was validated using patients from the NSABP B-14, no male patients were included in the study (24). Due to the rarity of male breast cancer, a validation study would be very hard to establish. However, a recent abstract presented at ASCO demonstrated similar tumor characteristics and recurrence score distribution between 347 male tumors and 82,434 female tumors (26). Although data is limited, we feel comfortable with the accuracy of predicting recurrences in male breast cancer.

For patients with higher risk factors (nodal disease, larger tumors, younger age, estrogen receptor negative tumors), adjuvant chemotherapy may offer a survival advantage. Unfortunately, there is very little data supporting the use of chemotherapy in this small population. Due to relative rarity of male breast cancers, the fact that these few cases generally occur in an older population, and that a large proportion of these tumors are estrogen receptor positive, significant retrospective support of chemotherapy is limited (11,27,28). Given that the median age of male breast cancer patients is greater than that of female patients, age, comorbidities, and toxicity profiles should be considered when making adjuvant therapy decisions (4,29,30). Neoadjuvant therapy can be employed for locally advanced tumors to help aid resectability and to measure response to chemotherapy.

Although the distribution of tumor grades appeared similar to female breast cancer, other characteristics of male breast tumors were significantly different. In our series, 100% of the tumors were estrogen receptor positive and only 14% were positive for HER-2 neu. These two differences in tumor characteristics may account for similar prognosis despite the diminished frequency of chemotherapy treatment in male patients.

Radiation

The primary role of post-mastectomy radiation in all breast cancers is to maximize local control; this holds true in the male breast cancer population as well. Although local control provides a survival benefit in long term follow-up for female node positive breast cancers, there have been no studies demonstrating a survival benefit in male breast cancer (31–33). Our current institutional recommendations for radiation in male breast cancer patients are similar to female patients in that tumor size, margin status, and nodal involvement are all taken into consideration. Compared to female patients, male patients are more likely to receive radiation due to a more advanced stage at presentation (11,34). Some centers advocate a lower threshold for post-mastectomy radiation due to the smaller volume of the male breast and favor radiation for tumor size greater than 1 cm or any nodal involvement (35). As with female breast cancer, although it is relatively well-tolerated, decisions regarding the use of adjuvant radiation should be made within the context of comorbid conditions (36).

Imaging and Follow-up

For the male patient with breast cancer, a common question following their treatment revolves around the best strategy for follow-up. Due to the scarcity of occurrence of male breast cancer, there has never been any reported benefit of screening mammogram of the contralateral breast. The benefit of other modalities such as MRI or screening ultrasound would also be unlikely to provide benefit. The relative risk of developing a second contralateral breast cancer is 30-fold greater than the general population, however, the absolute risk is only 0.1% per year (10,37). Obviously, this risk needs to take into account younger patients, BRCA carriers, men of Jewish ancestry, Klinefelter's disease, testicular disease, or any other specific risk factors for male breast cancer (38,39). Mammography may be most beneficial for this subset of patients. Clinical examination and self examination are perhaps the most important aspects to follow-up as most male breast cancers present with a palpable mass.

Future Directions

As our general understanding of breast cancer increases, male breast cancer outcomes should continue to improve. Perhaps the greatest need for improvement of male breast cancer is in the area of awareness, an area that has greatly benefitted the female breast cancer population. Lack of awareness may contribute to the increased risk of male breast cancer presenting with a more advanced stage of disease, possibly due to lack of understanding that a male breast mass could be a cancer (15,40). Increased awareness may not only lead to earlier detection, but also improved survival and decreased treatment morbidity, as seen in the female breast cancer population.

Finally, due to the rarity of these cancers, a national registry should be opened or adopted by organizations

such as the NCCN. This would allow accrual of data on male breast cancer throughout the United States. Through the aggregation of institutional datasets into a comprehensive registry, guidelines specific to male breast cancer may be established and validated.

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