

Clinicopathologic Features and Radiation Therapy Utilization in Patients with Male Breast Cancer: A National Cancer Database Study

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ABSTRACT: Male breast cancer (MBC) accounts for approximately 1% of all breast cancers, limiting the data characterizing clinicopathologic features and treatment outcomes in patients with MBC. This paucity of data has led to most of our treatment guidance being extrapolated from patients with female breast cancer (FBC). From 1998 to 2012, data were captured using the National Cancer Database to identify patients with nonmetastatic MBC ($n = 23305$) and FBC ($n = 2678061$). Tumor and clinicopathologic features were obtained and compared. Patients with MBC were more likely to have invasive disease, T2-4 tumors, centrally located tumors, positive lymph nodes, estrogen receptor–positive or progesterone receptor–positive tumors, lymphovascular space invasion, and were less likely to have Her2/neu–positive or triple-negative tumors. All of these differences were statistically significant ($P < .001$). Treatment comparisons showed that patients with MBC were more likely to undergo mastectomy and less likely to undergo breast-conserving surgery with postoperative radiation utilization found to be less in patients with MBC, both as part of breast-conserving therapy (BCT) and for postmastectomy radiation treatment (PMRT) ($P < .001$). Stage-by-stage comparisons showed that median survival, 5-year, and 10-year overall survival (OS) rates are lower in patients with MBC vs patients with FBC ($P < .001$). The utilization of adjuvant radiation, both BCT and PMRT, was shown to improve 5- and 10-year OS ($P < .001$). Male breast cancer clinicopathologic features appear to be unfavorable in relation to FBC and adjuvant radiation is shown beneficial in survival outcomes. Further investigation is needed to help guide future utilization and treatment with radiation, systemic, and endocrine manipulation in this small population of patients with MBC.

KEYWORDS: Male breast cancer, breast cancer, clinical features, radiotherapy

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Introduction

Male breast cancer (MBC) is an uncommon malignancy that accounts for approximately 1% of all breast cancers. In 2016, there were approximately 2400 new cases and 440 breast cancer–related deaths estimated among patients with MBC in the United States.¹ Because of the low incidence with MBC, data are limited on patient demographics, tumor characteristics, treatment utilization patterns, and treatment outcomes. To the best of our knowledge, no randomized trials have investigated treatment outcomes for only patients with MBC. Subsequently, there are limited data on the clinicopathologic features of MBC and most of data for treatment guidance have been extrapolated from female breast cancer (FBC) studies. We aim to describe and characterize the clinicopathologic features of MBC, specifically in relation to treatment utilization and their outcomes using patients captured in the National Cancer Database (NCDB). Our secondary aim is to compare these findings with those of patients with FBC and their respective clinicopathologic features.

Materials and Methods

Data for this study were obtained using the 2012 NCDB's Participant User File (PUF) for breast cancer. The NCDB, established in 1989, is a joint project of the American Cancer

Society and the Commission on Cancer (CoC) of the American College of Surgeons. The NCDB serves as a nationwide, facility-based, comprehensive clinical surveillance resource of oncology data that currently captures approximately 70% of all newly diagnosed malignancies annually in the United States.² Data are made available through a Business Associate Agreement that includes a data use agreement between the American College of Surgeons and each of its CoC-accredited hospitals. The PUF for breast cancer is a HIPAA-compliant data file that contains deidentified information at the patient level without identifying the institution, the providers, or the patients. The CoC's NCDB and the hospitals participating in the CoC NCDB are the source of the deidentified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors. This study was awarded “Does not meet the criteria for human subject research” status when reviewed by our institutional review board.

Study population and statistical analysis

Encompassing patients from 1998 to 2012, available data for patients meeting the criteria of nonmetastatic MBC were extracted using the 2012 PUF data file and related to data from



patients with FBC. Data collection included demographic, clinicopathologic, and treatment characteristics for the identified patients with MBC and FBC. Factors that were analyzed for potential impact on survival for patients with MBC included age, race, year of diagnosis, Charlson/Deyo comorbidity score (CDCC), histology, behavior, grade, laterality, estrogen receptor/progesterone receptor (ER/PR) status, her2/neu status, tumor size, number of positive lymph nodes, pathologic T and N stage, analytic stage group, type of surgery, surgical margins, and the use of radiotherapy (RT), hormonal therapy, or systemic therapy. Age was analyzed 2 ways: (1) age was grouped into categorical variable as either <70 or ≥70 for assessment of outcomes for “younger” and “older” patients and (2) it was grouped at 5-year intervals for multivariate analysis. For ER/PR status, breast cancers that had at least 1% of cells staining positive for the corresponding receptors on immunohistochemistry (IHC) were considered positive. For Her2/neu status, 3+ staining on IHC was considered positive. Locally advanced breast cancer was defined as patients with T3/T4 or lymph node–positive breast cancer. Statistical analysis was performed with SPSS version 22. Categorical variables were summarized using descriptive statistics and compared using χ^2 test.³ Overall survival (OS) curves were estimated using Kaplan-Meier method⁴ and compared between groups using the log-rank test. Multivariate Cox proportional hazard modeling⁵ was used to evaluate the benefit of RT while taking other covariates into account. Only variables significant on univariate analysis were included on stepwise multivariate modeling. All comparisons are 2 tailed with statistical significance defined as a *P* value less than .05.

Results

Study population

A total of 23 305 male patients and 2 678 061 female patients with nonmetastatic breast cancer were identified in the NCDB. Of the patients with MBC, 14 483 were under the age of 70 (younger patient group) and 8822 patients were 70 years or older (older patient group). Median follow-up was 55 months for all male patients and 64 months for all female patients. The patient, tumor, and treatment characteristics are summarized in Table 1. Median age, median tumor size, CDCC, and the number of lymph nodes sampled were larger in the MBC group.

Tumor and treatment characteristics

Overall, 92.2% of patients with MBC had ER- or PR-positive tumors, approaching nearly 95% in the older MBC patient group. Only 11.6% of patients with MBC had Her2/neu-positive tumors, and 5.3% of patients had triple-negative (TN) tumors. Younger patients with MBC were more likely to have TN disease compared with older patients with MBC. In relation to patients with FBC, male patients were more likely to

have invasive, ER/PR-positive, and her2/neu-negative tumors with a higher rate of lymphovascular space invasion (LVSI) positivity and lower rates of TN tumors. Similarly, patients with MBC were more likely to have T2-T4 disease and node-positive disease, which resulted in higher stage group rates when compared with patients with FBC. All of these differences were statistically significant with a *P* value of <.001. Although the median number of positive lymph nodes was 0 in both groups, patients with MBC were more likely to have lymph node–positive disease compared with patients with FBC. When patients were separated into older and younger patient groups, a similar pattern of tumor characteristics were seen throughout.

Treatment characteristics are shown in Table 2. Patients with MBC were less likely to undergo breast-conserving surgery (BCS) and more likely to undergo mastectomy compared with patients with FBC. The use of radiation therapy after BCS was significantly lower (60.4% vs 73.5%) in patients with MBC compared with patients with FBC. The use of postmastectomy radiation therapy (PMRT) for locally advanced breast cancer was similar between patients with MBC and FBC for all comers. However, when separated by age, older patients with MBC were more likely to receive PMRT compared with older patients with FBC (40.1% vs 31.9%).

When evaluated together, there was no significant difference in the usage of systemic therapy in patients with MBC compared with patients with FBC (36.2% vs 35.8%). However, older patients with MBC were more likely to receive systemic therapy compared with older patients with FBC (19.1% vs 13.0%). Interestingly, there were differences in the use of hormonal therapy between patients with MBC and FBC (46.2% vs 55.5%) despite the higher incidence of ER- or PR-positive tumors. This difference was more prominent in the younger patient population than the older patient population.

Treatment outcome

Survival outcomes are shown in Table 3 and Figure 1. For analytic stage 0 to III, there was a statistically significant lower median survival for patients with MBC when compared with patients with FBC. This remained when comparisons were made for stage-by-stage or by age group. The only exception was found in stage III patients where both patients with MBC and FBC had similar outcomes. As shown in Figure 1D, in patients with MBC undergoing BCS, the use of adjuvant radiation therapy was associated with a statistically significant improvement in survival (median OS 155.4 months vs not reached, *P*<.001). For patients with locally advanced breast cancer, there was also an association with adjuvant radiation therapy after mastectomy and survival. However, the magnitude of the 10-year OS benefit was smaller (70% vs 67%, *P*<.001) and was only statistically significant in older patients (29% vs 23%, *P*<.001).

Table 1. Patient and tumor characteristics.

FEATURE		MBC	FBC	P VALUE	YOUNGER MBC	YOUNGER FBC	OLDER MBC	OLDER FBC
Age	Median	65	60	<.001	58	55	77	77
CDCC	0	81.3%	86.3%	<.001	84.8%	88.9%	75.4%	79.5%
	1	14.6%	11.3%		12.3%	9.4%	18.5%	16.2%
	2	4.1%	2.4%		2.9%	1.7%	6.1%	4.3%
Behavior	Invasive	86.0%	79.5%	<.001	83.7%	78.0%	89.8%	83.5%
Grade	I	14.3%	18.6%	<.001	14.1%	17.2%	14.7%	22.4%
	II	42.1%	35.8%		40.4%	34.6%	45.0%	38.9%
	III	29.3%	29.3%		30.5%	31.6%	27.4%	23.2%
	Undiff.	0.9%	1.3%		1.0%	1.4%	0.8%	1.1%
	Unknown	13.3%	14.9%		14.1%	16.6%	12.2%	15.5%
ER or PR positive	Positive	92.2%	81.6%	<.001	90.7%	80.2%	94.6%	85.5%
Her2/neu positive	Positive	11.6%	14.6%	<.001	13.5%	16.2%	8.7%	17.2%
Triple negative	TN	5.3%	12.9%	<.001	6.4%	13.8%	3.5%	12.4%
LVSI	Present	27.7%	16.6%	<.001	26.8%	17.5%	29.2%	14.6%
Tumor size	Median	20mm	15	<.001	19mm	15	20mm	15
Lymph nodes sampled	Median	5	3	<.001	6	4	5	3
Tumor stage	Tis	11.4%	16.4%	<.001	12.9%	17.7%	8.2%	13.0%
	T1	41.5%	47.3%		41.7%	46.4%	41.2%	49.8%
	T2	28.1%	19.7%		27.0%	20.0%	29.9%	18.9%
	T3	2.3%	3.0%		2.7%	3.2%	1.8%	2.6%
	T4	4.8%	1.5%		4.0%	1.2%	6.1%	2.1%
	Other ^b	12.2%	12.0%		11.8%	11.5%	12.9%	13.5%
Nodal stage	Nx	17.0%	18.1%	<.001	15.5%	16.4%	19.5%	22.6%
	N0	53.8%	61.0%		54.4%	61.1%	52.8%	61.0%
	N1	21.1%	15.8%		21.5%	17.1%	20.6%	12.5%
	N2	5.7%	3.5%		2.5%	1.6%	2.0%	1.2%
	N3	2.3%	1.5%		6.1%	3.8%	5.0%	2.8%
Analytic stage grouping	0	13.4%	16.9%	<.001	15.5%	21.4%	9.9%	16.1%
	I	32.4%	48.7%		31.6%	38.0%	33.8%	46.3%
	II	35.5%	26.6%		34.4%	28.0%	37.2%	25.2%
	III	13.3%	7.8%		13.1%	8.7%	13.5%	7.4%
	Unknown	5.3%	4.2%		5.0%	3.9%	5.3%	5.0%

Abbreviations: CDCC, Charlson/Deyo comorbidity score; ER, estrogen receptor; FBC, female breast cancer; LVSI, lymphovascular space invasion; MBC, male breast cancer; PR, progesterone receptor.

^aUnless otherwise noted, patients with unknown values were excluded from frequency calculations. (Most of the variables had missing or unknown values in ≤10% of cases, CDCC, ER/PR, and Her2/neu had approximately 1/3 of the values as unknown and grade had approximately 15% of the values as unknown in both male patients and female patients.)

^bOther includes patients with T0, Tx, or unknown classifications.

Table 2. Treatment characteristics.

FEATURE		MBC	FBC	P VALUE	YOUNGER MBC	YOUNGER FBC	OLDER MBC	OLDER FBC
BCS RT after BCS	All patients	26.6% 60.4%	56.4% 73.5%	<.001	29.2% 64.5%	56.3% 77.5%	22.2% 51.6%	56.6% 63.1%
Mastectomy ^a RT after mastectomy	T3-4, or N1-3	44.9% 45.0%	27.9% 45.6%	<.001	25.9% 48.0%	18.8% 50.0%	26.6% 40.1%	15.7% 31.9%
Systemic therapy used		36.2%	35.8%	.202	46.3%	44.4%	19.1%	13.0%
Hormonal therapy used	ER/ PR- positive patients	46.2%	55.5%	<.001	46.4%	57.4%	45.8%	50.9%

Abbreviations: BCS, breast-conserving surgery; ER, estrogen receptor; FBC, female breast cancer; MBC, male breast cancer; PR, progesterone receptor; RT, radiotherapy.

^aOnly patients with locally advanced disease (T3-4 and/or N1-3) was considered in the mastectomy group.

Table 3. Survival outcomes.

OUTCOME	PATIENT CATEGORIES	MBC	FBC	P VALUE	YOUNGER MBC	YOUNGER FBC	OLDER MBC	OLDER FBC
Median OS, mo	Stage 0	180	NR	<.001	NR	NR	119.6	134.8
	Stage I	168	189		NR	NR	100.6 73.7	121.2 91.5
	Stage II	120	180		NR	190.4		
	Stage III	78	98		98.6	126.9	53.6	50.7
5-y OS	All patients	77%	85%	<.001	86%	91%	62%	72%
10-y OS	All patients	55%	70%		70%	81%	32%	45%
10-y OS BCS+RT BCS+no RT	MBC	74% 60%		RT vs no RT (<i>P</i> <.001)	84% 78%		48% 33%	
10-y OS M+RT M+no RT	MBC (T34 or N1-3)	44% 41%		RT vs no RT (<i>P</i> <.001)	52% 56%		29% 23%	

Abbreviations: BCS, breast-conserving surgery (all patients with male breast cancer undergoing BCS); FBC, female breast cancer; M, mastectomy (male breast cancer undergoing mastectomy with advanced-stage disease (T3-4, and/or N1-3); MBC, male breast cancer; OS, overall survival; RT, radiotherapy.

Factors associated with survival

Covariates associated with improved survival on multivariate analysis are shown in Table 4. In patients with MBC, significant factors included age, CDCC, tumor size, number of positive lymph nodes, surgical margins, use of RT, use of hormonal therapy, and use of systemic therapy. Nonsignificant variables included race, histology, behavior, grade, laterality, and ER/PR/Her2/neu positivity. Analytic stage grouping showed a trend toward significance (*P* = .060). For patients with FBC, all the variables except for laterality were significant for OS.

Discussion

In a large, hospital-based data set, our study demonstrates a unique set of clinicopathologic features for patients with MBC

when compared with patients with FBC. Compared with patients with FBC, male patients were more likely to have higher grade, invasive breast cancer, larger tumors, more likely to have positive lymph nodes, and more likely to have LVSI. Patients with MBC were also more likely to have ER/PR-positive tumors (over 90%) and less likely to have TN tumors. Despite these favorable features, patients with MBC tended to have survival outcomes that were lower than patients with FBC. The only exception to this was in the older patients with stage III disease, where the median survival was similar for the 2 groups when outcomes were corrected for confounding covariates.

These findings are consistent with what has been reported in the literature. Iorfida et al⁶ reported on 99 patients with MBC case matched to 198 patients with FBC. For patients

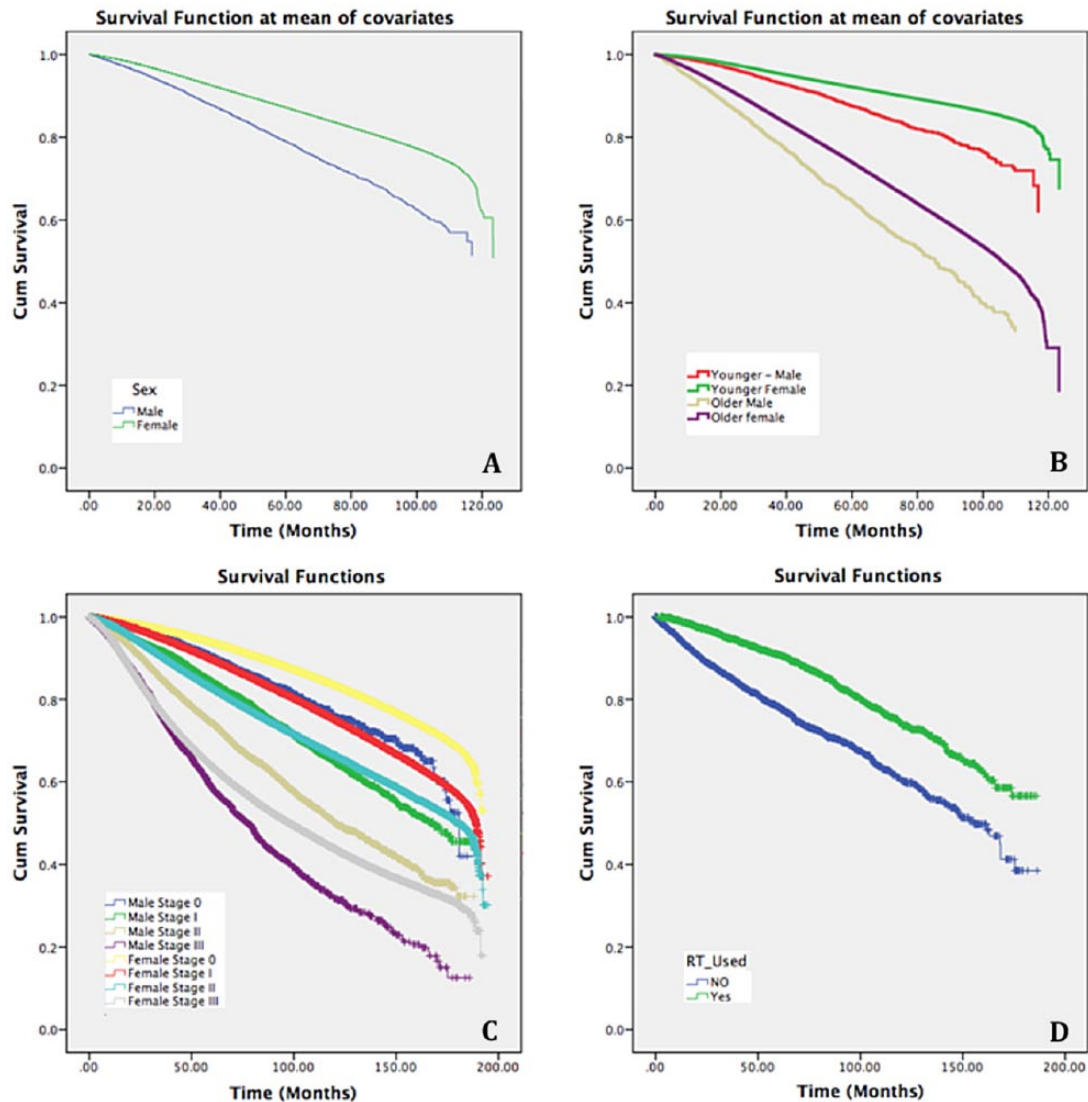


Figure 1. Overall survival curves for male patients with breast cancer. (A) Male patients vs female patients (all comers), (B) male patients vs female patients by age, (C) male patients vs female patients by analytic stage, and (D) male patients undergoing breast-conserving surgery with or without adjuvant radiation therapy. Curves adjusted for pathologic T and N stage, estrogen receptor/progesterone receptor status, and the presence of lymphovascular space invasion. RT indicates radiation therapy.

with MBC, 96% were ER positive, 8% were her2/neu positive, and 49% had lymph node–positive disease. When comparing survival outcomes, patients with MBC had worse 5- and 10-year OS and disease-free survival rates when compared with patients with FBC. In their series, patients with MBC also had higher rates of contralateral breast cancer and secondary malignancies compared with patients with FBC. Giordano et al⁷ reported similar outcomes on a population-based study from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (NCI SEER) program on 2537 patients with MBC. When evaluating patients with available data, over 90% of their patients were ER positive and 42.3% were lymph node positive. About 6% of their patients had stage IV disease, and in 8.5% of their patients, the stage was unknown. They reported a 5-year OS rate of 63% and a 10-year OS of 41% in patients with MBC. Contrary to these results, Kaushik et al,⁸ in a series of 57 patients with MBC,

noted similarly high rates of ER and PR positivity, ranging from 60% to 100% expression for ER and 40% to 86% expression for PR receptor, but an improved OS rate for patients with MBC.

Numerous factors could be associated with worse treatment outcomes in MBC. These include delay in initiation of therapy, more advanced stage at presentation, and decreased use of adjuvant radiation therapy as a part of local therapy, among others. However, when correcting for the potential covariates in this study, patients with MBC continued to have worse outcome when compared with patients with FBC. This may, in part, be related to a different biology in MBC when compared with FBC. There is growing evidence that differences exist between MBC and FBC both at the histologic level and the molecular level.^{7,9–12} Although, an in-depth discussion regarding the molecular regulators of MBC is beyond the scope of this article, it is likely that these differences contribute, at least

Table 4. Covariates associated with survival on multivariate analysis for patients with MBC and FBC.

COVARIATE	PATIENTS WITH MBC			PATIENTS WITH FBC		
	P VALUE	HAZARD RATIO	95% CI	P VALUE	HAZARD RATIO	95% CI
Age ^a	<.001	1.223	1.140-1.311	<.001	1.19	1.182-1.199
Race	.369	0.921	0.771-1.101	.004	0.969	0.949-0.990
CDCC	<.001	1.871	1.541-2.272	<.001	1.552	1.510-1.595
Histology	.087	1.015	0.998-1.033	<.001	0.994	0.991-0.996
Behavior	.162	4.24	0.560-32.127	<.001	1.487	1.242-1.780
Grade	.157	1.060	0.978-1.149	<.001	1.030	1.020-1.040
Laterality	.338	0.874	0.663-1.151	.259	0.981	0.950-1.014
ER positive	.830	1.070	0.579-1.975	<.001	0.785	0.742-0.832
PR positive	.40	0.636	0.413-0.980	<.001	0.690	0.657-0.724
Her2/neu positive	.622	1.113	0.728-1.701	<.001	0.702	0.668-0.738
Tumor size	.001	1.154	1.059-1.259	<.001	1.130	1.120-1.141
No. of positive LNs	<.001	1.008	1.004-1.012	<.001	1.007	1.007-1.008
Pathologic T stage	.622	1.042	0.884-1.228	.001	1.031	1.013-1.049
Pathologic N stage	.382	1.091	0.898-1.326	<.001	1.258	1.231-1.287
Analytic stage group	.060	1.326	0.988-1.781	<.001	1.551	1.497-1.607
Type of surgery ^b	.275	0.785	0.509-1.212	.002	1.067	1.024-1.113
Surgical margins	.031	1.095	1.008-1.188	<.001	1.101	1.091-1.110
RT used	.027	0.658	0.454-0.953	<.001	0.552	0.530-0.575
HT used	<.001	0.480	0.356-0.648	<.001	0.502	0.481-0.524
Systemic therapy used	.003	0.562	0.382-0.827	<.001	0.725	0.692-0.759

Abbreviations: CDCC, Charlson/Deyo Comorbidity score; CI, confidence interval; ER, estrogen receptor; FBC, female breast cancer; HT, hormonal therapy; LNs, lymph nodes; MBC, male breast cancer; PR, progesterone receptor; RT, radiotherapy.

^aAge was grouped at 5-year intervals except for first group which was 18 to 25 years.

^bType of surgery: breast-conserving surgery vs other.

in part, to the differences observed between patients with MBC and FBC noted in this study. It should also be noted that in our study population, patients with MBC had a higher median age compared with patients with FBC. This factor, along with the shorter expected survival for men compared with women, may contribute to the worse survival rates after diagnosis in patients with MBC compared with patients with FBC.

There are no clear guidelines for local therapy in patients with MBC. However, in general, men are more likely to undergo mastectomy and less likely to receive adjuvant radiation therapy. This was also the case in the current series. Even in patients who underwent BCS, only 60% of male patients received postlumpectomy radiation therapy. Patten et al¹³ reiterate in their review that there continues to be a lack of consistent and conclusive evidence supporting the use of adjuvant RT, but they do discuss 2 single institutional reviews that show a benefit from radiation in terms of locoregional failure rates.

However, there was no survival advantage seen in these small series analyses. To date, there are no randomized trials demonstrating a benefit to adjuvant radiation therapy after BCS in patients with MBC. This current series suggests an association between the use of radiation therapy after BCS and improved OS. Based on this, consideration should be given to the addition of radiation therapy as adjuvant therapy after limited surgery in male patients with breast cancer. There also was an association between the addition of radiation therapy after mastectomy in the setting of locally advanced breast cancer and improved survival. However, the magnitude of this benefit was smaller and only significant in the older population. This suggests that a different set of criteria may need to be developed for the use of PMRT in patients with MBC.

To the best of our knowledge, this is the largest study on male patients with nonmetastatic breast cancer. The main advantage of our study is the large number of patients with long follow-up and the consistent manner in which the data

are collected. However, there are certain limitations to this work as well. Differences in age, comorbidities, tumor grade, and ER receptor status among other prognostic factors could account for some of the differences seen in this study. Although we attempted to correct for these variables, it is possible that we were not able to correct for all of the potential confounding variables. Also, because of the absence of Ki67 levels, and a preponderance of ER/PR-positive patients in the MBC group, we were not able to compare treatment outcomes based on intrinsic subtypes. Secondary to limitations in the available data in the NCDB, we were not able to evaluate any potential molecular or genetic factors that could explain some of the observed differences. Finally, although the NCDB captures approximately 70% of all newly diagnosed cancer cases, the data are hospital based, and caution should be used in applying these data to the general population.

In conclusion, our review of a large population of patients with nonmetastatic MBC suggests a different set of clinicopathologic factors including higher ER receptor levels as well as higher grade, higher tumor stage, and higher nodal stages in patients with MBC when compared with FBC. Despite correcting for multiple covariates, patients with MBC had worse outcome compared with patients with FBC. This was the case when patients were evaluated by age or by stage and likely points to potential differences in the tumor biology between the 2 patient groups. Secondary to the limited number of MBC cases diagnosed, multi-institutional studies, such as those through the International Male Breast Cancer Consortium, will be required to further characterize this disease process.

Author Contributions

JW conducted the literature review, data collection, data interpretations and writing of the manuscript; YZ conducted the data analyses and tests; TH provided conceptual advice and oversight; and OA contributed to data interpretations, editing of manuscript, conceptual advice and supervision of study processes and manuscript formulation.

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