Title

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Is Breast Conserving Therapy Appropriate for Male Breast Cancer Patients? A National Cancer Database Analysis

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Abstract

Background: Current treatment guidelines for male breast cancer are predominantly guided by female-only clinical trials. With scarce research, it is unclear if breast conserving therapy (BCT) is equivalent to mastectomy in men. We sought to compare overall survival (OS) among male breast cancer patients who underwent BCT versus mastectomy.

Methods: We performed a retrospective analysis of 8,445 stage I-II (T1–2 N0–1 M0) male breast cancer patients from the National Cancer Database (2004–2014). Patients were grouped according to surgical and radiation therapy (RT). BCT was defined as partial mastectomy followed by RT. Multivariable and inverse probability of treatment weighted (IPTW) Cox proportional hazards models were used to compare OS between treatment groups, controlling for demographic and clinicopathologic characteristics.

Results: Most patients underwent total mastectomy (61.2%), while 18.2% underwent BCT, 12.4% underwent total mastectomy with RT, and 8.2% underwent partial mastectomy alone. In multivariable and IPTW models, partial mastectomy alone, total mastectomy alone, and total mastectomy with RT were associated with worse OS compared to BCT ($p<0.001$ all). Ten-year OS was 73.8% for BCT, while 56.3%, 58.0% & 56.3% for other treatment approaches. Older age,

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Conflicts of interest: None.

higher T/N stage, histological grade, and triple negative receptor status were associated with poorer OS ($p<0.05$). Subgroup analysis by stage demonstrated similar results.

Conclusion: In this national sample of male breast cancer patients, BCT was associated with greater survival. The underlying mechanisms of this association warrant further study, since more routine adoption of BCT in male breast cancer appears to translate into clinically meaningful improvements in survival.

Introduction

With approximately 2,400 estimated new cases in the US in 2017, male breast cancer is a rare disease comprising less than 1% of all new breast cancer diagnoses.[1] As such, research investigating optimal local regional treatment for male breast cancer is sparse and current treatment guidelines for men are predominantly based on clinical trials comprised of female participants.[2] For example, the landmark National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 study compared total mastectomy to breast conserving therapy (BCT, i.e. partial mastectomy followed by radiation therapy (RT)) only in women. This study still strongly influences breast cancer treatment recommendations due to the finding of equivalent overall survival (OS) for BCT and mastectomy.[3] Although this recommendation is applied to men, high-level evidence supporting this recommendation is lacking. Moreover, the few retrospective studies investigating male breast cancer have largely consisted of small cohorts and/or have been descriptive in nature.[4–12] One exception, Cloyd et al., performed a retrospective analysis comparing partial to total mastectomy in male breast cancer patients using the Surveillance, Epidemiology and End Results (SEER) database; however, RT, an important factor for local recurrence and survival, was not used to categorize patients and was reported at low rates, potentially secondary to underreporting.[13,14]

Such limitations in male breast cancer research are significant, as they impair treating clinicians' ability to provide evidence-based recommendations to male breast cancer patients. Although the National Comprehensive Cancer Network guidelines recommend that men be treated similar to postmenopausal women,[2] a multidisciplinary expert panel has advised that male breast cancer is distinct from female breast cancer with significant biologic, clinicopathologic, and prognostic differences and should be treated accordingly.[15–18] For example, a recent population-based study found significant differences in tumor gene expression in male breast cancer patients compared to female patients.[18] This is problematic since we are currently using female data to make assumptions about male patients. Thus, there is a need for greater research investigating the impact of different therapeutic modalities on outcomes in male breast cancer patients to optimize therapy and patient counseling. The purpose of this study was to compare OS among male breast cancer patients treated with BCT, partial mastectomy alone, and total mastectomy with and without RT using a large national database, the National Cancer Database (NCDB). We hypothesized that BCT will be equivalent to total mastectomy with and without RT, while partial mastectomy alone will be associated with worse OS.

Methods

We performed a retrospective analysis of male breast cancer patients using the NCDB from 2004–2014. The NCDB is a joint American College of Surgeons and American Cancer Society project, in which patient-level data has been collected from all cancer patients seen at Commission on Cancer (COC) sites.[19,20] Although approximately 30% of US hospitals are COC sites, NCDB captures data from 70% of all newly diagnosed cancer patients in the US.

We identified 18,984 male patients with invasive breast cancer, not including sarcomas and lymphomas. We excluded patients with stage III-IIV/unknown, T3-T4, multicentric/diffuse, or Paget's disease to replicate the NSABP B-06 cohort clinicopathologic characteristics (Supplement, Figure S1). RT was defined as postoperative external beam RT to the breast and/or chest wall +/− axilla. Patients with unknown RT including sequence/type/location; who underwent brachytherapy; or preoperative RT were excluded. Patients were excluded if survival data was missing/unknown or if they did not undergo surgery with partial or total mastectomy. The final cohort consisted of 8,445 patients, categorized into the following groups based on surgery and RT: 1,539 BCT patients (partial mastectomy with RT), 695 partial mastectomy alone patients, 5,165 total mastectomy alone patients, and 1,046 total mastectomy with RT patients. As patient information was de-identified, the study protocol was exempt from the University of California, Davis Institutional Review Board approval.

We abstracted patient demographic, clinicopathologic characteristic, and treatment information from NCDB. The Charlson-Deyo comorbidity index (CDCI) measured patient medical comorbidities. Tumors were classified by histology based on international classification of disease oncology codes (ICD-O-3; Supplement). Staging was defined by AJCC TNM pathologic stage and only by clinical stage if pathologic staging data were missing (n=581, 6.9%). Immunotherapy was categorized as 'chemotherapy' since Trastuzumab was classified as chemotherapy until 2013. As NCDB reports the number of lymph nodes examined and not the type of nodal surgery performed, we defined sentinel lymph node biopsy (SLNB) as examining 1–5 nodes and axillary lymph node dissection (ALND) as examining ≥6 nodes based on previously described methods[21,22] and the limited clinical utility in obtaining >5 nodes in a SLNB.[23] Patients' vital status and months from diagnosis to last contact and/or death were used to determine OS.

Statistical Analysis

Patient demographics, clinicopathologic characteristics, and additional therapies were compared between treatment groups using Chi-Square, Kruskal Wallis, and ANOVA for categorical, non-normally distributed continuous, and normally distributed continuous variables respectively. We compared OS between groups using the Kaplan-Meier method, log-rank test, and Cox proportional hazards models. We performed both multivariable and inverse probability of treatment weighted (IPTW; using propensity scores) Cox regression models to account for selection bias/confounding and determine clinical factors associated with OS.[24,25] Propensity scores were created by estimating the probability of selection into the four treatment groups with a multinomial logistic regression model consisting of covariates associated with treatment group differences in univariate analyses ($p \leq 0.15$). The

same covariates were clinically relevant to OS and, therefore, also included in the multivariable Cox model. Model covariates included age, race, CDCI, income, insurance, facility, histology, grade, hormone receptor/HER-2 status, T/N/overall stage, axillary nodal surgery, surgical margins, chemotherapy, hormone therapy, and year of diagnosis. Evaluation of standardized differences determined appropriate balance of all covariates after IPTW. The proportional hazards assumption was not violated as assessed by Schoenfeld residuals. Missing data was incorporated into the model as 'unknown' for each respective covariate.

HER-2 was not reported until 2010; therefore, 45.8% of patients had missing/unknown HER-2 status (n=3,871). We performed sensitivity analyses comparing multivariable Cox models for OS of all patients and with HER-2 unknown patients excluded. As there were no significant differences between models, we are presenting analyses including all patients.

Subgroup analyses by overall and T stage were performed using multivariable Cox proportional hazards regression models controlling for the same covariates as performed on the entire cohort. Statistical analysis was performed using SAS (version 9.4, SAS Institute, Cary, NC). All tests were two sided. P-values <0.05 were considered significant.

Results

Of the 8,445 males with invasive breast cancer, most underwent total mastectomy alone (61.2%, n=5,165), while 18.2% (n=1,539) underwent BCT, 12.4% (n=1,046) underwent total mastectomy with RT, and 8.2% (n=695) underwent partial mastectomy alone. Table 1 describes key demographic and clinicopathologic characteristics by treatment approach. There were significant differences between treatment groups for age, race, CDCI, histology, tumor size, grade, T, N and overall stage, hormone receptor/HER-2 status, surgical margins, nodal surgery, chemotherapy, and hormone therapy between treatment groups ($p<0.05$). Hormone receptor positive/HER-2 negative disease was more common among patients who underwent total mastectomy alone and with RT compared to BCT and partial mastectomy alone patients (45.5% & 47.1% vs. 40.4% & 35.5%), while rates of triple negative receptor status were greatest among BCT patients compared to patients who underwent partial mastectomy alone, total mastectomy alone, and total mastectomy with RT (4.9% vs. 3.0%, 1.4% & 1.4%, $p<0.0001$). Median follow-up for the entire cohort was 52 months (IQR 30–79).

After controlling for demographic and clinicopathologic group differences, in both the multivariable (Table 2) and IPTW models, partial mastectomy alone (multivariable: aHR 1.73, 95%CI 1.39–2.14, $p<0.0001$; IPTW: HR 1.60, 95%CI 1.14–2.24, $p=0.006$), total mastectomy alone (multivariable: aHR 1.54, 95%CI 1.29–1.83, $p<0.0001$; IPTW: HR 1.62, 95%CI 1.27–2.07, $p<0.0001$) and total mastectomy with RT (multivariable: aHR 1.44, 95%CI 1.16–1.79, $p=0.001$; IPTW: HR 1.58, 95%CI 1.15–2.18, $p=0.005$) were associated with poorer OS compared to BCT. Older age, higher CDCI scores, histological grade, T and N stage, and triple negative receptor status were associated with worse OS, while SLNB, ALND, hormone therapy, and chemotherapy were associated with improved OS (Table 2). Figures 1.A-B illustrate crude and IPTW Kaplan Meier survival curves by treatment approach. At 5- and 10-years, OS rates (with IPTW adjustment) were 86.8% & 73.8% for

BCT, 84.9% & 56.3% for partial mastectomy alone, 80.6% & 58.0% for total mastectomy alone, and 81.9% & 56.3% for total mastectomy with RT patients.

Subgroup analyses by overall and T stage are presented in Figures 2.A-B and 3.A-B and Table S1 (Supplement). For stage I and T1 disease, there were no OS differences for BCT and total mastectomy with RT patients ($p>0.05$, Table S1). Total and partial mastectomy alone were associated with worse OS compared to BCT ($p<0.05$, Table S1). For stage II and T2 disease, total mastectomy alone and with RT and partial mastectomy alone were associated with worse OS compared to BCT ($p<0.05$, Table S1).

Discussion

In this NCDB analysis of male breast cancer patients, despite total mastectomy being performed more commonly, BCT was associated with greater survival compared to total mastectomy with and without RT and partial mastectomy alone. These findings were surprising as current consensus guidelines based on randomized clinical trials with female patients regard BCT and total mastectomy to be oncologically equivalent.[2,3,26] Therefore, these findings are particularly important as they underscore the need for greater consideration and adoption of BCT for male breast cancer patients.

This study strengthens the current limited body of research investigating oncologic outcomes among male breast cancer patients. In a retrospective SEER analysis, Cloyd et al. found equivalent disease-specific and OS among men with breast cancer who underwent partial mastectomy compared to those who underwent total mastectomy.[13] Although Cloyd et. al. included RT in the multivariable analysis, they did not stratify partial mastectomy patients by receipt of RT. As shown in our analysis, there were significant differences in age, comorbidities, surgical margins, and systemic therapy for BCT and partial mastectomy alone patients, suggesting that partial mastectomy patients who did and did not undergo RT are distinct patient cohorts. Additionally, after controlling for these group differences, we found that BCT was associated with greater survival compared to partial mastectomy alone. These findings highlight the importance of RT to improve oncologic outcomes in male breast cancer patients who undergo partial mastectomy.

Although the oncologic benefit of RT in breast cancer has been widely cited in female literature,[27,28] RT in male breast cancer research is predominantly limited to retrospective single institution studies (many including patients from the 1960s and 1970s).[29,30] Although a number of these male-specific studies have shown an improvement in locoregional control with RT, few have observed a survival benefit.[29,31,32] Therefore, the findings from the present study are noteworthy as they highlight a survival benefit associated with RT in male breast cancer. Additionally, the equivalent survival observed for stage I and T1 tumors treated with BCT or total mastectomy with RT suggests that RT may provide greater oncologic benefit than extensive surgical resection in small tumors. A recent study by Jatoi et al. suggested an ‘abscopal effect’ to explain such findings.[33] The ‘abscopal effect’ refers to the potential for RT to have both a localized and systemic anti-tumor effect from immunostimulation, leading to lower incidence of distant recurrence and greater survival. Despite such oncologic benefits, multiple studies have observed lower rates of RT

compliance among male breast cancer patients compared to female patients.[11,12] Therefore, although our findings suggest BCT is appropriate therapy in men, BCT is only beneficial in those in which RT is feasible, as lumpectomy alone is not associated with the same survival benefit.

Although we acknowledge the potential influence of selection bias in this retrospective analysis, the similarities in tumor size, nodal disease, and surgical margins between patients who underwent BCT and mastectomy alone provides further confidence in the validity of our findings. Although the median tumor size was slightly larger for total mastectomy alone patients, the median tumor size for both groups was small (1.4–1.8cm). Additionally, most patients in both cohorts were without nodal metastases (75–81%) and had high rates of negative surgical margins (96%−98%). We acknowledge that the mastectomy with RT patients are a distinct group with larger tumors (median 2.3cm) and high rates of nodal disease (67%) and, therefore, at greater risk of confounding. However, the clinical similarities between patients who underwent BCT and mastectomy alone (in addition to stratification by stage and robust multivariable and propensity score analyses) provides credence to our findings of a survival benefit associated with BCT compared to total mastectomy alone.

Additionally, recent retrospective population-based studies comparing BCT to total mastectomy alone has observed similar results in female breast cancer patients, further validating our results.[34–37] Agarwal et al. performed a retrospective analysis comparing BCT to total mastectomy in female breast cancer patients with tumors ≤4cm and ≤3 positive lymph nodes using the SEER database and found greater survival in BCT patients compared to women who underwent total mastectomy with and without RT.[35] A separate SEER analysis of female patients by Bagaria et al. found similar results, with worse disease-specific survival among women who underwent total mastectomy compared to BCT in low-, intermediate-, and high-risk tumors based on hormone status and grade.[34] Furthermore, in a multicenter prospective cohort study of young women with breast cancer in the United Kingdom, although BCT was associated with earlier local recurrence, BCT was associated with improved distant disease-free interval and OS compared to total mastectomy.[37] Our findings complement this body of research by demonstrating similar findings in male patients, specifically that BCT is associated with improved survival compared to total mastectomy.

The present study has important implications for post-therapeutic surveillance in male breast cancer. Current guidelines for post-therapeutic surveillance in men are the same as those recommended for women, which include history and physical examination every 4–6 months for the first 5 years and annually afterwards.[2,38] BCT patients should also undergo annual mammography. Future research is needed to determine if this surveillance regimen is adequate in men, as these guidelines were created based on research with predominantly female patients.

Despite this study's strengths, it does have limitations inherent to administrative data. This study was retrospective and patients were not randomized to treatment approaches. Despite extensive multivariable analyses and model adjustment with propensity scores, our results

may still have been confounded by selection bias related to nuanced clinical, pathologic, or sociodemographic features that could affect choice of therapy, including patients' and physicians' preferences. For example, in addition to the higher rate of triple negative receptor status among BCT patients compared to mastectomy alone patients (4.9% vs. 1.4%, which we controlled for in our IPTW and multivariable analyses), patient preferences may also potentially explain why BCT patients were more commonly treated with adjuvant systemic therapies compared to mastectomy alone patients. BCT patients may have been more amenable to additional therapies in general, including systemic therapy and RT, whereas mastectomy alone patients may have preferred to avoid additional therapies, which is why they selected total mastectomy over BCT. We acknowledge that many patients had missing HER-2 status. However, this likely had negligible influence on our results as most male breast cancer patients have been shown to be HER-2 negative and our sensitivity analyses revealed no significant survival differences when excluding HER-2 unknown patients.[12] As NCDB does not provide detailed information regarding systemic therapeutics, we were not able to control for specific adjuvant regimens or assess if patients completed their entire course of adjuvant therapy. NCDB does not provide data on cause of death or recurrence, limiting our primary outcome to OS. Lastly, we lacked information regarding treatment complications and adverse side-effects, which have the potential to influence surgical and RT treatment decisions and patient quality of life.

In conclusion, in this analysis of a large, national cohort of male breast cancer patients, although total mastectomy was more commonly performed, BCT was associated with improved survival compared to total mastectomy. These findings suggest that BCT is a viable treatment approach for male breast cancer patients and should be given greater consideration by surgeons and oncologists. However, as RT compliance is an essential component in BCT, careful, personalized, shared decision-making between physicians and male breast cancer patients is necessary to ensure the selected treatment approach, whether BCT or mastectomy, is reasonable for the patient.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Synopsis:

Breast conserving therapy (BCT) in men was associated with greater survival compared to total mastectomy +/− radiation and partial mastectomy alone suggesting that BCT is a viable therapy for men and should be given greater consideration by surgical oncologists.

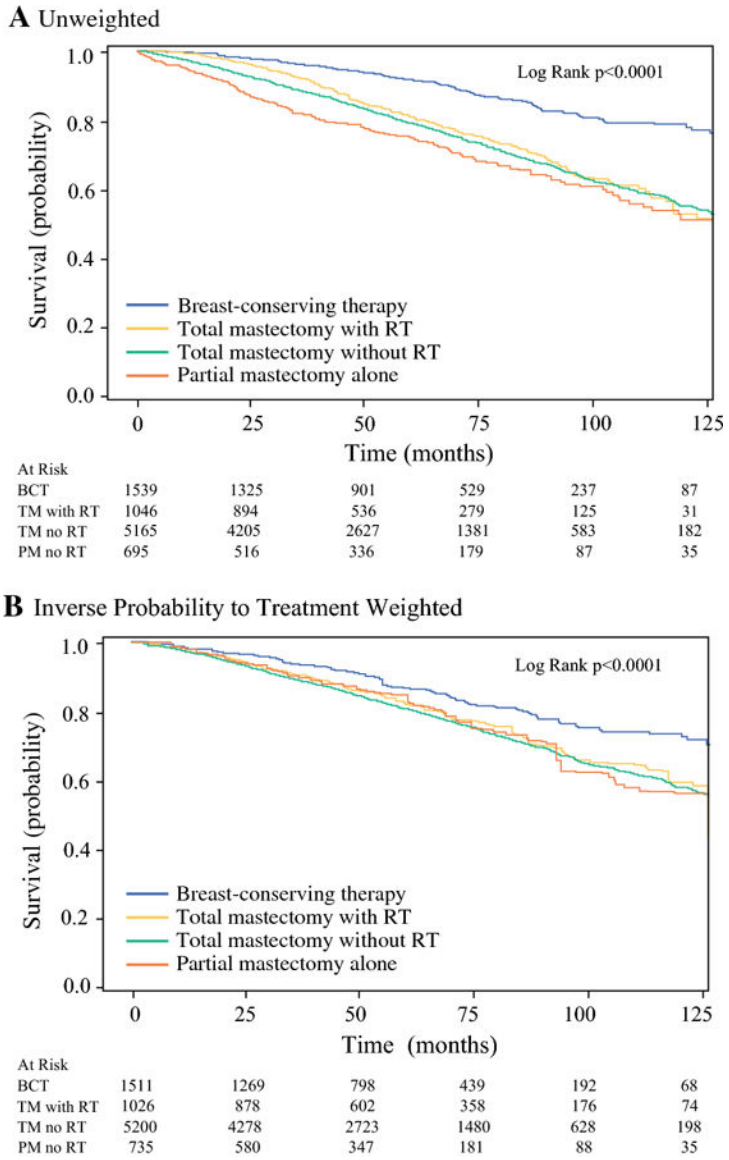

Figure 1.

A-B. Crude (A) and inverse probability of treatment weighted (B) overall survival for male breast cancer patients with breast conserving therapy (BCT), total mastectomy with (TM with RT) and without radiation therapy (TM no RT), and partial mastectomy alone (PM no RT).

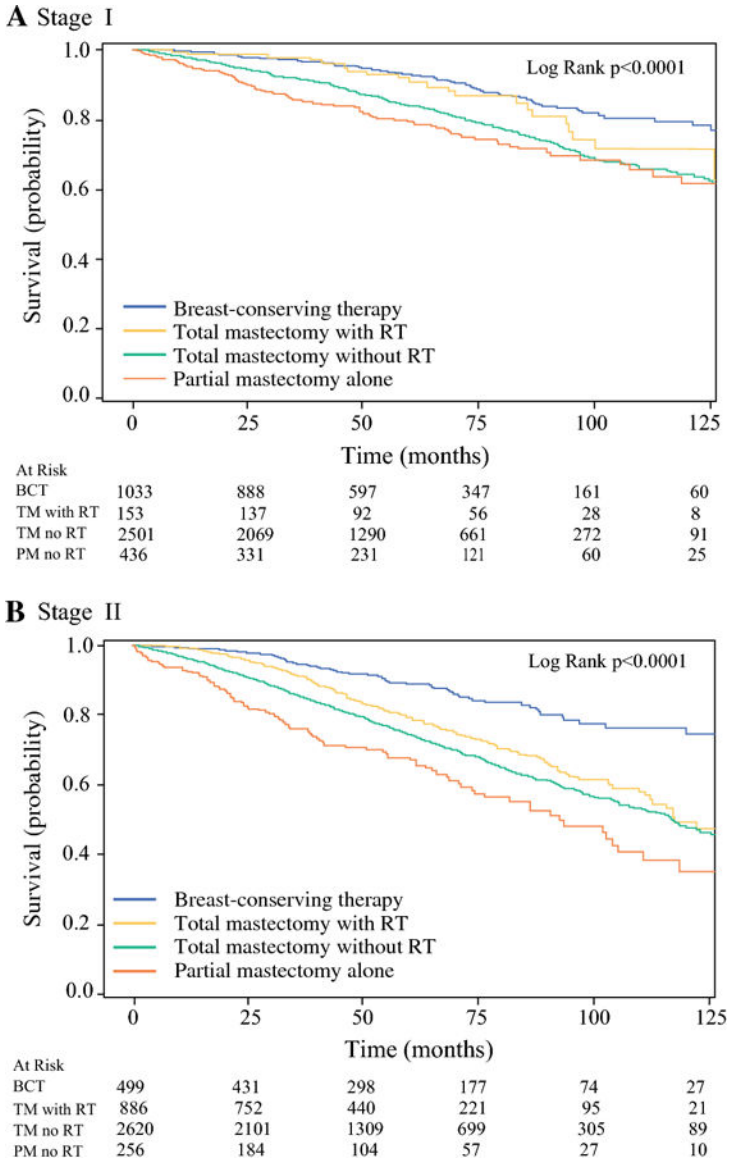

Figure 2.

A-B. Univariate overall survival for breast conserving therapy (BCT) compared to partial mastectomy alone (PM no RT), total mastectomy alone (TM no RT) and total mastectomy with radiation therapy (TM with RT) by stage.

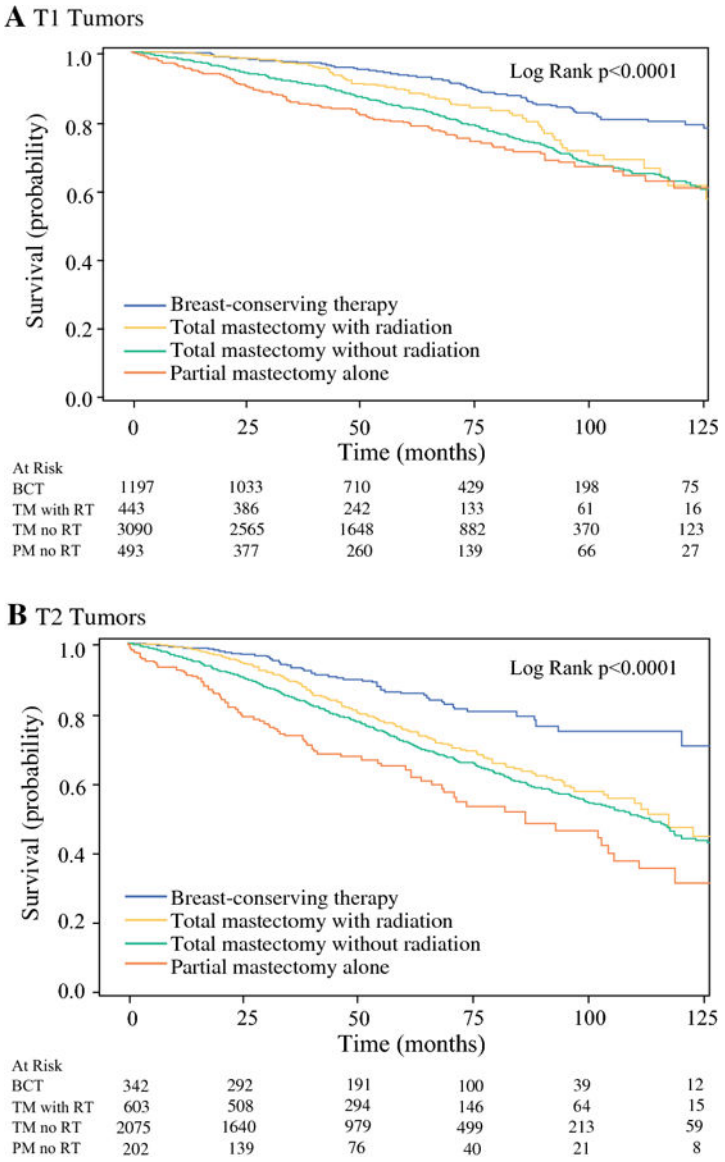

Figure 3.

A-B. Univariate overall survival for breast conserving therapy (BCT) compared to partial mastectomy alone (PM no RT), total mastectomy alone (TM no RT) and total mastectomy with radiation therapy (TM with RT) by T stage.

Table 1.

Patient demographics and clinicopathologic characteristics by treatment approach.

	Breast Conserving Therapy N=1,539		Partial Mastectomy Alone N=695		Total Mastectomy Alone N=5,165		Total Mastectomy with Radiation N=1,046		P-value
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	
Age (mean, SD, years)	61.4	12.0	66.7	14.7	66.3	12.6	63.4	12.5	<0.001
Race									
Caucasian	1,305	84.8%	586	84.3%	4,495	87.0%	879	84.0%	0.0006
African American	179	11.6%	68	9.8%	501	9.7%	132	12.6%	
Asian/Pacific Islander	29	1.9%	15	2.2%	89	1.7%	17	1.6%	
Other/Unknown	26	1.7%	26	3.7%	80	1.6%	18	1.7%	
Charlson-Deyo Comorbidity Index									
0	1,326	86.2%	576	82.9%	3,921	75.9%	846	80.9%	<0.0001
1	174	11.3%	83	11.9%	939	18.2%	161	15.4%	
2	34	2.2%	25	3.6%	236	4.6%	30	2.9%	
≥3	5	0.3%	11	1.6%	69	1.3%	9	0.9%	
Income									
<$38,000	220	14.3%	102	14.7%	714	13.8%	167	16.0%	0.15
$38,000–47,999	339	22.0%	171	24.6%	1,061	20.5%	212	20.3%	
$48,000–62,999	413	26.8%	165	23.7%	1,363	26.4%	279	26.7%	
≥$63,000	559	36.3%	248	35.7%	1,984	38.4%	380	36.3%	
Unknown	8	0.5%	9	1.3%	43	0.8%	8	0.8%	
Insurance Status									
Uninsured	22	1.4%	12	1.7%	82	1.6%	25	2.4%	<0.0001
Private	833	54.1%	286	41.2%	2,099	40.6%	486	46.4%	
Government	657	42.7%	386	55.5%	2,918	56.5%	527	50.4%	
Unknown	27	1.8%	11	1.6%	66	1.3%	9	0.9%	
Facility Type									
Comprehensive Cancer	730	47.4%	318	45.8%	2,373	45.9%	519	49.6%	0.0006
Community Cancer	207	13.5%	102	14.7%	578	11.2%	122	11.7%	
Academic/Research	385	25.0%	176	25.3%	1,545	29.9%	278	26.7%	
Other	217	14.1%	99	14.2%	669	13.0%	127	12.1%	
Histology									
Invasive Ductal (IDC)	1,211	78.7%	555	79.9%	4,387	84.9%	929	88.8%	<0.0001
Invasive Lobular (ILC)	163	10.6%	50	7.2%	205	4.0%	45	4.3%	
Mixed IDC/ILC	58	3.8%	21	3.0%	179	3.5%	33	3.2%	
Medullary	3	0.2%	2	0.3%	5	0.1%	2	0.2%	
Papillary	17	1.1%	21	3.0%	179	3.5%	8	0.8%	
Mucinous	33	2.1%	16	2.3%	62	1.2%	5	0.5%	
NOS	54	3.5%	30	4.3%	148	2.9%	24	2.3%	

	Breast Conserving Therapy N=1,539		Partial Mastectomy Alone N=695		Total Mastectomy Alone N=5,165		Total Mastectomy with Radiation N=1,046		P-value
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	
Tumor size (median, IQR, cm)	1.4	0.9–2.0	1.5	1.0–2.2	1.8	1.3–2.5	2.3	1.7–3.0	<0.0001
T Stage									
T1	1,197	77.8%	493	70.9%	3,090	59.8%	443	42.4%	<0.0001
T2	342	22.2%	202	29.1%	2,075	40.2%	603	57.7%	
N Stage									
N0	1,251	81.3%	588	84.6%	3,856	74.7%	343	32.8%	<0.0001
N1	288	18.7%	107	15.4%	1,309	25.3%	703	67.2%	
Stage									
1	1,040	67.6%	439	63.2%	2,545	49.3%	160	15.3%	<0.0001
2	499	32.4%	256	36.8%	2,620	50.7%	886	84.7%	
Grade									
Well differentiated	398	25.9%	163	23.5%	773	15.0%	95	9.1%	<0.0001
Moderately differentiated	656	42.6%	281	40.4%	2,697	52.2%	507	48.5%	
Poorly differentiated/ Anaplastic	382	24.8%	196	27.8%	1,460	28.3%	405	38.7%	
Unknown	103	6.7%	55	7.9%	235	4.6%	39	3.7%	
ER Status									
Positive	1,284	83.5%	567	81.6%	4789	92.7%	985	94.2%	<0.0001
Negative	225	14.6%	83	11.9%	223	4.3%	42	4.0%	
Unknown	29	1.9%	45	6.5%	153	3.0%	19	1.8%	
PR Status									
Positive	1,162	75.5%	499	71.8%	4,372	84.6%	892	85.3%	<0.0001
Negative	344	22.4%	150	21.6%	624	12.1%	132	12.6%	
Unknown	33	2.1%	46	6.6%	169	3.3%	22	2.1%	
HER-2 Status									
Positive	105	6.8%	46	6.6%	424	8.2%	95	9.1%	<0.0001
Negative	698	45.4%	268	38.6%	2,429	47.0%	509	48.7%	
Unknown	736	47.8%	381	54.8%	2,312	44.8%	442	42.3%	
Negative Surgical Margins Nodal Surgery	1,478	96.0%	626	90.1%	5,040	97.6%	1,004	96.0%	<0.0001
None	75	4.9%	174	25.0%	164	3.2%	21	2.0%	<0.0001
Sentinel Lymph Node Biopsy	1,093	71.0%	361	51.9%	2,500	48.4%	298	28.5%	
Axillary Dissection	354	23.0%	145	20.9%	2,472	47.9%	720	68.8%	
Unknown	17	1.1%	15	2.2%	29	0.6%	7	0.7%	
Chemotherapy[a]	572	37.2%	153	22.0%	1,565	30.3%	685	65.5%	<0.0001
Hormone therapy	1,038	67.5%	220	31.7%	3,074	59.5%	796	76.1%	<0.0001

SD, standard deviation; NOS, not otherwise specified.

[a]Chemotherapy includes immunotherapies (i.e. Trastuzumab).

Table 2.

Multivariable Model for Overall Survival of Male Breast Cancer Patients (N=8,445).

	Hazard Ratio	95% CI	P value
Surgery			
Breast Conserving Therapy	Reference		
Partial Mastectomy Alone	1.73	1.39–2.14	<0.0001
Total Mastectomy Alone	1.54	1.29–1.83	<0.0001
Total Mastectomy with Radiation	1.44	1.16–1.79	0.001
Age	1.05	1.04–1.05	<0.0001
Race			
Caucasian	Reference		
African American	1.17	1.00–1.38	0.06
Asian/Pacific Islander	0.82	0.52–1.31	0.41
Charlson-Deyo Comorbidity Index			
0	Reference		
1	1.69	1.51–1.89	<0.0001
2	2.68	2.24–3.21	<0.0001
≥3	3.53	2.67–4.68	<0.0001
Income			
<$38,000	Reference		
$38,000–47,999	1.02	0.87–1.19	0.83
$48,000–62,999	1.01	0.87–1.17	0.90
≥$63,000	0.83	0.72–0.96	0.02
Insurance Status			
Uninsured	Reference		
Private	0.69	0.44–1.09	0.11
Government	0.92	0.59–1.45	0.73
Facility Type			
Comprehensive Cancer	Reference		
Community Cancer	1.06	0.92–1.22	0.43
Academic/Research	0.77	0.69–0.87	<0.0001
Histology			
Invasive Ductal (IDC)	Reference		
Invasive Lobular (ILC)	0.86	0.68–1.08	0.18
Mixed IDC/ILC	1.05	0.79–1.39	0.73
Medullary	0.37	0.05–2.63	0.32
Papillary	1.04	0.76–1.43	0.81
Mucinous	0.78	0.48–1.27	0.32
Grade			
Well differentiated	Reference		
Moderately differentiated	1.32	1.14–1.54	0.0003
Poorly differentiated	1.66	1.41–1.96	<0.0001

	Hazard Ratio	95% CI	P value
Hormone Receptor/HER-2			
HR+/HER-2-	Reference		
HR+/HER-2+	1.20	0.94−−1.53	0.15
HR-/HER-2+	1.68	0.79–3.58	0.19
HR-/HER-2-	1.87	1.26–2.77	0.002
Stage II	0.97	0.82–1.16	0.76
T2	1.58	1.36–1.83	<0.0001
N1	1.53	1.34–1.74	<0.0001
Nodal Surgery			
None	Reference		
Sentinel Lymph Node Biopsy	0.47	0.40–0.57	<0.0001
Axillary Dissection	0.54	0.45–0.65	<0.0001
Positive Surgical Margins	1.03	0.79–1.36	0.81
Hormone therapy	0.74	0.67–0.82	<0.0001
Chemotherapy[a]	0.70	0.61–0.80	<0.0001

CI, confidence interval.

[a]Chemotherapy includes immunotherapies (i.e. Trastuzumab).