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Postmastectomy Radiation in Breast Cancer Patients with Pathologically Positive Lymph Nodes After Neoadjuvant Chemotherapy: Utilization Rates and Survival Trends

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Abstract

Background—To analyze postmastectomy radiation therapy (PMRT) utilization and its association with overall survival (OS) in breast cancer patients with pathologically positive lymph nodes after neoadjuvant chemotherapy (NAC).

Methods—Using the National Cancer Data Base (NCDB), we identified women with non-metastatic breast cancer diagnosed between 2004 and 2013 who received NAC and underwent mastectomy with macroscopic pathologically positive lymph nodes. Joinpoint regression models were used to assess temporal trends in annual PMRT utilization. Multivariable regression models identified factors associated with PMRT use. A time-dependent Cox model was used to evaluate predictors of mortality.

Results—The study included 29,270 patients, of whom 62.5% received PMRT. PMRT was markedly underutilized among all nodal subgroups, particularly among ypN2 (68.4%) and ypN3 (67.0%) patients. Hispanic patients and those with Medicaid/Medicare insurance were less likely to receive PMRT compared to non-Hispanics and patients with other insurance carriers. Adjusted 5-year OS rates were similar in ypN1 and ypN2 patients with or without PMRT but were significantly higher in ypN3 patients receiving PMRT (66% vs. 63%, $p=0.042$). In multivariable analysis, PMRT was associated with improved survival only among ypN3 patients after adjusting for patient, facility, and tumor variables (multivariable hazard ratio 0.85, 95% CI 0.74 to 0.97).

Conclusion(s)—A considerable portion of breast cancer patients with advanced residual nodal disease after NAC did not receive appropriate adjuvant radiation. There are socioeconomic

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disparities in national PMRT practice patterns. Patients with ypN3 disease may derive a survival benefit from PMRT.

Introduction

Neoadjuvant chemotherapy (NAC) is commonly used for patients with locally advanced breast cancer. The potential benefits of NAC include pathologic down-staging to facilitate breast conserving surgery, avoiding delays in systemic therapy due to post-operative wound healing complications, and upfront treatment of micrometastatic disease. [1, 2] Another possible advantage, currently under investigation in national clinical trials, is the opportunity to limit subsequent locoregional therapy, depending on the initial clinical stage and the tumor's response to treatment.

While the benefits of postmastectomy radiation therapy (PMRT) after upfront surgical resection with or without adjuvant chemotherapy are well-established [3–5], the role of PMRT after NAC is more controversial due to a lack of randomized data in this setting. A pooled analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 and B-27 studies as well as several retrospective series have attempted to address the benefits of PMRT after NAC. The available data suggests that both pre-chemotherapy clinical stage and post-chemotherapy pathologic stage predict for locoregional recurrence and should inform adjuvant locoregional management. [6–9]

In the absence of compelling randomized evidence to guide locoregional therapy, however, there is likely wide variation in national PMRT practice patterns after NAC. We analyzed the National Cancer Data Base (NCDB) to evaluate recent trends in PMRT utilization and assess the impact of PMRT on overall survival (OS) in patients with pathologically positive lymph nodes after NAC.

Patients and Methods

Data Source

The NCDB, a joint program of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society (ACS), is a registry comprising data from more than 1,500 hospitals with CoC-accredited cancer programs in the United States (US) and includes approximately 70% of all newly diagnosed cases of cancer. Data are collected by participating cancer program's registries and include patient characteristics, cancer staging, tumor histological characteristics, type of first course treatment administered, and outcomes. The NCDB has previously been described in detail. [10] This study utilized de-identified data and was granted human research exemption from the Icahn School of Medicine at Mount Sinai institutional review board. The ACS and CoC have not verified and are not responsible for the analytic or statistical methodology employed or the conclusions drawn from these data.

Patient Selection

The NCDB was queried to identify patients with invasive, non-metastatic breast cancer diagnosed between 2004 and 2013 who received NAC, underwent mastectomy, and had

macroscopic pathologically positive lymph nodes. NAC was defined by an interval from initiation of chemotherapy to surgery of 80 days and 270 days. Patients with clinical or pathologic evidence of metastatic disease were excluded, as were patients with bilateral or inflammatory breast cancer. Patients who received neoadjuvant hormonal therapy, neoadjuvant radiation therapy, and intraoperative chemotherapy were also excluded. Finally, patients who did not receive any treatment at the reporting facility were excluded, as recommended by the NCDB.

PMRT was defined as delivery of 45 Gray (Gy) or more of external beam radiation therapy to the chest wall with or without regional lymph node irradiation. Patients who received an undefined dose of radiation or those coded as receiving a dose less than 45Gy, which likely represents a palliative treatment, were included in the no PMRT group. To analyze trends in PMRT utilization, we used data from 2004 to 2013. The survival analyses were limited to data from 2004 to 2008 to ensure a minimum follow-up of 5 years from diagnosis and limit censoring bias.

Predictor Variables

We considered patient, facility, and tumor level variables in the analyses. Patient level variables included age, race, ethnicity, insurance status, median income quartile by zip code, and the Charlson-Deyo comorbidity score (truncated by the NCDB into 0, 1, and 2). Facility-level variables included the type of facility, assigned by the CoC based on annual caseload and available services, distance from patient area of residence to the reporting facility, and geographical region (corresponding to the US census divisions). Tumor specific variables included pathologic stage (as per the American Joint Committee on Cancer/Union for International Cancer Control TNM system), laterality, grade, surgical margin status, number of regional nodes examined, receipt of hormone therapy, and presence of an immediate breast reconstruction.

Missing Data

Missing data for the predictor variables outlined above were handled by multiple imputation using chained equations. [11] Among these variables, facility type and geographical region had the highest frequencies of missing data at 14.9%, followed by grade (9.3%), ethnicity (5.7%), pathologic T category (4.4%), hormonal therapy (3.9%), number of regional nodes examined (1.8%), and surgical margin status (1.8%). All other variables were missing for less than 1% of patients. Data appeared to be missing at random (MAR), meaning missing information was related only to observed variables, rather than missing completely at random (MCAR), when missing information is unrelated to observed and unobserved data. Multiple imputation has been shown to be superior with regards to analytic bias compared to alternative approaches, such as complete case analysis, when data are MAR. [12] Additionally, because 41.6% of patients were missing at least one prognostic variable, a complete case analysis would likely have resulted in a substantial loss of statistical power.

The sequential regression imputation method, referred to as chained equations, was implemented using the IVEware software system. [11] The process begins for each variable with missing values being imputed using a univariable logistic, ordinal, multinomial logistic

or predictive mean matching regression model conditional on all other variables. The process cycles iteratively through the variables containing missing values until the procedure is stable. We performed 10 repetitions of this cycle to generate 15 imputed datasets.

Statistical Analyses

The primary objectives of this study were to identify trends in PMRT utilization from 2004 to 2013 and to compare OS between patients who received PMRT and those who did not. OS was measured from the date of diagnosis to the date of death from any cause. Secondary objectives were to determine the impact of PMRT on OS in clinically relevant patient subsets. All statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC) and R Version 3.2.1 (R Project for Statistical Computing, Vienna, Austria). Hypothesis testing was two-sided and conducted at the 5% level of significance.

Trends in PMRT Utilization

We used the Joinpoint Regression Program (Version 4.2.0.2), developed by the US National Cancer Institute, to assess temporal trends in annual PMRT utilization rates for all patients combined and by age, race, and facility location. The Joinpoint software fits the simplest model to describe the utilization rate trend data, starting with a straight line (0 joinpoints) and then adding more joinpoints to determine whether multiple connecting lines better describe the data points. The software identifies the year(s) when the annual percentage change trends appear to shift upward or downward and whether these trends are statistically significant.

Patient, Facility, and Tumor Variables by Treatment Group

Patients who received PMRT and those who did not (no PMRT) were compared with respect to the patient, facility, and tumor level variables previously outlined. Continuous variables were reported as median [range], and nominal variables were reported as n (%). Multivariable log-binomial regression models were used to estimate adjusted prevalence ratios and 95% confidence intervals (95% CI) to evaluate the association between each variable and treatment status while adjusting for all other variables.

Survival Modeling

Since PMRT initiation dates varied among patients, hazard ratios (HRs) and 95% CIs were estimated with a time-dependent Cox regression model (TDCRM), adjusting for all patient, facility, and tumor level variables. In the TDCRM model, PMRT exposure was treated as a time-dependent variable with a patient coded as having received no PMRT before radiation therapy initiation, then recoded to PMRT on the date when radiation therapy was initiated. Among patients who never received radiation, coding as no PMRT was applied throughout. By using this method to address the immortal time bias, which is introduced by the variation in timing of PMRT initiation, the effect estimate for PMRT is less prone to overestimation. [13]

In addition, a landmark analysis was performed that only included patients who were alive 12 months following diagnosis. The conventional Cox proportional hazards (CPH) model was used to estimate HRs and CIs for the landmark dataset. This model was used to generate

2- and 5-year OS estimates and corresponding confidence intervals. The landmark analysis served as a sensitivity analysis to the time dependent cox regression modeling approach, both of which were used to address the issue of immortal time bias.

To account for the multiple imputation of missing data, the Cox regression (for time-dependent and landmark analyses) was performed on each of the 15 imputed datasets, and estimates of corresponding HRs and CIs were then appropriately combined using the MIANALYZE procedure in SAS. [14, 15] Finally, we assessed heterogeneity of treatment effects by nodal stage with subgroup analyses in both the time-dependent and landmark models.

Results

We identified 29,270 patients who fulfilled the study inclusion criteria, of whom 18,284 (62.5%) received PMRT (eFigure 1). The median age of the cohort was 51 years (range, 19–90 years). Most patients were White (77.6%) and had Charlson-Deyo co-morbidity scores of 0–1 (98.3%). Fifty-four percent of patients had ypN1 disease, 31.0% had ypN2 disease, and 14.7% had ypN3 disease. The PMRT utilization rates among ypN1, ypN2, and ypN3 patients were 57.8%, 68.4%, and 67.0%, respectively. Among patients who received PMRT, 72.5% received regional nodal irradiation (RNI).

Table 1 shows baseline patient, facility, and tumor characteristics by PMRT utilization. Multiple factors independently associated with PMRT use were identified on multivariable analysis. Patients who received PMRT were more likely to be non-Hispanic and have lower Charlson-Deyo co-morbidity scores (0 vs. 2). Patients with non-Medicaid/Medicare insurance, those who lived closer to the reporting facility (< 50 vs. >50 miles), patients treated at a comprehensive cancer or academic facility compared to those treated in a community practice, and those diagnosed in year 2008 or later compared to year 2004 were also more likely to receive PMRT. Tumor characteristics associated with increased PMRT use included increasing pathologic N category and greater number of lymph nodes examined. Patients who received hormone therapy were more likely to receive PMRT, while patients with an immediate breast reconstruction were less likely to receive PMRT. Age (< 50 vs. >50), race, median income quartile, grade, laterality, and pathologic T category were not significantly associated with PMRT use.

Overall PMRT utilization rates increased over the study period, from 54.4% in 2004 to 63.3% in 2013. eTable 1 summarizes patterns in PMRT utilization by annual percent change (APC) for the overall cohort and by age, race, and facility location. For the overall cohort, there was a significant increase in PMRT utilization from 2004 to 2011 (APC 3.21, 95% CI 2.55 to 3.86). A similar trend was seen for patients age <50 years (APC 3.84, 95% CI 3.17 to 4.50), White patients (APC 3.02, 95% CI 2.31 to 3.74), and Black patients (APC 4.12, 95% CI 2.54 to 5.73).

After excluding patients diagnosed after 2008 and those with incomplete follow-up data, a total of 11,626 patients remained in the cohort for the survival analyses (eFigure 1). Multiple independent predictors of mortality were identified in the TDCRM model (Table 2). Older

age, Black race, higher Charlson-Deyo score, higher grade disease, positive surgical margins, increasing pathologic T category, and increasing pathologic N category were associated with decreased survival. Patients with private insurance or managed care and those with higher median income quartile had improved survival, as did patients who received hormone therapy, patients with greater number of lymph nodes examined, and those with an immediate breast reconstruction.

The impact of PMRT on OS was analyzed in the TDCRM model and the CPH model using a 12 month landmark from diagnosis for all patients as well as the ypN1, ypN2, and ypN3 subsets (Table 3). In both models, PMRT was not associated with improved survival for all patients, ypN1 patients, and ypN2 patients on multivariable analysis. For ypN3 patients, PMRT was associated with improved survival in both the landmark CPH and TDCRM models (multivariable HR 0.870, 95% CI 0.760 to 0.995 and multivariable HR 0.848, 95% CI 0.744 to 0.967, respectively).

There were 1,422 patients who did not have a radiation dose coded, 118 patients who were coded as receiving an unknown dose of radiation, and 627 patients coded as receiving <45Gy. Together, these patients account for 7.4% of the cohort. We restricted our PMRT group to patients receiving 45Gy or more to the chest wall +/- regional LNs to exclude patients who may have received palliative radiation therapy. By using this definition, 2% of patients receiving less than 45Gy were included in the no PMRT group. Additionally, another 5% of patients were coded as receiving radiation but without a specified dose, and they were also included in the no PMRT group. Because this categorization may introduce a bias towards the null, we re-ran the TDCRM model in a sensitivity analysis including these patients in the PMRT group, and the results were unchanged (eTable 2).

Figure 1 shows the unadjusted Kaplan-Meier estimates of OS for all patients stratified by PMRT receipt using the CPH landmark dataset, and Figure 2 shows the adjusted HRs for PMRT among all patients and the ypN1, ypN2, and ypN3 subsets using the TDCRM model. PMRT was again associated with improved survival among ypN3 patients only (HR 0.85, 95% confidence limit 0.74 to 0.97). After adjusting for patient, facility, and tumor variables (Table 4), 5-year OS rates were similar in the PMRT and no PMRT groups for all patients (80 vs. 80%, $p=0.963$), ypN1 patients (77 vs. 78%, $p=0.377$), and ypN2 patients (76 vs. 77%, $p=0.220$). The adjusted 5-year OS rate was significantly higher in the PMRT group for ypN3 patients (66 vs. 63%, $p=0.042$).

Discussion

In this large national cancer registry-based retrospective analysis, we found that the overall PMRT utilization rates for patients who receive NAC and have pathologically positive nodes at mastectomy increased from 54.4% in 2004 to 63.3% in 2013, with a significant increase in annual percent change from 2004 to 2011 ($p<0.001$). Multiple factors including non-Hispanic ethnicity, lower Charlson-Deyo score, non-Medicaid/Medicare insurance, treatment at a comprehensive care or academic facility, later year of diagnosis, and absence of an immediate breast reconstruction were associated with increased PMRT utilization. While patients with ypN2 and ypN3 disease were more likely to receive PMRT than patients

with ypN1 disease, the PMRT utilization rates within both subgroups were only 68.4% and 67.0%, respectively.

In survival analyses, younger age, non-Black race, lower Charlson-Deyo score, private insurance, higher median income quartile, receipt of hormone therapy, lower grade disease, negative surgical margins, lower pathologic T and N categories, and greater number of lymph nodes examined were independently associated with improved survival. After adjustment for other covariates, PMRT was associated with improved survival among ypN3 patients in both the time-dependent and landmark analyses.

Our data provides important insight into the national PMRT practice patterns within this patient population over the past decade. This is an area of increasing clinical relevance, as recently published data demonstrates that the use of preoperative systemic therapy in breast cancer is increasing. [16] We observed statistically significant variations in PMRT utilization patterns in breast cancer patients treated with NAC depending on co-morbidity score and stage of disease. More notably, multiple socioeconomic factors including ethnicity and insurance type were independently associated with receipt of PMRT following NAC. Previous studies using national cancer registry data showed similar associations between socioeconomic factors and different types of breast cancer treatment modalities, highlighting the importance of standardized care not only in the setting of NAC, but in all aspects of breast cancer management. [17–19]

While the benefits of PMRT in the setting of adjuvant chemotherapy have been demonstrated in multiple randomized trials as well as the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis, [3–5] data from ongoing NAC trials has yet to mature. [20, 21] It is unclear whether the indications for PMRT in the absence of NAC may be extrapolated to this setting, as NAC can lead to significant tumor down-staging. [2] Without strong evidence to guide PMRT decision-making after NAC, current National Comprehensive Cancer Network (NCCN) guidelines recommend using pre-chemotherapy tumor characteristics to determine adjuvant locoregional management. [22]

In contrast, the available retrospective data suggests that post-chemotherapy pathologic nodal stage can predict for locoregional recurrence (LRR) and therefore should be considered in clinical decision-making for PMRT. For example, Buchholz et al. found that pathologic involvement of four or more lymph nodes after NAC was independently associated with LRR (HR 2.7, $p=0.008$). [7] This observation was validated by Garg et al. in a similar analysis of patients clinically presenting with early-stage disease who had large residual nodal disease burden. [23] Another series by Huang et al. showed a significant improvement in 10-year LRR with the addition of PMRT in patients with at least 4 involved lymph nodes (59 vs. 16%, $p<0.0001$). [8] Despite the available evidence supporting PMRT use in patients with high nodal disease burden after NAC, the present analysis demonstrated that many ypN2 and ypN3 patients treated over the past decade did not receive PMRT.

Published data on the benefits of PMRT in patients with 1–3 pathologically positive lymph nodes after NAC is less clear. The above series reported LRR rates ranging between 10 and 20% in the absence of PMRT, [7, 8] which was corroborated by the pooled analysis from the

NSABP B-18 and B-27 trials. [6] However, PMRT has not been shown to significantly improve local control in these patients. [8] Conflicting results were seen in a recent NCDB analysis by Rusthoven et al. of patients presenting with clinical N1 disease, which showed improved OS with PMRT in all pathologic nodal subgroups (ypN0, ypN1, and ypN2–3, all $p < 0.05$). The discrepancies between this analysis and ours may be attributed to the varying inclusion criteria and statistical methodologies employed. Rusthoven et al. analyzed patients with upfront clinical N1 disease, whereas only 49% of patients had upfront clinical N1 disease in the present analysis. About 15% of patients were clinically node negative, 20% had clinical N2/N3 disease, and clinical N stage was unknown for 16% of patients. Because it can be challenging to ascertain an accurate upfront clinical stage, we believe our inclusion criteria may address a more practical clinical question. We also used a more rigorous statistical approach to address missing data with the multiple imputation method (compared to analyzing unknown values categorically). Finally, while Rusthoven et al. used the propensity score matching method to analyze the relationship between PMRT and OS, we did not perform this analysis. Studies have shown that multivariable logistic regression modeling is the technique of choice when there are at least 8 events per confounder. The multivariable logistic regression empirical coverage probability increases as the number of events per confounder increases, while the propensity score empirical coverage probability decreases after 8 or more events per confounder. [24, 25] With 4,415 deaths and 18 confounders, we were well over 8 events per confounder. Therefore, multivariable logistic regression was the optimal method for analyzing this database.

The optimal adjuvant locoregional management of patients with 1–3 positive lymph nodes remains an area of controversy, both in the setting of neoadjuvant chemotherapy and adjuvant chemotherapy. The lower national rate of PMRT utilization within the ypN1 subset observed in this analysis may be a reflection of this ongoing controversy. There are likely certain subsets within the 1–3 lymph node positive population that are at higher risk of LRR and thus may benefit from PMRT. There is increasing interest in looking at tumor biology and response to NAC to help identify these patients. [26] Older series even suggest that patients with less extensive locoregional disease and favorable tumor biology may derive a larger benefit from PMRT in the setting of adjuvant chemotherapy. [27, 28] In the present analysis, it is possible that a survival benefit with PMRT was not seen in the ypN1 and ypN2 subsets because of advances in surgical techniques and systemic therapies in the modern era. Longer follow-up may also be needed to observe a benefit in these lower-risk subgroups.

Our study has several limitations to address. The NCDB does not contain all relevant treatment information that should be considered, such as chemotherapy agents administered or the specific nodal regions targeted with radiation. Additionally, the only long-term endpoint available is overall survival, which is further limited in this analysis by the relatively short follow-up period for breast cancer. Another endpoint of particular interest to this analysis is locoregional recurrence rate. Finally, limitations inherent to national cancer registry data include both patient selection and institutional reporting bias. We also cannot account for any errors in reporting or coding. While we attempted to address the issue of missing data with multiple imputation analysis, this also assumes that the incomplete data are missing at random. However, using the NCDB, we were able to analyze a very large and

homogeneous patient cohort. This is noteworthy, as our study corroborates the findings from previous smaller series.

In conclusion, we report PMRT treatment patterns and the impact of PMRT on OS in patients treated with NAC and mastectomy with residual pathologic nodal disease. We found that PMRT was underutilized in patients with advanced pathologic ypN3 nodal disease who may derive a survival benefit from treatment. We also identified multiple independent socioeconomic disparities in national PMRT utilization.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Kaplan-Meier survival curves for all patients stratified by PMRT receipt using the 12 month landmark dataset. Abbreviations: PMRT, postmastectomy radiation.

Figure 2.

Forest plot of the impact of PMRT on OS in all patients and each nodal subgroup.

Abbreviations: PMRT, postmastectomy radiation; OS, overall survival; CL, confidence limit; HR, hazard ratio; LCL, lower confidence limit; UCL, upper confidence limit.

Table 1
Baseline patient, facility, and disease characteristics by PMRT receipt and factors effecting treatment selection

Characteristic	No PMRT (N = 10,986) No. (%) ^a	PMRT (N = 18,284) No. (%)	Multivariable Prevalence Ratio [†]	95% CI	P
Age, years					
50	5,176 (36.8)	8,873 (63.2)		Reference	
>50	5,810 (38.2)	9,411 (61.8)	0.994	0.979–1.009	0.474
Median (range)	51 [20–90]	51 [19–90]			
Race					
Missing	120 (41.0)	173 (59.0)			
White	8,382 (36.9)	14,343 (63.1)		Reference	
Black	1,997(40.0)	2,996 (60.0)	1.001	0.980–1.023	0.909
Other	487 (38.7)	772 (61.3)	0.985	0.948–1.024	0.446
Hispanic ethnicity					
Missing	647 (38.8)	1,021 (61.2)			
No	9,362 (36.9)	15,975 (63.1)		Reference	
Yes	977 (43.1)	1,288 (56.9)	0.959	0.930–0.989	0.007
Charlson-Deyo score					
0	9,620 (37.2)	16,242 (62.8)		Reference	
1	1,131 (39.0)	1,771 (61.0)	0.984	0.961–1.008	0.198
2	235 (46.4)	271 (53.6)	0.923	0.868–0.982	0.011
Primary payer					
Missing	205 (46.6)	235 (53.4)			
Not insured	501 (37.3)	842 (62.7)		Reference	
Private insurance/Managed care	6,880 (36.2)	12,106 (63.8)	1.003	0.969–1.038	0.882
Medicaid/Medicare	3,276 (40.1)	4,887 (59.9)	0.962	0.929–0.997	0.034
Other government insurance	124 (36.7)	214 (63.3)	0.954	0.883–1.031	0.230
Median income quartile by zip code					
Missing	173 (44.6)	215 (55.4)			

Characteristic	No PMRT (N = 10,986) No. (%)	PMRT (N = 18,284) No. (%)	Multivariable Prevalence Ratio [†]	95% CI	P
<\$38,000	2,052 (40.0)	3,079 (60.0)	Reference	Reference	
\$38,000–\$47,999	2,309 (37.0)	3,927 (63.0)	1.008	0.984–1.032	0.522
\$48,000–\$62,999	2,849 (37.4)	4,762 (62.6)	0.989	0.966–1.013	0.365
\$63,000+	3,603 (36.4)	6,301 (63.6)	0.987	0.964–1.011	0.280
Distance from the reporting facility, miles					
Missing	164 (44.9)	201 (55.1)			
50	9,709 (36.5)	16,887 (63.5)		Reference	
>50	1,113 (48.2)	1,196 (51.8)	0.903	0.876–0.931	<0.001
Median (range)	10.4 [0–3800]	9.1 [0–3692]			
Facility type					
Missing	1,636 (37.5)	2,728 (62.5)		Reference	
Community	906 (38.8)	1,428 (61.2)			
Comprehensive	4,331 (37.4)	7,257 (62.6)	1.027	1.000–1.054	0.050
Academic	4,102 (37.5)	6,836 (62.5)	1.031	1.005–1.059	0.022
Other	11 (23.9)	35 (76.1)	1.102	0.905–1.342	0.332
Facility location					
Missing	1,636 (37.5)	2,728 (62.5)		Reference	
Northeast	1,595 (35.2)	2,933 (64.8)			
South	4,426 (42.6)	5,972 (57.4)	0.955	0.935–0.976	0.001
Central	1,892 (30.5)	4,322 (69.6)	1.032	1.010–1.055	0.004
West	1,437 (38.2)	2,329 (61.8)	0.973	0.949–0.998	0.032
Year of diagnosis					
2004	888 (45.6)	1,058 (54.4)		Reference	
2005	856 (43.0)	1,137 (57.0)	1.018	0.971–1.066	0.466
2006	945 (42.7)	1,269 (57.3)	1.027	0.982–1.073	0.246
2007	1,116 (41.8)	1,556 (58.2)	1.029	0.986–1.074	0.192
2008	1,114 (38.9)	1,753 (61.1)	1.054	1.011–1.099	0.013
2009	1,161 (37.3)	1,952 (62.7)	1.055	1.012–1.099	0.011
2010	1,144 (34.6)	2,164 (65.4)	1.077	1.036–1.121	<0.001

Characteristic	No PMRT (N = 10,986) No. (%)	PMRT (N = 18,284) No. (%)	Multivariable Prevalence Ratio [†]	95% CI	P
2011	1,176 (32.2)	2,476 (67.8)	1.094	1.053–1.137	<0.001
2012	1,197 (32.2)	2,522 (67.8)	1.104	1.062–1.148	<0.001
2013	1,389 (36.7)	2,397 (63.3)	1.086	1.044–1.130	<0.001
Grade					
Missing	1,029 (37.8)	1,693 (62.2)			
Well differentiated	743 (36.8)	1,279 (63.3)		Reference	
Moderately differentiated	3,670 (34.7)	6,893 (65.3)	1.022	0.994–1.050	0.133
Poorly differentiated/Undifferentiated/Anaplastic	5,544 (39.7)	8,419 (60.3)	1.028	0.999–1.057	0.059
Surgical Margins					
Missing	237 (44.6)	295 (55.4)			
Negative	9,871 (37.2)	16,690 (62.8)		Reference	
Positive	878 (40.3)	1,299 (59.7)	0.964	0.936–0.992	0.013
Laterality					
Missing	8 (27.6)	21 (72.4)			
Right	5,403 (37.5)	8,999 (62.5)		Reference	
Left	5,575 (37.6)	9,264 (62.4)	1.001	0.987–1.016	0.848
TNM pathologic T category					
Missing	537 (41.4)	761 (58.6)			
ypT0-Tis	566 (40.0)	850 (60.0)		Reference	
ypT1-T2	6,990 (37.7)	11,571 (62.3)	0.999	0.963–1.037	0.956
ypT3-T4	2,893 (36.2)	5,102 (63.8)	1.016	0.977–1.056	0.440
TNM pathologic N category					
ypN1	6,692 (42.1)	9,184 (57.9)		Reference	
ypN2	2,872 (31.6)	6,214 (68.4)	1.090	1.072–1.108	<0.001
ypN3	1,422 (33.0)	2,886 (67.0)	1.084	1.061–1.109	<0.001
Regional nodes examined					
Missing	222 (43.1)	293 (56.9)		Reference	
<10	4,162 (39.5)	6,363 (60.5)			

Characteristic	No PMRT (N = 10,986) No. (%) [*]	PMRT (N = 18,284) No. (%)	Multivariable Prevalence Ratio [†]	95% CI	P
10–50	6,589 (36.2)	11,610 (63.8)	1.018	1.002–1.034	0.030
>50	13 (41.9)	18 (58.1)	0.918	0.701–1.202	0.533
Median (range)	13 [0–68]	13 [0–90]			
Hormone therapy					
Missing	682 (60.2)	451 (39.8)			
No	5,524 (48.6)	5,842 (51.4)		Reference	
Yes	4,780 (28.5)	11,991 (71.5)	1.179	1.158–1.199	<0.001
Immediate breast reconstruction					
No	8,124 (37.2)	13,717 (62.8)		Reference	
Yes	2,862 (38.5)	4,567 (61.5)	0.967	0.949–0.985	<0.001
Months to chemotherapy from diagnosis					
Median (range)	1.02 [0–30.28]	0.95 [0–24.92]			
Months to mastectomy from diagnosis					
Median (range)	5.92 [2.63–33.33]	5.88 [2.70–29.36]			

Abbreviations: PMRT, postmastectomy radiation therapy; CI, confidence interval

^{*} Row percentages may not sum to 100% as a result of rounding.

[†] Prevalence Ratios (95% Confidence Intervals and P-values) computed from multivariable logistic regression model adjusted for all covariates shown in table.

Table 2

Association between baseline characteristics and overall mortality (N=11,626) with multiple imputation

Characteristic	Multivariable HR [†]	95% CI	P
Age, years			
50		Reference	
>50	1.166	1.082–1.256	<0.001
Race			
White		Reference	
Black	1.284	1.183–1.393	<0.001
Other	0.811	0.677–0.973	0.024
Hispanic ethnicity			
No		Reference	
Yes	0.903	0.797–1.023	0.108
Charlson-Deyo score			
0		Reference	
1	1.189	1.078–1.310	<0.001
2	1.501	1.205–1.870	<0.001
Primary payer			
Not insured		Reference	
Private insurance/Managed care	0.800	0.696–0.920	0.002
Medicaid/Medicare	1.051	0.911–1.213	0.495
Other government insurance	1.009	0.741–1.374	0.954
Median income quartile by zip code			
<\$38,000		Reference	
\$38,000–\$47,999	0.966	0.865–1.078	0.536
\$48,000–\$62,999	0.865	0.775–0.965	0.010
\$63,000+	0.813	0.711–0.929	0.003
Distance from the reporting facility, miles			
50		Reference	
>50	0.869	0.770–0.979	0.022
Facility type			
Community		Reference	
Comprehensive	0.970	0.857–1.098	0.624
Academic	0.882	0.773–1.007	0.063
Other	0.720	0.193–2.689	0.625
Facility location			
Northeast		Reference	
South	0.961	0.875–1.057	0.412

Characteristic	Multivariable HR [†]	95% CI	P
Central	1.011	0.913–1.119	0.840
West	0.905	0.801–1.023	0.110
Year of diagnosis			
2004		Reference	
2005	0.930	0.845–1.024	0.138
2006	0.905	0.821–0.998	0.046
2007	1.010	0.919–1.110	0.830
2008	1.051	0.953–1.157	0.319
Hormone therapy			
No		Reference	
Yes	0.478	0.447–0.511	<0.001
Grade			
Well differentiated		Reference	
Moderately differentiated	1.291	1.104–1.510	0.001
Poorly differentiated/Undifferentiated/Anaplastic	1.929	1.655–2.248	<0.001
Surgical margins			
Negative		Reference	
Positive	1.294	1.171–1.429	<0.001
Laterality			
Right		Reference	
Left	1.006	0.948–1.067	0.855
TNM pathologic T category			
ypT0-Tis		Reference	
ypT1-T2	1.415	1.155–1.735	<0.001
ypT3-T4	2.056	1.671–2.530	<0.001
TNM pathologic N category			
ypN1		Reference	
ypN2	1.696	1.582–1.816	<0.001
ypN3	2.433	2.241–2.642	<0.001
Regional nodes examined			
<10		Reference	
10–50	0.850	0.796–0.908	<0.001
>50	0.821	0.388–1.738	0.606
Immediate breast reconstruction			
No		Reference	
Yes	0.877	0.801–0.962	0.005

Abbreviations: HR, hazard ratio; CI, confidence interval.

[†]Hazard Ratios (95% Confidence Intervals and P-values) computed from multivariable logistic regression model adjusted for all covariates shown in table.

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Table 3

Univariable and multivariable hazard ratios for overall mortality; PMRT vs. no PMRT (N=11,626) with multiple imputation

	Univariable HR	95% CI	P	Multivariable HR [†]	95% CI	P
Overall						
CPH model with 12 month landmark N=11,254 (6,284 vs. 4,970)	0.978	0.920–1.040	0.4838	1.002	0.940–1.067	0.9626
TDCRM Model N=11,626 (6,726 vs. 4,900)	0.973	0.917–1.034	0.3773	0.996	0.936–1.06	0.9018
ypN1						
CPH model with 12 month landmark N=5,921 (2,914 vs. 3,007)	0.984	0.894–1.084	0.7457	1.046	0.946–1.157	0.3772
TDCRM Model N=6,059 (3,196 vs. 2,863)	1.003	0.912–1.103	0.9531	1.064	0.964–1.175	0.2143
ypN2						
CPH model with 12 month landmark N=3,575 (2,241 vs. 1,334)	0.921	0.831–1.021	0.1186	1.069	0.961–1.190	0.2195
TDCRM Model N=3,710 (2,396 vs. 1,314)	0.883	0.798–0.977	0.0161	1.042	0.938–1.158	0.4377
ypN3						
CPH model with 12 month landmark N=1,758 (1,036 vs. 722)	0.759	0.669–0.862	<0.0001	0.870	0.760–0.995	0.0419
TDCRM Model N=1,857 (1,134 vs. 723)	0.739	0.653–0.836	<0.0001	0.848	0.744–0.967	0.0137

Abbreviations: PMRT, postmastectomy radiation therapy; CPH, Cox proportional hazards; TDCRM, time-dependent Cox regression model; HR, hazard ratio; CI, confidence interval.

[†] Multivariable hazard ratio adjusted for age, race, ethnicity, Charlson-Deyo score, primary payer, median income quartile by zip code, distance from reporting facility, facility type, facility location, year of diagnosis, hormone therapy, grade, surgical margins, laterality, TNM pathologic T category, TNM pathologic N category, regional nodes examined, and immediate breast reconstruction.

Table 4

Adjusted 2 and 5 year overall survival estimates by nodal stage using the CPH model with 12 month landmark

	% Deaths/Total	Adjusted* 2-year OS 95% CI	Adjusted* 5-year OS 95% CI
Overall			
PMRT	63% 3,958/6,284	91% [88%–94%]	80% [74%–86%]
No PMRT	63% 3,146/4,970	91% [88%–94%]	80% [74%–86%]
ypN1			
PMRT	72% 2,163/3,007	90% [85%–95%]	77% [67%–87%]
No PMRT	72% 2,105/2,914	90% [85%–95%]	78% [68%–88%]
ypN2			
PMRT	58% 1,299/2,241	88% [82%–95%]	76% [65%–89%]
No PMRT	56% 749/1,334	89% [83%–95%]	77% [66%–89%]
ypN3			
PMRT	48% 496/1,036	84% [72%–98%]	66% [47%–96%]
No PMRT	40% 292/722	82% [69%–98%]	63% [41%–95%]

Abbreviations: CPH, Cox proportional hazards; PMRT, postmastectomy radiation therapy; OS, overall survival; CI, confidence interval.

* Estimates for patient with the following covariate risk factors: 50 years, White, non-Hispanic, uninsured, income <\$38,000, 50 miles from reporting facility, community facility, northeast location, diagnosed in 2004, no hormone therapy, well differentiated grade, negative surgical margins, right laterality, 0 T category, <10 regional nodes examined.