Original Article

Postmastectomy Radiation Therapy for Intermediate-Risk Breast Cancer Patients With 0-3 Positive Axillary Lymph Nodes: Emulating the SUPREMO Trial Using Real-World Data

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Abstract

Using real-world data from the National Cancer Database, we emulate the Selective Use of Postoperative Radiotherapy After Mastectomy (SUPREMO) phase III clinical trial to assess the impact of postmastectomy radiation therapy (PMRT) on overall survival (OS) among patients with intermediate-risk breast cancer. Among 49,335 patients who underwent mastectomy, 6882 (13.9%) received PMRT. There was no significant difference in OS between those who did and did not receive PMRT (HR: 0.98, 95% CI, 0.92-1.04). However, PMRT was associated with improved survival among the patient subgroup who had stage T3N0 breast cancer (HR: 0.72, 95% CI, 0.58-0.89).

Purpose: To emulate the Selective Use of Postoperative Radiotherapy After Mastectomy (SUPREMO) phase III clinical trial using real-world data to assess the impact of postmastectomy radiation therapy (PMRT) on overall survival (OS) among patients with intermediate-risk breast cancer. **Patients and Methods:** Using the National Cancer Database, women diagnosed between 2006 and 2013 with intermediate-risk breast cancer (defined as pT1-2N1; pT3N0; or pT2N0 and grade III or with lymphovascular invasion) and 0-3 positive axillary lymph nodes, who underwent total mastectomy, were identified as being in accordance with the SUPREMO trial protocol and included in this study. Multivariable logistic regression, Cox proportional hazards regression, and stabilized inverse probability of treatment weighting were used to explore the relationship between PMRT and OS. The effects of PMRT within subgroups were explored using multivariable interaction models. **Results:** In total, 49335 patients were included in the study, with 6882 (13.9%) receiving PMRT. Patients with stage T3N0 cancer, 1-3 positive axillary lymph nodes, or positive surgical margins were more likely to receive PMRT. Overall, PMRT was associated with no significant improvement in OS (HR: 0.98, 95% CI, 0.92-1.04). However, improved survival was observed among women with stage T3N0 cancer who received PMRT (HR: 0.72, 95% CI, 0.58-0.89). **Conclusion:** Although PMRT may not be associated with improved OS among all intermediate-risk breast cancer patients with 0-3 positive axillary lymph nodes, the subgroup of patients with stage T3N0 cancer seemed to benefit from PMRT. The study's retrospective nature introduces some uncertainty, but preliminary findings of the SUPREMO trial support these results.

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Keywords: Chest wall irradiation, Clinical trial emulation, Mastectomy, Overall survival, Postmastectomy radiation therapy

Introduction

Although it is widely accepted that breast cancer patients with 4 or more positive axillary lymph nodes should receive postmastectomy radiation therapy (PMRT),[1-3] the role of PMRT for patients with 1-3 positive axillary lymph nodes remains unclear. The results of the Early Breast Cancer Trialists' Collaborative Group's (EBCTCG) meta-analysis, which followed 8135 women diagnosed between 1964 and 1986 in 22 trials of postmastectomy chest wall

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and regional lymph node radiation therapy, suggested that PMRT was associated with reduced rates of locoregional recurrence, overall recurrence, and breast cancer mortality among women with 1-3 positive nodes.[4] Current National Comprehensive Cancer Network (NCCN) guidelines strongly recommend considering PMRT in patients with 1-3 positive axillary lymph nodes,[1] and the American Society of Clinical Oncology recently updated their guidelines to suggest that PMRT be used in these patients.[5] However, the international consensus at the 2019 St. Gallen conference was that PMRT may not benefit patients with 1-3 positive axillary lymph nodes.[6] Nevertheless, PMRT usage among these patients has increased over time.[7]

Similarly, it remains unclear as to whether PMRT benefits patients with intermediate-risk T3N0M0 breast cancer, with some studies suggesting that PMRT is associated with improved survival among this patient subgroup,[8] and others indicating no benefit[9,10] or improved survival only among those with additional high-risk features, such as lymphovascular invasion (LVI) or positive surgical margins.[11] The current NCCN guidelines recommend PMRT be used in T3N0 patients, especially when other high-risk features are present.[1]

The results of the Selective Use of Postoperative Radiotherapy After Mastectomy (SUPREMO) Medical Research Council (MRC) phase III clinical trial, which is now complete pending publication of the overall survival (OS) results, may help to guide these recommendations.[12] Preliminary results of the SUPREMO trial, presented at the San Antonio Breast Cancer Symposium (SABCS) in 2024, suggest that postmastectomy chest wall irradiation has no impact on OS among patients with 1-3 positive lymph nodes or among those with 0 positive lymph nodes and other high-risk features, when compared to those treated with mastectomy alone.[13]

The SUPREMO trial aims to assess whether PMRT improves survival outcomes among intermediate-risk breast cancer patients with 0-3 positive axillary lymph nodes. However, due to the strict inclusion/exclusion criteria and nature of clinical trials, the results may be limited in their generalizability to the larger population of interest or in their ability to identify risk characteristics among subgroups. Clinical trial emulation, in which real world data (RWD) from observational databases are used to mimic a randomized controlled trial (RCT), is 1 tool that can be used to supplement clinical trial results, with the potential to address these challenges.[14,15] A rigorous study design is essential for conducting observational studies in order to reduce bias and account for potential confounding. This requires careful construction of the study's inclusion/exclusion criteria and the application of advanced statistical techniques to generate pseudo populations with balanced covariate distributions between the treatment and control groups. Clinical trial emulation can be used prospectively to aid in the task of cohort specification during study design and provide insight into which patient subgroups might benefit from a particular treatment,[16] or they can be used retrospectively to construct external comparator cohorts for comparative efficacy analyses[17] or examine the concordance between RCTs and observational studies.[14]

Here, we aim to do the latter—to demonstrate that observational data can be used to successfully emulate and augment clinical trial results. We use the National Cancer Database (NCDB) to mimic the SUPREMO trial assessing the effects of PMRT in intermediate-risk breast cancer patients, defined as pT1-2N1; pT3N0; or pT2N0 and grade III or with LVI, with 0-3 positive axillary lymph nodes. Our approach also enables the identification of subgroups who may benefit from PMRT.

Patients and Methods

Data Source

The emulated trial cohort was constructed using the NCDB 2020 Participant User File (PUF) for Breast Cancer. The NCDB is a hospital-based registry system that includes more than 70% of all diagnosed cancers in the United States.[18,19] The Breast Cancer PUF contains data for patients diagnosed with or treated for breast cancer at Commission on Cancer (CoC)-accredited facilities between 2004 and 2020.[20] This database is characterized by a high level of completeness (accounting for 73.7% of cancer cases nationally), comparability (by implementing uniform standards for data collection), timeliness (hospital compliance with timely data submission is reported as 92.7%), and data validity (compliance with CoC standards is reported as > 90%).[21]

Inclusion and Exclusion Criteria

Patients diagnosed with breast cancer between 2004 and 2020 were queried. To mimic the SUPREMO trial, female patients diagnosed between 2006 and 2013 with pathologic stage T1-2N1M0 or T2N0M0, grade III histology unilateral breast cancer were included. This time frame was selected to match the enrollment period for the SUPREMO trial and allowed for longer follow-up. Patients diagnosed with T3N0M0 cancer between 2010 and 2013 were also included to match the amendment to the trial protocol that occurred in 2010.[12] Only patients who underwent total mastectomies and did not receive neoadjuvant radiation therapy or palliative care were included. Patients were further restricted to those with 0-3 positive axillary lymph nodes and whose breast cancer diagnosis was their only primary cancer or the first in the sequence. Only patients who received no PMRT or PMRT within 12 weeks of surgery (total dose: 40-70 Gy) were included.

Patients who received no adjuvant chemotherapy or adjuvant chemotherapy ending within 6 weeks of the start of PMRT (when PMRT was also given) were included. Patients who received neoadjuvant systemic therapy were excluded if diagnosed in 2006-2009 but included if diagnosed in 2010-2013 to reflect the amendment to the SUPREMO trial protocol made in 2010.[12] Cases where PMRT was not administered because it was not recommended by the treating physician were also excluded to mimic randomization.[18] Patients were further restricted to those receiving all treatment at the reporting facility, and only complete cases were used for analyses. In total, 49335 patients were included in the study (Figure 1).

Outcome

The primary outcome was OS, which was defined as the time from the date of mastectomy to the date of all-cause death or last contact, as reported in the NCDB.

Covariates

Facility and patient demographic variables included age, race/ethnicity, facility location by region, insurance type, and

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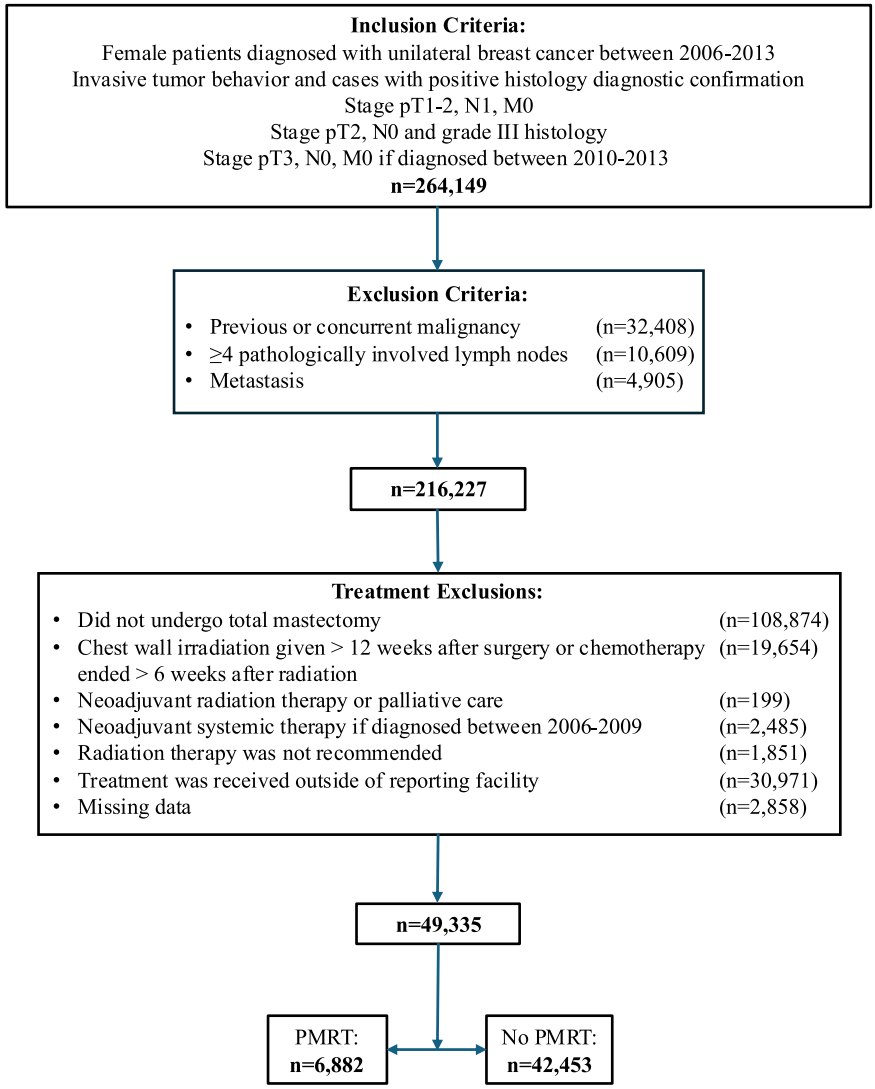
Figure 1 Inclusion and exclusion criteria applied to obtain the study cohort. Criteria was chosen to match that of the SUPREMO phase III clinical trial protocol. Bolded numbers represent the number of patients remaining after the prior set of exclusions. Numbers in parentheses represent the number of patients excluded in each step. PMRT = postmastectomy radiation therapy.



median income quartiles and educational attainment quartiles (measured as the percent without a high school degree) by zip code for 2008-2012 as surrogates for socioeconomic status. Patient clinical factors included Charlson-Deyo comorbidity score, T stage, adjuvant chemotherapy, adjuvant hormone therapy, neoadjuvant systemic therapy, secondary cancer occurrence, grade, LVI, number of positive axillary lymph nodes (0, 1-3), number of lymph nodes examined (1-3, 4-7, 8+), positive surgical margins, breast cancer subtype (Luminal A, Luminal B, HER2-enriched, triple negative, and unknown),[18,22] and time between date of diagnosis and date of surgery (days). Because of the sufficiently large sample size and use of a hospital-based registry that is subject to unmeasured confounders, we wanted to be inclusive of all possible confounders given the broad endpoint of overall survival.

Statistical Analysis

Descriptive statistics and univariate analyses (chi-square and analysis of variance (ANOVA)) were generated to capture the distribution of covariates. To assess covariate associations with PMRT usage, a multivariable logistic regression model was fitted to the data with binarized PMRT receipt as the outcome of interest. All model covariates described previously were included in the model, and a backward selection criterion of 0.05 was used. The fitted model was used to generate adjusted odds ratios (aORs) with 95% confidence intervals (CIs).

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Table 1 Baseline Characteristics by Treatment Cohort

			PMRT		
Covariate	**Level**	**Total** $N = 49,335$ (100%)	**No** $N = 42,453$ (86.1%)	**Yes** $N = 6882$ (13.9%)	***P*-Value**[a]
Follow-up time (years)	Mean (Std Dev)	8.5 (3.6)	8.5 (3.6)	8.6 (3.2)	.117
	Median (Q1-Q3)	8.9 (6.3-11)	8.9 (6.2-11.1)	8.8 (6.9-10.6)	
	Min - Max	0-16.1	0-16.1	0.2-15.9	
Death	No	37,530 (76.1)	31,976 (75.3)	5554 (80.7)	**< .001**
	Yes	11,805 (23.9)	10,477 (24.7)	1328 (19.3)	
Race	White	40,693 (82.5)	35,063 (82.6)	5630 (81.8)	.209
	Black	5716 (11.6)	4876 (11.5)	840 (12.2)	
	Other/Unknown	2926 (5.9)	2514 (5.9)	412 (6)	
Age at diagnosis (years)	Mean (Std Dev)	57.7 (14.1)	58.4 (14.2)	53.2 (12.5)	**< .001**
	Median (Q1-Q3)	57 (47-68)	58 (48-69)	52 (44-62)	
	Min - Max	19-90	19-90	19-90	
Median income of patient's area of residence[b]	<$38,000	7408 (15)	6463 (15.2)	945 (13.7)	**< .001**
	$38,000-$47,999	9918 (20.1)	8647 (20.4)	1271 (18.5)	
	$48,000-$62,999	12,346 (25)	10,738 (25.3)	1608 (23.4)	
	≥$63,000	15,334 (31.1)	13,080 (30.8)	2254 (32.8)	
	Unknown	4329 (8.8)	3525 (8.3)	804 (11.7)	
Percentage of adults in patient's area of residence without a high school degree[c]	≥21%	7577 (15.4)	6633 (15.6)	944 (13.7)	**< .001**
	13-20.9%	11,175 (22.7)	9823 (23.1)	1352 (19.6)	
	7-12.9%	14,486 (29.4)	12,536 (29.5)	1950 (28.3)	
	<7%	11,783 (23.9)	9950 (23.4)	1833 (26.6)	
	Unknown	4314 (8.7)	3511 (8.3)	803 (11.7)	
Primary payor	Not Insured/Unknown and Medicaid/Other Government	5991 (12.1)	4978 (11.7)	1013 (14.7)	**< .001**
	Private	28,412 (57.6)	23,861 (56.2)	4551 (66.1)	
	Medicare	14,932 (30.3)	13,614 (32.1)	1318 (19.2)	
Sequence number	No other cancer diagnosis in lifetime	45,138 (91.5)	38,884 (91.6)	6254 (90.9)	**.048**
	The current cancer diagnosis is the first in sequence	4197 (8.5)	3569 (8.4)	628 (9.1)	
Charlson-Deyo score	0	40,191 (81.5)	34,347 (80.9)	5844 (84.9)	**< .001**
	1	7268 (14.7)	6402 (15.1)	866 (12.6)	
	2+	1876 (3.8)	1704 (4)	172 (2.5)	
Grade	Well differentiated	5603 (11.4)	4893 (11.5)	710 (10.3)	**< .001**
	Moderately differentiated	17,513 (35.5)	14,629 (34.5)	2884 (41.9)	
	Poorly differentiated/ Undifferentiated	26,219 (53.1)	22,931 (54)	3288 (47.8)	
T stage	1	15,598 (31.6)	13,511 (31.8)	2087 (30.3)	**< .001**
	2	32,299 (65.5)	28,007 (66)	4292 (62.4)	
	3(N0)	1438 (2.9)	935 (2.2)	503 (7.3)	
Lymphovascular invasion (LVI)	Not present	15,854 (32.1)	13,539 (31.9)	2315 (33.6)	**< .001**
	Present	9449 (19.2)	7481 (17.6)	1968 (28.6)	
	Unknown	24,032 (48.7)	21,433 (50.5)	2599 (37.8)	
Number of positive axillary lymph nodes	0	16,225 (32.9)	15,113 (35.6)	1112 (16.2)	**< .001**
	1-3	33,110 (67.1)	27,340 (64.4)	5770 (83.8)	
Number of regional lymph nodes examined	1-3	12,262 (24.9)	11,155 (26.3)	1107 (16.1)	**< .001**
	4-7	9780 (19.8)	8610 (20.3)	1170 (17)	
	8+	27,293 (55.3)	22,688 (53.4)	4605 (66.9)	
Surgical margins	Negative	47,949 (97.2)	41,469 (97.7)	6480 (94.2)	**< .001**
	Positive	1386 (2.8)	984 (2.3)	402 (5.8)	

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Table 1 (*continued*)

Covariate	Level	Total $N = 49,335$ (100%)	PMRT		*P*-Value[a]
			No $N = 42,453$ (86.1%)	Yes $N = 6882$ (13.9%)	
N stage	0	15,278 (31)	14,237 (33.5)	1041 (15.1)	**< .001**
	1	34,057 (69)	28,216 (66.5)	5841 (84.9)	
Breast cancer molecular subtypes	Triple Negative	4913 (10)	4167 (9.8)	746 (10.8)	**< .001**
	Luminal A	18,128 (36.7)	14,933 (35.2)	3195 (46.4)	
	Luminal B	3398 (6.9)	2817 (6.6)	581 (8.4)	
	Her2 Enriched	1677 (3.4)	1457 (3.4)	220 (3.2)	
	Unknown	21,219 (43)	19,079 (44.9)	2140 (31.1)	
Estrogen receptor (ER)	Negative	12,438 (25.6)	10,914 (26.2)	1524 (22.2)	**< .001**
	Positive	36,137 (74.4)	30,805 (73.8)	5332 (77.8)	
Progesterone receptor (PR)	Negative	17,157 (35.4)	14,983 (36)	2174 (31.7)	**< .001**
	Positive	31,284 (64.6)	26,610 (64)	4674 (68.3)	
Human epidermal growth factor receptor 2 (HER2)	Negative	23,060 (46.7)	19,093 (45)	3967 (57.6)	**< .001**
	Positive	5076 (10.3)	4268 (10.1)	808 (11.7)	
	Unknown	21,199 (43)	19,092 (45)	2107 (30.6)	
Facility location	Northeast	7412 (15)	6198 (14.6)	1214 (17.6)	**< .001**
	South	18,307 (37.1)	16,480 (38.8)	1827 (26.5)	
	Midwest	11,480 (23.3)	9657 (22.7)	1823 (26.5)	
	West	7696 (15.6)	6586 (15.5)	1110 (16.1)	
	Unknown	4440 (9)	3532 (8.3)	908 (13.2)	
Days from diagnosis to surgical procedure	≤30	21,159 (42.9)	18,484 (43.5)	2675 (38.9)	**< .001**
	>30	28,176 (57.1)	23,969 (56.5)	4207 (61.1)	
Laterality	Right	24,195 (49.1)	20,824 (49.1)	3371 (49)	.933
	Left	25,124 (50.9)	21,617 (50.9)	3507 (51)	
Tumor size (pathological feature)	≤ 2 cm	15,440 (31.4)	13,578 (32.1)	1862 (27.1)	**< .001**
	2.1-5 cm	32,016 (65.1)	27,722 (65.5)	4294 (62.6)	
	> 5 cm	1750 (3.6)	1043 (2.5)	707 (10.3)	
Histological type	Adenocarcinoma	776 (1.6)	685 (1.6)	91 (1.3)	**.024**
	Ductal/Lobular	47,756 (96.8)	41,054 (96.7)	6702 (97.4)	
	Mucinous	328 (0.7)	295 (0.7)	33 (0.5)	
	Other	475 (1)	419 (1)	56 (0.8)	
Breast reconstruction	No	33,218 (67.3)	28,564 (67.3)	4654 (67.6)	.575
	Yes	16,117 (32.7)	13,889 (32.7)	2228 (32.4)	
Adjuvant chemotherapy	No	16,179 (32.8)	14,684 (34.6)	1495 (21.7)	**< .001**
	Yes	33,156 (67.2)	27,769 (65.4)	5387 (78.3)	
Adjuvant hormone therapy	No	17,532 (35.5)	15,678 (36.9)	1854 (26.9)	**< .001**
	Yes	31,803 (64.5)	26,775 (63.1)	5028 (73.1)	
Neoadjuvant systemic therapy	No	46,794 (94.8)	40,885 (96.3)	5909 (85.9)	**< .001**
	Yes	2541 (5.2)	1568 (3.7)	973 (14.1)	
Year of diagnosis	2006-2009	20,450 (41.5)	18,444 (43.4)	2006 (29.1)	**< .001**
	2010-2013	28,885 (58.5)	24,009 (56.6)	4876 (70.9)	

Abbreviations: PMRT = postmastectomy radiation therapy.
Bold values indicate significant P-values < 0.05.
[a] The parametric *P*-value is calculated by ANOVA for numerical covariates and Chi-square test for categorical covariates.
[b] Median household income in the patient's zip code based on census data spanning 2008-2012.
[c] Educational attainment is measured as the percentage of adults in the patient's zip code who did not graduate from high school based on census data spanning 2008-2012.

The unadjusted relationship between PMRT and OS was assessed using a Kaplan Meier plot and log-rank test. To further explore the effect of PMRT on OS, multivariable Cox proportional hazard regression was performed. All covariates described previously, which were chosen based on clinical relevance and data availability in the NCDB, were included in the model. A backward selection criterion of 0.05 was used to select for statistically significant covariates, and the fitted models were used to generate hazard ratios (HRs) and 95% CIs. An additional multivariable interaction model containing an interaction term for PMRT cohort x T stage was used to perform a subgroup analysis.

To further minimize confounding, stabilized inverse probability of treatment weighting (s-IPTW) was used. S-IPTW is a propensity score (PS)-based approach, where PS is defined as the condi-

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tional probability of receiving PMRT given the observed covariates[23] and estimated by logistic regression. The average treatment effect stabilized weights were calculated as the SP_{trt}/PS for PMRT cases and (1- SP_{trt})/(1-PS) for non-PMRT cases,[24,25] where SP_{trt} is the sample proportion of PMRT cases in this study population. Balance diagnostics were performed using absolute standardized difference (ASD), with ASD <0.1 indicating sufficient balance. To obtain PS-weighted subgroup-specific HRs, weighted versions of the previously described multivariate Cox proportional hazards regression models were used. Weighted product-limit survival estimates were also generated and plotted, and a log-rank test was performed.

A sensitivity analysis was also performed to assess the impact of immortal time bias on study results. The multivariate regression models were rerun after excluding all patients who did not receive PMRT and were lost to follow-up within 12 weeks of surgery ($n = 277$). The results can be found in the supplemental information.

All analyses were done in SAS V9.4 (Cary, NC) and SAS macros,[26] and the significance level was set at $P < .05$.

Results

Table 1 summarizes the baseline characteristics of the entire study population and among PMRT subgroups. Of the 49335 patients who underwent mastectomy for intermediate-risk breast cancer, 6882 (13.9%) also received PMRT. Median follow-up time was 8.9 years (interquartile range, 6.3-11 years) and did not differ significantly by PMRT treatment status. Compared to patients who did not receive PMRT, higher percentages of patients in the PMRT cohort had stage T3N0 cancer (7.3% vs. 2.2%), 1-3 positive axillary lymph nodes (83.8% vs. 64.4%), and positive surgical margins (5.8% vs. 2.3%) (all $P < 0.001$). A higher percentage of patients in the PMRT cohort were also treated with neoadjuvant systemic therapy, adjuvant chemotherapy, or adjuvant hormone therapy compared to those who did not receive PMRT ($P < .001$).

Similarly, on multivariate analysis, certain demographic and clinical factors were associated with an increased probability of receiving PMRT treatment. Patients were more likely to have received PMRT if they had stage T3N0 cancer (aOR = 20.0, 95% CI, 17.1-23.5), LVI (aOR = 1.37, 95% CI, 1.27-1.47), 1-3 positive lymph nodes (aOR = 5.3, 95% CI, 4.83-5.89), positive surgical margins (aOR = 2.57, 95% CI, 2.25-2.93), or triple-negative breast cancer (aOR = 1.41, 95% CI, 1.25-1.59), or had also been treated with neoadjuvant systemic therapy (aOR = 8.21, 95% CI, 7.30-9.25), adjuvant chemotherapy (aOR = 2.86, 95% CI, 2.62-3.12), or adjuvant hormone therapy (aOR = 1.81, 95% CI, 1.66-1.96) (all $P < .001$) (Table S1).

Overall, the unadjusted survival rates among intermediate-risk breast cancer patients who had undergone PMRT compared to those who had not were, respectively, 90% and 87% after 5 years, 80% and 75% after 10 years, and 70% and 62% after 15 years ($P < .001$) (Figure 2). However, after s-IPTW, the estimated weighted survival rates at all time points did not differ by PMRT treatment (5-year: 89% vs. 87%, 10-year: 75% vs. 76%, and 15-year: 64% vs. 63%, $P = .791$) (Figure 3).

To adjust for potential confounders and explore the impact of PMRT usage on OS, multivariable Cox proportional hazard regression analyses were performed, with and without PS-weighting. No significant differences in OS were observed among those receiving or not receiving PMRT, both before and after s-IPTW was used to achieve covariate balance (unweighted HR: 0.98, 95% CI, 0.92-1.04; weighted HR: 0.97, 95% CI, 0.92-1.03) (Table 2 , Figure S1). However, a subgroup analysis suggested that PMRT is associated with improved survival among those with stage T3N0 breast cancer (HR: 0.72, 95% CI, 0.58-0.89) (Table 3). This effect remained significant in the PS-weighted models (Table 3). Similar results were observed when patients with less than 12 weeks of follow-up time were excluded from the cohort that did not receive PMRT, suggesting that the risk of immortal time bias is minimal (Table S2).

Discussion

In this analysis, we emulate the ongoing SUPREMO phase III clinical trial using RWD from the NCDB and achieve similar results to those preliminarily reported by the SUPREMO trial.[13] Like the SUPREMO trial, we find that PMRT is not associated with improved OS among intermediate-risk breast cancer patients with 0-3 positive axillary lymph nodes. However, select subgroups, such as patients with T3N0 disease, may benefit from treatment with PMRT. By applying the strict inclusion/exclusion criteria of the trial, paying careful attention to study design, and utilizing advanced statistical techniques to adjust for confounding, we anticipate and supplement the trial results with less bias and greater validity than could be achieved with standard approaches to observational studies.[27] In doing so, we show that it is feasible to replicate clinical trials using an observational database. This approach can supplement ongoing trials to provide further insight into the patient subgroups that could benefit the most from treatment. Furthermore, this sets the groundwork for future studies to use observational databases to aid in the design and analysis of RCTs.

To closely resemble the SUPREMO trial, we chose to restrict patients to those meeting the eligibility criteria defined in the trial protocol,[12] with the added restriction that all treatment be received at the reporting facility (Figure 1). However, due to the observational nature of the data, the covariate distributions and likelihood of PMRT usage in our treatment cohorts differed from each other, which would not be observed in a RCT. For example, patients with 1-3 positive axillary lymph nodes or high-risk features such as grade 3, LVI, or triple negative tumors were more likely to receive PMRT (Tables 1, S1). These trends are consistent with the current NCCN guidelines for PMRT usage,[1] but they do not match the covariate distribution in the SUPREMO trial population, given its randomized design.[28]

To account for this, we used s-IPTW to construct pseudo-populations with more balanced covariate distributions (Figure S1).[16,25,27] After s-IPTW, PMRT was not associated with improved survival among the entire cohort (Table 2). This suggests that overall, PMRT does not have a significant survival benefit among intermediate-risk breast cancer patients with 0-3 positive axillary lymph nodes, which is supported by previous studies.[29-33] However, results from our subgroup analyses suggest that PMRT may be beneficial among patients with stage T3N0M0 breast cancer (Table 3), which aligns with the recommended usage of PMRT in this patient subgroup.[1]

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Figure 2 Kaplan Meier plot of overall survival among intermediate-risk breast cancer patients who were treated with postmastectomy radiation therapy (PMRT) (red) compared to those who were not treated with PMRT (blue). The results of a log-rank test show differences in overall survival by PMRT treatment ($P < .0001$).

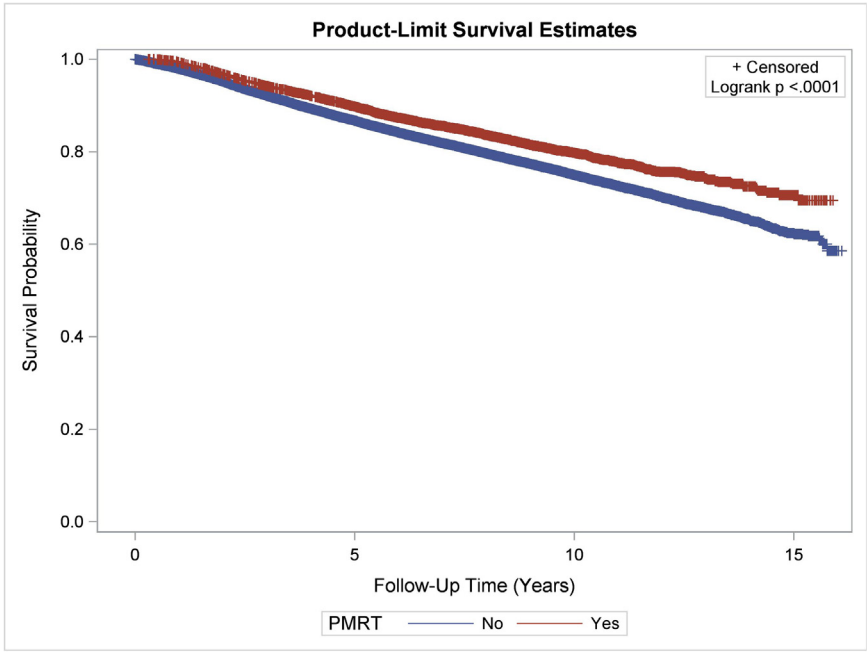

Figure 3 Weighted product-limit survival estimates among intermediate-risk breast cancer patients who were treated with postmastectomy radiation therapy (PMRT) (red) compared to those who were not treated with PMRT (blue). The results of a log-rank test show no difference in overall survival by PMRT treatment after propensity-score weighting ($P = .791$).

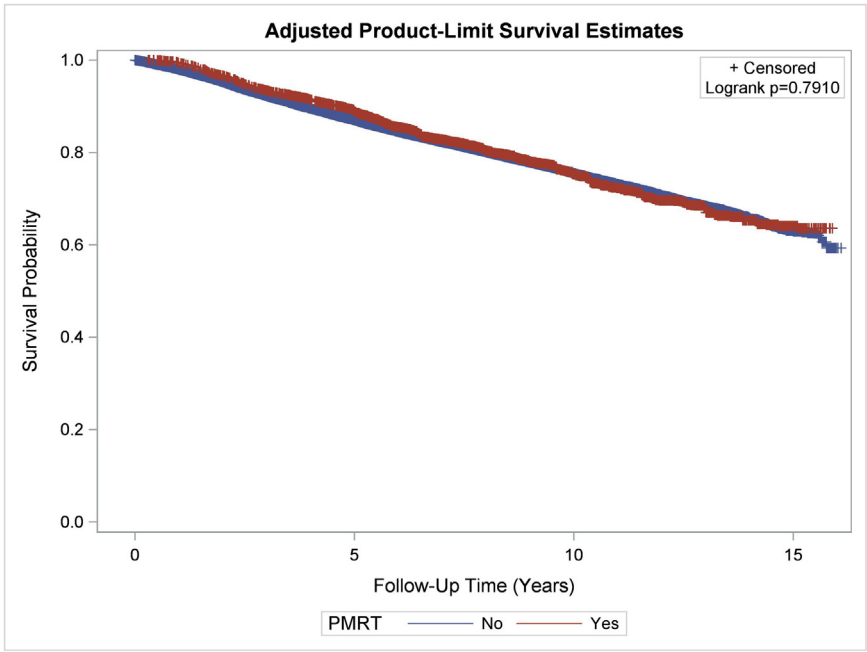

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Table 2 Multivariate Cox Proportional Hazard Regression Analysis to Assess the Impact of Postmastectomy Radiation Therapy (PMRT) on Overall Survival Among the Entire Cohort (Reference Group: no PMRT), With and Without Stabilized Inverse Probability of Treatment Propensity Score (PS) Weighting

		Unweighted[a]			PS-Weighted[a]		
Covariate	**Level**	**HR (95% CI)**	**HR *P*-Value**	**Type 3 *P*-Value**	**HR (95% CI)**	**HR *P*-Value**	**Type 3 *P*-Value**
PMRT	Yes	0.98 (0.92-1.04)	.554	.554	0.97 (0.92-1.03)	.337	.337
	No	-	-		-	-	
Race	Black	1.09 (1.03-1.16)	**.002**	**< .001**	1.13 (1.06-1.19)	**< .001**	**< .001**
	Others/Unknown	0.73 (0.66-0.80)	**< .001**		0.74 (0.67-0.82)	**< .001**	
	White	-	-		-	-	
Age at diagnosis (years)	≤50	0.26 (0.24-0.29)	**< .001**	**< .001**	0.26 (0.24-0.28)	**< .001**	**< .001**
	51-60	0.36 (0.33-0.38)	**< .001**		0.35 (0.33-0.38)	**< .001**	
	61-70	0.47 (0.44-0.49)	**< .001**		0.46 (0.44-0.49)	**< .001**	
	>70	-	-		-	-	
Median income of patient's area of residence[b]	$38,000-$47,999	0.91 (0.86-0.97)	**.003**	**< .001**	0.93 (0.87-0.99)	**.016**	**< .001**
	$48,000-$62,999	0.89 (0.83-0.95)	**< .001**		0.92 (0.86-0.98)	**.010**	
	≥$63,000	0.81 (0.75-0.88)	**< .001**		0.84 (0.78-0.90)	**< .001**	
	Unknown	0.59 (0.19-1.85)	.369		0.59 (0.18-1.96)	.390	
	<$38,000	-	-		-	-	
Percentage of adults in patient's area of residence without a high school degree[c]	13-20.9%	1.11 (1.04-1.17)	**< .001**	**< .001**	1.07 (1.01-1.14)	**.020**	**.017**
	7-12.9%	1.13 (1.05-1.20)	**< .001**		1.09 (1.02-1.16)	**.015**	
	<7%	1.03 (0.95-1.12)	.458		1.01 (0.93-1.10)	.757	
	Unknown	1.38 (0.44-4.30)	.578		1.39 (0.42-4.61)	.591	
	≥21%	-	-		-	-	
Primary payor	Not Insured/ Medicaid/Other Government/ Unknown	1.43 (1.34-1.53)	**< .001**	**< .001**	1.42 (1.33-1.51)	**< .001**	**< .001**
	Medicare	1.47 (1.39-1.55)	**< .001**		1.46 (1.38-1.55)	**< .001**	
	Private	-	-		-	-	
Sequence number	No other cancer diagnosis in lifetime	1.16 (1.09-1.23)	**< .001**	**< .001**	1.16 (1.09-1.23)	**< .001**	**< .001**
	The current cancer diagnosis is the first in sequence	-	-		-	-	
Charlson-Deyo score	1	1.36 (1.30-1.43)	**< .001**	**< .001**	1.33 (1.27-1.39)	**< .001**	**< .001**
	2+	2.12 (1.99-2.27)	**< .001**		2.07 (1.94-2.21)	**< .001**	
	0	-	-		-	-	
Grade	Poorly Differentiated/ Undifferentiated	1.65 (1.53-1.77)	**< .001**	**<.001**	1.63 (1.52-1.75)	**< .001**	**< .001**
	Moderately Differentiated	1.21 (1.13-1.29)	**< .001**		1.20 (1.12-1.28)	**< .001**	
	Well Differentiated	-	-		-	-	
T stage	3	2.20 (1.97-2.46)	**< .001**	**<.001**	2.34 (2.11-2.60)	**< .001**	**< .001**
	2	1.51 (1.44-1.58)	**< .001**		1.49 (1.43-1.56)	**< .001**	
	1	-	-		-	-	
Number of positive axillary lymph nodes	1-3	1.48 (1.41-1.56)	**< .001**	**<.001**	1.47 (1.41-1.54)	**< .001**	**< .001**
	0	-	-		-	-	

(*continued on next page*)

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Table 2 (*continued*)

Covariate	Level	Unweighted[a] HR (95% CI)	Unweighted[a] HR *P*-Value	Unweighted[a] Type 3 *P*-Value	PS-Weighted[a] HR (95% CI)	PS-Weighted[a] HR *P*-Value	PS-Weighted[a] Type 3 *P*-Value
Number of regional lymph nodes examined	1-3	1.05 (1.00-1.10)	.069	**0.038**	-	-	-
	4-7	1.06 (1.01-1.11)	**.019**		-	-	
	8+	-	-		-	-	
Surgical margin	Positive	1.26 (1.13-1.40)	**< .001**	**<.001**	1.34 (1.21-1.47)	**< .001**	**< .001**
	Negative	-	-		-	-	
Lymphovascular invasion (LVI)	Present	1.21 (1.14-1.28)	**< .001**	**<.001**	1.19 (1.13-1.26)	**< .001**	**< .001**
	Unknown	1.03 (0.97-1.10)	.319		1.00 (0.94-1.07)	.934	
	Not present	-	-		-	-	
Breast cancer molecular subtypes	Triple negative	1.33 (1.24-1.43)	**< .001**	**<.001**	1.40 (1.30-1.50)	**< .001**	**< .001**
	Luminal B	1.04 (0.95-1.13)	.375		1.03 (0.94-1.12)	.562	
	Her2 enriched	0.90 (0.80-1.01)	.065		0.91 (0.81-1.03)	.137	
	Unknown	1.00 (0.94-1.07)	.981		1.03 (0.96-1.10)	.405	
	Luminal A	-	-		-	-	
Facility location	Northeast	0.99 (0.93-1.05)	.653	**0.015**	0.96 (0.91-1.02)	.195	**.005**
	Midwest	1.03 (0.98-1.08)	.190		1.01 (0.96-1.06)	.674	
	West	0.93 (0.88-0.99)	**.017**		0.92 (0.87-0.97)	**.002**	
	Unknown	1.06 (0.96-1.18)	.254		1.06 (0.96-1.17)	.252	
	South	-	-		-	-	
Days from diagnosis to surgical procedure	≤30	1.06 (1.02-1.10)	**.005**	**.005**	1.06 (1.02-1.10)	**.005**	**.005**
	>30	-	-		-	-	
Adjuvant chemotherapy	Yes	0.56 (0.54-0.59)	**< .001**	**< .001**	0.55 (0.53-0.58)	**< .001**	**< .001**
	No	-	-		-	-	
Adjuvant hormone therapy	Yes	0.72 (0.69-0.76)	**< .001**	**< .001**	0.74 (0.70-0.77)	**< .001**	**< .001**
	No	-	-		-	-	
Neoadjuvant systemic therapy	Yes	1.32 (1.21-1.44)	**< .001**	**< .001**	1.34 (1.23-1.45)	**< .001**	**< .001**
	No	-	-		-	-	

[a] Number of observations used = 49335. Backward selection with an alpha level of removal of .05 was used. No variables were removed from the unweighted model. The following variables were removed from the weighted model: number of regional lymph nodes examined.
[b] Median household income in the patient's zip code based on census data spanning 2008-2012.
[c] Educational attainment is measured as the percentage of adults in the patient's zip code who did not graduate from high school based on census data spanning 2008-2012.

Table 3 **Multivariate Cox Proportional Hazard Regression Analysis to Assess the Impact of Postmastectomy Radiation Therapy (PMRT) on Overall Survival Within T Stage Subgroups (Reference Group: no PMRT), With and Without Stabilized Inverse Probability of Treatment Propensity Score (PS) Weighting**

T Stage Subgroup[a]	Unweighted HR (95% CI)	*P*-Value	Interaction *P*-Value	PS-Weighted HR (95% CI)	*P*-Value	Interaction *P*-Value
T1	1.08 (0.96-1.22)	**.019**	**.004**	1.13 (1.03-1.25)	**.014**	**< .001**
T2	0.98 (0.92-1.06)	.662		0.95 (0.89-1.01)	.082	
T3(N0)	0.72 (0.58-0.89)	**.003**		0.62 (0.46-0.83)	**.001**	

[a] Number of observations used = 49335. Backward selection with an alpha level of removal of .05 was used. No variables were removed from either model.

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It is important to note that even after s-IPTW is used to achieve covariate balance, the covariate distribution of our study population still differs from that of the SUPREMO trial population. For example, 3.6% of our study population had tumor size > 5 cm, compared to <1% of the SUPREMO trial cohort; 33% had 0 positive axillary lymph nodes compared to 25% of the SUPREMO trial cohort; and 67% and 65% received adjuvant chemotherapy and hormone therapy, respectively, compared to 83% and 73% of the SUPREMO trial cohort.[28] However, this is to be expected, as the underlying study populations are different. The SUPREMO trial is an international study primarily conducted in the UK and the Netherlands,[34] whereas we use the NCDB, which is a national US database containing RWD from patients treated only at US hospitals. Because international treatment guidelines differ and the population from which we draw our study sample is different than that used for the SUPREMO trial, we do not expect the covariate distributions to be the same. This helps to illustrate why the results of emulated clinical trials cannot and should not be directly compared to RCTs; instead, they should be used to supplement or extend RCT results,[14,15,35,36] as we do here.

Some limitations of this study include the potential for unmeasured confounding due to the observational nature of the NCDB and the lack of available data for toxicity, quality of life, systemic therapy agents, and cancer-specific outcomes, such as local/metastatic recurrence or cancer-specific survival. This may result in unmeasured imbalances between the 2 cohorts and could contribute to the observed lack of a survival advantage overall. Furthermore, because the cohort was restricted to patients diagnosed in 2006-2013, some PMRT techniques utilized at the time of treatment may now be outdated (ie, less rigorous cardiac avoidance with deep inspiration breath hold or treatment imaging verification), potentially limiting the generalizability of the results to current techniques.

Another limitation of this study is the potential for immortal time bias, which is introduced by the requirement that patients in the PMRT cohort survive until receipt of PMRT within 12 weeks of the surgery. This will not be the case in the SUPREMO clinical trial if the intent-to-treat analysis is carried out, where the deaths between surgery and radiation for the PMRT cohort will be captured. Nevertheless, the time of surgery was used as the start time in survival analyses because of its clinical relevance for assessing survival differences between those who did and did not receive PMRT. Furthermore, the impact of this time lag on the survival analysis results is very small (Table S2), since only 0.6% of the cohort was lost to follow-up within 12 weeks of surgery.

Conclusion

In conclusion, using RWD from the NCDB, we demonstrate the feasibility of target trial emulation in the context of the SUPREMO trial. By implementing careful selection criteria that matches the trial protocol and using s-IPTW to achieve covariate balance, we build on the preliminary results of the SUPREMO trial and provide further evidence that PMRT may not improve overall survival among intermediate-risk breast cancer patients with 1-3 positive axillary lymph nodes. However, we show that in select patients with pT3N0 disease, PMRT may improve survival, which supports its continued usage in this patient subgroup. Early results of the SUPREMO trial support these findings, but the inherent uncertainty associated with the retrospective, observational nature of this analysis requires that we await publication of the complete results of the SUPREMO trial for a more comprehensive assessment of the benefits of PMRT among patients with intermediate-risk breast cancer.

Clinical Practice Points

- The role of PMRT for intermediate-risk breast cancer patients (i.e. pT1-2N1; pT3N0; or pT2N0 and grade III or with LVI, with 0-3 positive axillary lymph nodes) is unclear.
- Professional guidelines currently recommend consideration of PMRT for these patients, and utilization of PMRT in this population in the United States is rising.
- Long-term efficacy results of the SUPREMO phase three randomized trial, which evaluates the role of PMRT in this population, are pending.
- This retrospective large database analysis of nearly 50,000 patients using RWD from the United States, with careful selection criteria and s-IPTW matching, found no survival benefit with the addition of PMRT amongst all patients with intermediate-risk disease.
- In select patients with pT3N0 disease, however, PMRT may result in a significant survival benefit.
- These results highlight the nuanced nature of adjuvant treatment recommendations in this group of intermediate-risk breast cancer patients, whose management will be further informed by mature results of the SUPREMO trial.

Disclosure

The authors have stated that they have no conflicts to interest.

CRediT authorship contribution statement

Sarah E. Kulkarni: Writing – original draft, Visualization, Software, Methodology, Formal analysis, Conceptualization. **Sagar A. Patel:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Chen Jiang:** Software, Formal analysis, Conceptualization. **Lara Schwieger:** Writing – review & editing, Conceptualization. **Lauren M. Postlewait:** Writing – review & editing, Conceptualization. **Cletus A. Arciero:** Writing – review & editing, Conceptualization. **Theresa W. Gillespie:** Writing – review & editing, Conceptualization. **Yuan Liu:** Writing – review & editing, Writing – original draft, Software, Methodology, Funding acquisition, Formal analysis, Conceptualization.

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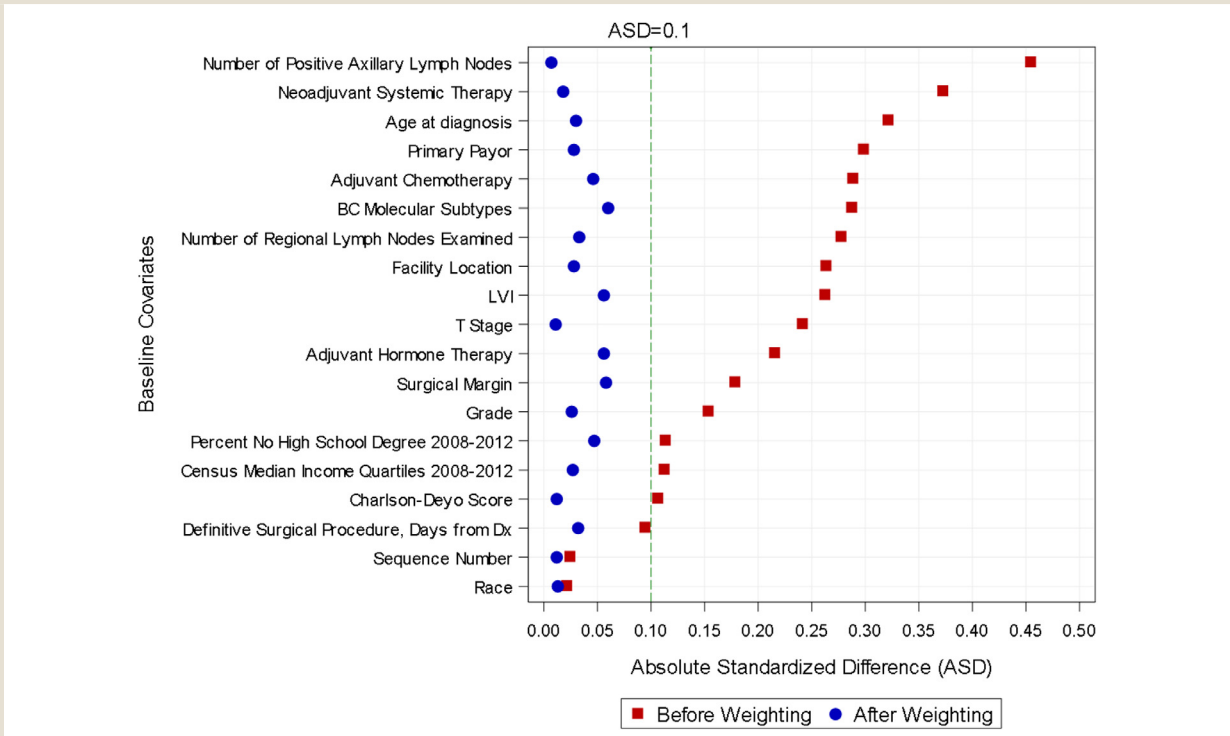
Postmastectomy Radiation Therapy for Intermediate-Risk Breast

Supplemental Information

Supplementary Figure 1 Summary of covariate balance improvement measured by absolute standardized difference (ASD) before and after stabilized inverse probability of treatment propensity score weighting, indicated by red squares and blue circles, respectively. A covariate was considered sufficiently balanced if ASD < 0.1 (indicated by the green dashed line). After weighting, balanced covariate distributions were achieved among cohorts. LVI: lymphovascular invasion.



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Supplementary Table 1 Multivariate logistic regression analysis for post-mastectomy radiation therapy (PMRT) usage.

			PMRT=Yes		
Covariate[1]	**Level**	**N**	**Adjusted Odds Ratio (95% CI)**	**aOR *P*-value**	**Type 3 *P*-value**
Race	Black	5716	1.10 (1.01-1.21)	**0.032**	**0.015**
	Other/Unknown	2926	0.90 (0.80-1.01)	0.077	
	White	40693	-	-	
Age at diagnosis (years)	≤50	16998	1.55 (1.37-1.76)	**<.001**	**<.001**
	51-60	12220	1.30 (1.14-1.47)	**<.001**	
	61-70	10283	1.18 (1.06-1.33)	**0.003**	
	>70	9834	-	-	
Median income of patient's area of residence[2]	$38,000-$47,999	9918	0.92 (0.82-1.02)	0.100	**0.003**
	$48,000-$62,999	12346	0.84 (0.75-0.94)	**0.002**	
	≥$63,000	15334	0.80 (0.70-0.90)	**<.001**	
	Unknown	4329	0.47 (0.06-3.67)	0.474	
	<$38,000	7408	-	-	
Percentage of adults in patient's area of residence without a high school degree[3]	13-20.9%	11175	1.03 (0.93-1.14)	0.523	**<.001**
	7-12.9%	14486	1.17 (1.05-1.31)	**0.004**	
	<7%	11783	1.35 (1.20-1.53)	**<.001**	
	Unknown	4314	2.92 (0.38-22.64)	0.305	
	≥21%	7577	-	-	
Primary payor	Not Insured/ Unknown and Medicaid/Other Government	5991	1.08 (0.99-1.17)	0.078	**0.004**
	Medicare	14932	0.89 (0.81-0.97)	**0.013**	
	Private	28412	-	-	
Grade	Poorly differentiated/ Undifferentiated	26219	1.28 (1.16-1.41)	**<.001**	**<.001**
	Moderately differentiated	17513	1.16 (1.06-1.28)	**0.002**	
	Well differentiated	5603	-	-	
T stage	3(N0)	1438	20.03 (17.08-23.49)	**<.001**	**<.001**
	2	32299	1.58 (1.48-1.68)	**<.001**	
	1	15598	-	-	
Number of positive axillary lymph nodes	1-3	33110	5.33 (4.83-5.89)	**<.001**	**<.001**
	0	16225	-	-	
Surgical margins	Positive	1386	2.57 (2.25-2.93)	**<.001**	**<.001**
	Negative	47949	-	-	
Lymphovascular invasion (LVI)	Present	9449	1.37 (1.27-1.47)	**<.001**	**<.001**
	Unknown	24032	0.91 (0.83-1.00)	**0.045**	
	Not present	15854	-	-	
Breast cancer molecular subtypes	Triple Negative	4913	1.41 (1.25-1.59)	**<.001**	**<.001**
	Luminal B	3398	0.81 (0.72-0.90)	**<.001**	
	Her2 Enriched	1677	1.00 (0.84-1.19)	0.978	
	Unknown	21219	0.73 (0.67-0.81)	**<.001**	
	Luminal A	18128	-	-	
Number of regional lymph nodes examined	1-3	12262	0.79 (0.73-0.86)	**<.001**	**<.001**
	4-7	9780	0.88 (0.81-0.95)	**<.001**	
	8+	27293	-	-	
Facility location	Northeast	7412	1.71 (1.57-1.87)	**<.001**	**<.001**
	Midwest	11480	1.61 (1.49-1.74)	**<.001**	
	West	7696	1.59 (1.46-1.74)	**<.001**	

(*continued on next page*)

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Supplementary Table 1 (*continued*)

Covariate[1]	Level	N	PMRT=Yes Adjusted Odds Ratio (95% CI)	PMRT=Yes aOR *P*-value	PMRT=Yes Type 3 *P*-value
	Unknown	4440	1.65 (1.49-1.83)	**<.001**	
	South	18307	-	-	
Days from diagnosis to surgical procedure	>30	28176	0.87 (0.82-0.92)	**<.001**	**<.001**
	≤30	21159	-	-	
Adjuvant chemotherapy	Yes	33156	2.86 (2.62-3.12)	**<.001**	**<.001**
	No	16179	-	-	
Adjuvant hormone therapy	Yes	31803	1.81 (1.66-1.96)	**<.001**	**<.001**
	No	17532	-	-	
Neoadjuvant systemic therapy	Yes	2541	8.21 (7.30-9.25)	**<.001**	**<.001**
	No	46794	-	-	

[1] Number of observations used = 49335. Backward selection with an alpha level of removal of .05 was used. The following variables were removed from the model: Charlson Deyo Score and Sequence Number.
[2] Median household income in the patient's zip code based on census data spanning 2008-2012.
[3] Educational attainment is measured as the percentage of adults in the patient's zip code who did not graduate from high school based on census data spanning 2008-2012.

Supplementary Table 2 **Sensitivity analysis to assess immortal time bias: multivariate Cox proportional hazard regression for overall survival among patients with at least 12 weeks of follow-up time (reference group: no PMRT), with and without stabilized inverse probability of treatment propensity score (PS) weighting.**

Covariate	Level	Unweighted[1] HR (95% CI)	Unweighted[1] HR *P*-value	Unweighted[1] Type 3 *P*-value	PS-Weighted[2] HR (95% CI)	PS-Weighted[2] HR *P*-value	PS-Weighted[2] Type 3 *P*-value
PMRT	Yes	0.99 (0.93-1.05)	0.750	0.750	0.99 (0.94-1.04)	0.610	0.610
	No	-	-		-	-	
Race	Black	1.10 (1.04-1.16)	**0.002**	**<.001**	1.13 (1.07-1.20)	**<.001**	**<.001**
	Others/Unknown	0.73 (0.66-0.81)	**<.001**		0.75 (0.68-0.82)	**<.001**	
	White	-	-		-	-	
Age at diagnosis (years)	≤50	0.26 (0.24-0.28)	**<.001**	**<.001**	0.26 (0.24-0.28)	**<.001**	**<.001**
	51-60	0.36 (0.33-0.38)	**<.001**		0.35 (0.33-0.38)	**<.001**	
	61-70	0.46 (0.44-0.49)	**<.001**		0.46 (0.44-0.49)	**<.001**	
	>70	-	-		-	-	
Median income of patient's area of residence[3]	$38,000-$47,999	0.91 (0.86-0.97)	**0.002**	**<.001**	0.93 (0.87-0.99)	**0.018**	**<.001**
	$48,000-$62,999	0.88 (0.83-0.94)	**<.001**		0.92 (0.86-0.98)	**0.010**	
	≥$63,000	0.81 (0.75-0.87)	**<.001**		0.84 (0.77-0.90)	**<.001**	
	Unknown	0.60 (0.19-1.87)	0.379		0.60 (0.18-2.00)	0.407	
	<$38,000	-	-		-	-	
Percentage of adults in patient's area of residence without a high school degree[4]	13-20.9%	1.11 (1.05-1.18)	**<.001**	**<.001**	1.08 (1.02-1.15)	**0.014**	**0.019**
	7-12.9%	1.13 (1.06-1.21)	**<.001**		1.09 (1.01-1.16)	**0.017**	
	<7%	1.04 (0.96-1.12)	0.396		1.02 (0.94-1.10)	0.708	
	Unknown	1.36 (0.44-4.23)	0.597		1.36 (0.41-4.51)	0.617	
	≥21%	-	-		-	-	
Primary Payor	Not Insured/ Medicaid/Other Government/ Unknown	1.42 (1.33-1.52)	**<.001**	**<.001**	1.40 (1.31-1.50)	**<.001**	**<.001**

(*continued on next page*)

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Supplementary Table 2 (*continued*)

Covariate	Level	Unweighted[1] HR (95% CI)	Unweighted[1] HR *P*-value	Unweighted[1] Type 3 *P*-value	PS-Weighted[2] HR (95% CI)	PS-Weighted[2] HR *P*-value	PS-Weighted[2] Type 3 *P*-value
	Medicare	1.46 (1.38-1.55)	**<.001**		1.46 (1.38-1.54)	**<.001**	
	Private	-	-		-	-	
Sequence Number	No other cancer diagnosis in lifetime	1.15 (1.08-1.23)	**<.001**	**<.001**	1.15 (1.08-1.23)	**<.001**	**<.001**
	The current cancer diagnosis is the first in sequence	-	-		-	-	
Charlson-Deyo Score	1	1.36 (1.29-1.42)	**<.001**	**<.001**	1.33 (1.27-1.39)	**<.001**	**<.001**
	2+	2.11 (1.97-2.26)	**<.001**		2.06 (1.92-2.20)	**<.001**	
	0	-	-		-	-	
Grade	Poorly Differentiated/ Undifferentiated	1.66 (1.55-1.79)	**<.001**	**<.001**	1.65 (1.54-1.78)	**<.001**	**<.001**
	Moderately Differentiated	1.21 (1.13-1.29)	**<.001**		1.20 (1.12-1.28)	**<.001**	
	Well Differentiated	-	-		-	-	
T Stage	3	2.21 (1.98-2.47)	**<.001**	**<.001**	2.37 (2.14-2.63)	**<.001**	**<.001**
	2	1.51 (1.44-1.58)	**<.001**		1.49 (1.42-1.56)	**<.001**	
	1	-	-		-	-	
Number of Positive Axillary Lymph Nodes	1-3	1.45 (1.39-1.52)	**<.001**	**<.001**	1.47 (1.40-1.54)	**<.001**	**<.001**
	0	-	-		-	-	
Surgical Margin	Positive	1.26 (1.13-1.40)	**<.001**	**<.001**	1.33 (1.21-1.47)	**<.001**	**<.001**
	Negative	-	-		-	-	
Lymphovascular invasion (LVI)	Present	1.21 (1.14-1.28)	**<.001**	**<.001**	1.19 (1.13-1.26)	**<.001**	**<.001**
	Unknown	1.03 (0.97-1.10)	0.380		1.01 (0.94-1.07)	0.871	
	Not present	-	-		-	-	
Breast cancer molecular subtypes	Triple Negative	1.38 (1.28-1.48)	**<.001**	**<.001**	1.45 (1.35-1.56)	**<.001**	**<.001**
	Luminal B	1.04 (0.95-1.13)	0.423		1.03 (0.94-1.12)	0.573	
	Her2 Enriched	0.93 (0.83-1.05)	0.258		0.95 (0.84-1.07)	0.385	
	Unknown	1.02 (0.95-1.09)	0.585		1.04 (0.98-1.11)	0.208	
	Luminal A	-	-		-	-	
Facility Location	Northeast	0.99 (0.93-1.05)	0.643	**0.017**	0.96 (0.91-1.02)	0.219	**0.007**
	Midwest	1.03 (0.99-1.08)	0.161		1.01 (0.96-1.06)	0.676	
	West	0.94 (0.88-0.99)	**0.025**		0.92 (0.87-0.97)	**0.003**	
	Unknown	1.06 (0.96-1.18)	0.236		1.07 (0.96-1.18)	0.211	
	South	-	-		-	-	
Days from diagnosis to surgical procedure	≤30	1.05 (1.01-1.09)	**0.008**	**0.008**	1.05 (1.02-1.10)	**0.006**	**0.006**
	>30	-	-		-	-	
Adjuvant Chemotherapy	Yes	0.56 (0.54-0.59)	**<.001**	**<.001**	0.56 (0.53-0.58)	**<.001**	**<.001**
	No	-	-		-	-	
Adjuvant Hormone Therapy	Yes	0.76 (0.73-0.79)	**<.001**	**<.001**	0.77 (0.73-0.80)	**<.001**	**<.001**
	No	-	-		-	-	
Neoadjuvant Systemic Therapy	Yes	1.34 (1.23-1.46)	**<.001**	**<.001**	1.35 (1.24-1.46)	**<.001**	**<.001**
	No	-	-		-	-	

Abbreviations: PMRT: post-mastectomy radiation therapy.
[1] Number of observations used = 49184. Backward selection with an alpha level of removal of .05 was used. The following variables were removed from the model: number of regional lymph nodes examined.
[2] Number of observations used = 49068. Backward selection with an alpha level of removal of .05 was used. The following variables were removed from the model: number of regional lymph nodes examined.
[3] Median household income in the patient's zip code based on census data spanning 2008-2012.
[4] Educational attainment is measured as the percentage of adults in the patient's zip code who did not graduate from high school based on census data spanning 2008-2012.

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