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Original Article

# Postmastectomy radiation therapy for triple negative, node-negative breast cancer

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ABSTRACT

*Purpose:* The use of post-mastectomy radiation therapy (PMRT) for patients with node-negative, triple negative breast cancer (TNBC) is controversial. This study of a large, contemporary US database described national practice patterns and addressed the impact of PMRT on survival for patients with node-negative TNBC.

*Methods:* The National Cancer Data Base was queried (2004–2014) for women with non-metastatic TNBC with pT1-4N0M0 disease undergoing mastectomy. Use of PMRT was assessed. Multivariable logistic regression ascertained factors associated with PMRT use. The Kaplan–Meier analysis evaluated overall survival (OS) between patients managed with either PMRT or observation following mastectomy when stratifying by pT stage. Cox proportional hazards modeling determined variables associated with OS.

*Results:* A total of 14,464 patients met the selection criteria; of these, 1,569 (10.8%) received PMRT, whereas 12,895 (89.2%) did not receive PMRT. Use of PMRT varied significantly with pT stage, with only 5.7% of T1 patients undergoing PMRT, while 51.6% of patients with T3 disease underwent PMRT. Use of PMRT was associated with superior OS for patients with pT3 disease but not for patients with other T stages. Greater age was associated with decreased likelihood of PMRT use, while increased T stage and positive surgical margins were associated with use of PMRT. On multivariate analysis, increased age, T stage, and positive surgical margins were associated with worse OS.

*Conclusions:* In the largest study to date evaluating the use of PMRT in patients with node-negative TNBC, the use of PMRT was low in patients with T1 and T2 disease. Additionally, while an OS benefit was observed with the use of PMRT in patients with T3 disease, there was no benefit with the use of PMRT in other T stage groups. Further prospective studies are recommended to further elucidate the benefit on PMRT in patients with node-negative TNBC.



The National Comprehensive Cancer Network (NCCN) currently recommends post-mastectomy radiation therapy (PMRT) for invasive breast cancer with ≥4 positive axillary nodes, with strong consideration for 1–3 positive nodes, and a consideration for negative axillary nodes but >5 cm primary tumor [1]. This recommendation is based on three randomized trials that have shown an overall survival (OS) benefit with the use of PMRT in patients with breast cancer with positive surgical margins, tumor size >5 cm, or positive axillary lymph nodes, as well as a meta-analysis demonstrating higher OS with PMRT in women with breast cancer and positive axillary nodal disease [2–5]. It should be noted that while these trials guide current management regarding indications for PMRT, the systemic treatment used was different than what is typically used for patients with breast cancer today. Namely, women in the Danish 82b trial conducted in premenopausal women, received chemotherapy with Cyclophosphamide, Methotrexate, and Fluorouracil (CMF) (2); women in the Danish 82c trial, conducted in postmenopausal women, received Tamoxifen alone (3); and women in the British Columbia trial also received CMF chemotherapy (4).

The aforementioned trials describing the efficacy of PMRT were performed before the era in which tumor markers were used to guide treatment management. The current era of cancer management, however, is increasingly shifting toward personalized medicine. To this extent, numerous studies have examined the predictive and/or prognostic impacts of gene panels on various endpoints [6,7]. In some instances, gene profiling has demonstrated a greater degree of accuracy than clinicopathologic factors in predicting the risk of distant recurrence following surgery [8–10].

As such, a major focus of ongoing investigation is to determine whether there may be subsets of patients with more biologically

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aggressive disease, such as patients with triple negative breast cancer (TNBC), who may warrant PMRT even in the setting of early stage, node-negative disease. One large retrospective review from Canada demonstrated that women with T1-2N0 TNBC treated with modified radical mastectomy without PMRT had worse local control than patients treated with breast conserving surgery and radiation therapy [11]. Furthermore, a randomized Chinese trial has demonstrated that the addition of PMRT to patients with stage I-II TNBC led to improvements in 5 year OS [12].

Given the current dearth of information, the NCCN does not incorporate tumor markers into recommendations regarding TNBC. The goal of this large, national database investigation was to evaluate trends and practice patterns of PMRT in patients with node-negative TNBC, along with assessing the clinical benefit from PMRT in this patient population.

## Materials & methods

The National Cancer Data Base (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society, which consists of de-identified information regarding tumor characteristics, patient demographics, and patient survival for approximately 70% of the US population [13–15]. All pertinent cases are reported regularly from CoC-accredited centers and compiled into a unified dataset, which is then validated. The NCDB contains information not included in the Surveillance, Epidemiology, and End Results (SEER) database, including details regarding use of systemic therapy. The data used in the study were derived from a de-identified NCDB file (2004–2013). The American College of Surgeons and the CoC have not verified and are neither responsible for the analytic or statistical methodology employed nor the conclusions drawn from these data by the investigators. As all patient information in the NCDB database is de-identified, this study was exempt from institutional review board evaluation.

Inclusion criteria for this study were women with newly diagnosed, non-metastatic TNBC with clinically and pathologically N0 disease and pT1-4 disease treated with mastectomy. Patients with either clinically or pathologically node-positive disease were excluded from the present analysis. A record of radiation therapy use was required for inclusion in the study, and patients included in the PMRT category were treated with conventionally fractionated radiation. Information regarding whether or not the regional nodes were included in the field in addition to the chest wall in the radiation therapy field was not available for a majority of patients and consequently this variable was not factored into the analysis. In accordance with the variables in NCDB files, information collected on each patient broadly included demographic, clinical, and treatment data.

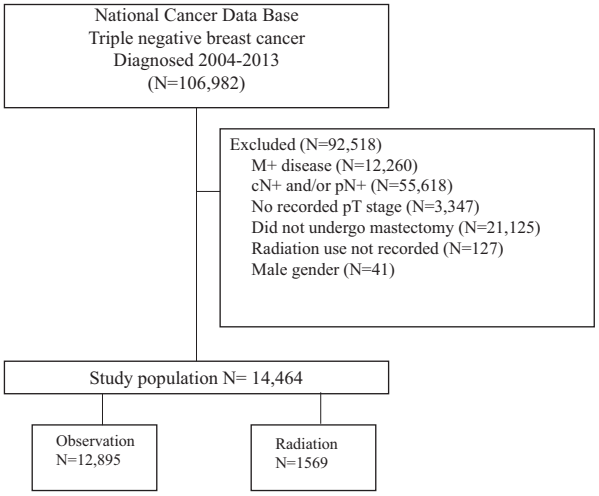


**Fig. 1.** Patient selection diagram.

All statistical tests were two-sided, with a threshold of $p < 0.05$ for statistical significance, and were performed using STATA (version 14, College Station, TX). Multivariable logistic regression modeling determined characteristics predictive for PMRT. Survival analysis was per the Kaplan–Meier method, with group comparisons done with the log-rank test. When conducting the Kaplan–Meier test to compare OS between patients either receiving or not receiving PMRT, patients were stratified by T stage. OS referred to the interval between the date of diagnosis and the date of death, or censored at last contact. Univariate analysis determined factors associated with overall survival; subsequently, Cox multivariate analysis was performed and included variables that were significant on univariate analysis with a $p$ value < 0.05.

## Results

A complete patient selection diagram is presented in Fig. 1. A total of 14,464 patients met the selection criteria (Table 1). A total

**Table 1**
Demographic and clinical characteristics for all patients.

| Characteristic | No radiation $n$ = 12895 (%) | Radiation $n$ = 1569 (%) | $P$ value |
|---|---|---|---|
| Age | | | |
| ≤50 | 3882 (30.1%) | 628 (40.0%) | <0.001 |
| 51–60 | 3259 (25.3%) | 436 (27.8%) | |
| 61–70 | 2972 (23.1%) | 284 (18.1%) | |
| 71+ | 2782 (21.6%) | 221 (14.1%) | |
| Race | | | |
| White | 10,465 (81.2%) | 1188 (75.7%) | <0.001 |
| African American | 1807 (14.0%) | 307 (19.6%) | |
| Other | 623 (4.8%) | 74 (4.7%) | |
| Charlson–Deyo's Score | | | |
| 0 | 10,431 (80.9%) | 1312 (83.6%) | 0.032 |
| 1 | 1944 (15.1%) | 295 (13.1%) | |
| ≥2 | 520 (4.0%) | 52 (3.3%) | |
| Insurance status | | | |
| Medicaid | 896 (7.0%) | 213 (13.6%) | <0.001 |
| Private | 7058 (54.7%) | 873 (55.6%) | |
| Medicare | 4412 (34.2%) | 378 (24.1%) | |
| Not insured | 260 (2.0%) | 71 (4.5%) | |
| Other | 269 (2.1%) | 34 (2.2%) | |
| Median Income | | | |
| ≤$62999 | 8655 (67.1%) | 1127 (71.8%) | 0.001 |
| ≥$63000 | 4196 (32.5%) | 438 (27.9%) | |
| Not recorded | 44 (0.3%) | 4 (0.3%) | |
| Facility type | | | |
| Non academic | 8180 (63.4%) | 950 (60.6%) | <0.001 |
| Academic | 3537 (27.4%) | 376 (24.0%) | |
| Not recorded | 1178 (9.1%) | 243 (15.5%) | |
| T stage | | | |
| 1 | 7560 (58.6%) | 457 (29.1%) | <0.001 |
| 2 | 4828 (37.4%) | 611 (38.9%) | |
| 3 | 388 (3.0%) | 413 (26.3%) | |
| 4 | 119 (0.9%) | 88 (5.6%) | |
| Systemic chemotherapy | | | |
| Yes | 10,488 (81.3%) | 1480 (94.3%) | <0.001 |
| No | 2344 (18.2%) | 89 (5.7%) | |
| Not recorded | 63 (0.5%) | 0 (0.0%) | |
| Surgical margins | | | |
| Positive | 225 (1.7%) | 94 (6.0%) | <0.001 |
| Negative | 12,604 (97.7%) | 1452 (92.5%) | |
| Not reported | 66 (0.5%) | 23 (1.5%) | |

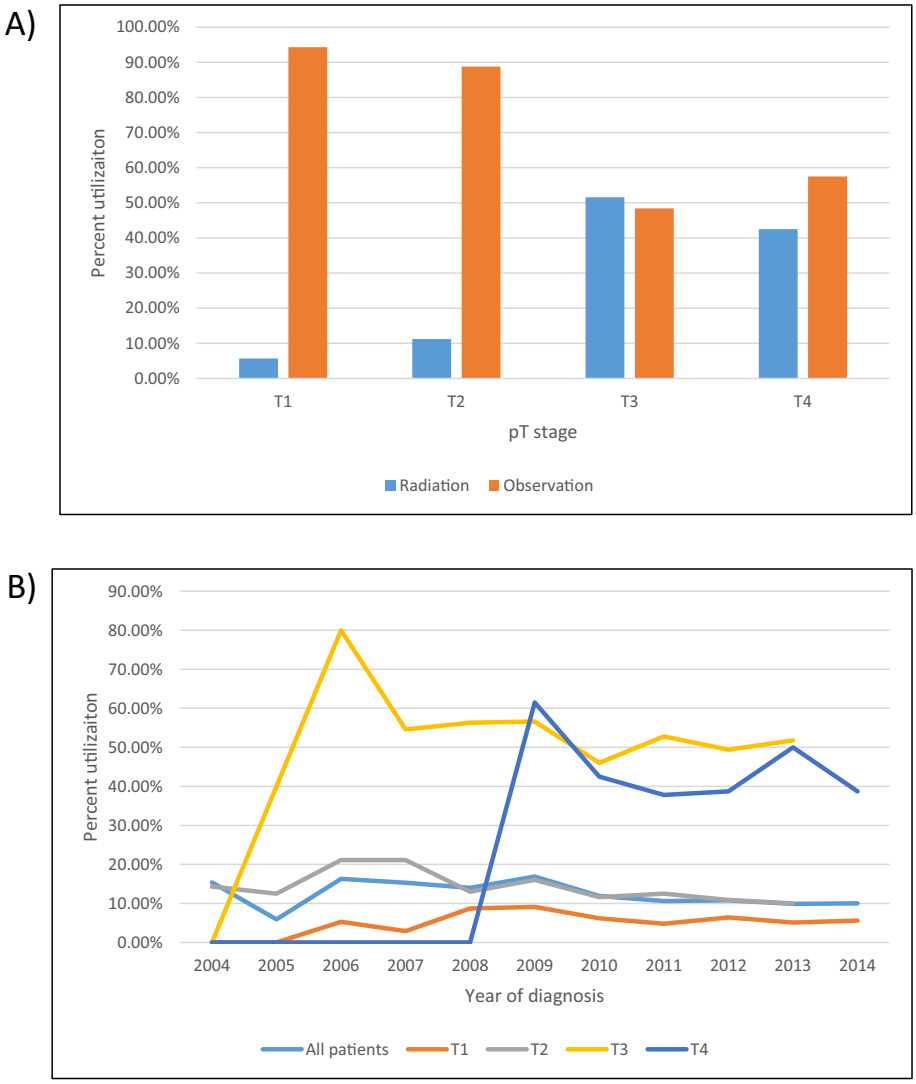


**Fig. 2.** (A) Post-mastectomy radiation therapy use by T stage. (B) Post-mastectomy radiation therapy utilization by year of diagnosis.

of 1569 (10.8%) received PMRT, whereas 12,895 (89.2%) did not receive PMRT. An analysis of the rates of PMRT by stage (Fig. 2A) demonstrated significant variation of PMRT utilization by T stage ($p < 0.001$). PMRT use was 5.7% for patients with pT1 disease, 11.2% for patients with pT2 disease, 51.6% for patients with pT3 disease, and 42.5% for patients with pT4 disease. PMRT use also varied by surgical margin status, with 29.5% of patients with positive surgical margins undergoing PMRT, whereas 10.3% of patients with negative surgical margins received PMRT ($p < 0.001$). No significant differences were found when analyzing use of PMRT among all patients (Fig. 2B) over time.

On multivariable logistic regression analysis (Table 2), increasing age, private and Medicare insurance, treatment at an academic facility, negative surgical margins, and omission of systemic chemotherapy were associated with omission of PMRT. Increasing pT stage was associated with an increased likelihood of PMRT use.

Median follow-up using the reverse Kaplan–Meier method was 38.2 months (interquartile range, 25.9–51.7 months). When substratifying for pT stage, there was no difference in OS between PMRT or observation for patients with pT1 disease (5 year OS 86.9% vs. 83.4%, $p = 0.083$, Fig. 3A), pT2 disease (5 year OS 77.8% vs. 72.2%, $p = 0.250$, Fig. 3B), or pT4 disease (5 year OS 51.7% vs. 49.3%, $p = 0.362$, Fig. 3D). However, for patients with pT3 disease, use of PMRT was associated with improved OS (5 year OS 62.6% vs. 74.3%, $p < 0.001$, Fig. 3C).

In the overall cohort, there were several predictors of improved OS on Cox multivariate analysis (Table 3). These included younger age, fewer comorbidities, private insurance, higher socioeconomic status, lower pT stage, negative surgical margins, and use of chemotherapy. While use of PMRT was associated with worse OS on univariate analysis (hazard ratio [HR] 0.622 for observation compared to use of PMRT, 95% confidence interval [CI] 0.541–0.715, $p < 0.001$), this association did not persist on multivariate analysis (HR 0.883, 95% CI 0.754–1.033, $p = 0.119$).

## Discussion

The present investigation using U.S. hospital-based data is the largest study to date of present-day practice patterns regarding the utilization of PMRT for patients with node-negative TNBC. The results presented herein demonstrate that among this patient cohorts, PMRT is used in a minority of patients, though its utilization varies significantly with pT stage. Additionally, younger age, positive surgical margins, and use of chemotherapy were associated with PMRT use in this patient population. Importantly, PMRT

**Table 2**
Multivariable logistic regression analysis for factors predictive of post-mastectomy radiation therapy.

| Characteristic | Odds ratio | 95% Confidence interval | *P* value |
|---|---|---|---|
| Age | | | |
| ≤50 | 1 (reference) | | |
| 51–60 | 0.976 | 0.832–1.145 | 0.765 |
| 61–70 | 0.768 | 0.631–0.934 | 0.008 |
| 71+ | 0.661 | 0.515–0.845 | 0.001 |
| Race | | | |
| White | 1 (reference) | | |
| African American | 1.162 | 0.998–1.355 | 0.054 |
| Other | 1.084 | 0.832–1.414 | 0.549 |
| Charlson–Deyo's Score | | | |
| 0 | 1 (reference) | | |
| 1 | 0.864 | 0.728–1.027 | 0.097 |
| ≥2 | 0.816 | 0.591–1.126 | 0.215 |
| Insurance status | | | |
| Medicaid | 1 (reference) | | |
| Private | 0.723 | 0.600–0.873 | 0.001 |
| Medicare | 0.638 | 0.501–0.814 | <0.001 |
| Not insured | 0.914 | 0.647–1.292 | 0.612 |
| Other | 0.665 | 0.435–1.016 | 0.059 |
| Median Income | | | |
| ≤$62999 | 1 (reference) | | |
| ≥$63000 | 0.923 | 0.812–1.050 | 0.223 |
| Not recorded | 0.716 | 0.238–2.152 | 0.552 |
| Facility type | | | |
| Non academic | 1 (reference) | | |
| Academic | 0.842 | 0.733–0.966 | 0.014 |
| Not recorded | 1.265 | 1.040–1.538 | 0.019 |
| T stage | | | |
| 1 | 1 (reference) | | |
| 2 | 1.902 | 1.671–2.164 | <0.001 |
| 3 | 17.978 | 5.052–21.473 | <0.001 |
| 4 | 12.519 | 9.178–17.077 | <0.001 |
| Systemic chemotherapy | | | |
| Yes | 1 (reference) | | |
| No | 0.343 | 0.270–0.436 | <0.001 |
| Not recorded | – | – | – |
| Surgical margins | | | |
| Positive | 1 (reference) | | |
| Negative | 0.271 | 0.206–0.358 | <0.001 |
| Not reported | 0.75 | 0.418–1.344 | 0.334 |

use was not associated with improved OS in all patients, though its use was found to be associated with improved OS among patients with pT3 disease. These results have implications on the appropriate use of PMRT in the setting of node-negative TNBC, and suggest that the current NCCN guidelines of not including TNBC status as a criterion to include PMRT in patients with T1-2N0 disease is appropriate.

The present results suggest that physicians are not routinely using TNBC status alone as an indication for PMRT use for patients with node-negative disease. Only 5.7% of patients with pT1N0 disease and 11.2% of patients with pT2N0 disease received PMRT. However, the utilization of PMRT increased to 51.6% for patients with pT3N0 TNBC and to 42.5% for patients with pT4N0 disease, again suggesting that physicians may be using the NCCN guidelines of considering PMRT use in patients with T3 or higher disease. Importantly, the utilization rates of PMRT remain low, even for patients with pT3 or pT4 disease, and are significantly lower than rates of PMRT for patients with ypN1 (57.9%), ypN2 (68.4%), or ypN3 (67.0%) disease [16], though it should be noted that these PMRT rates are from a study of patients undergoing neoadjuvant chemotherapy, and it may be that these higher PMRT rates are due to the residual nodal positive even after neoadjuvant treatment. The lack of routine PMRT even for patients with T3 or higher disease may be reasonable despite the inclusion of these patients in the early trials investigating the efficacy of PMRT, as the Early Breast Cancer Trialists Cooperative Group (EBCTCG) demonstrated that for patients with node-negative disease, the local recurrence rate without PMRT was only 1.6% [5]. While there are factors that are predictive for local recurrence in patients with node-negative breast cancer having undergone mastectomy, including lymphovascular space invasion (LVSI), premenopausal status, and tumor size >2 cm [17–20], TNBC has not been demonstrated to be a risk factor necessitating the use of PMRT, and the present results indicate physicians in the U.S. have not been using TNBC status alone as a factor to determine the need for PMRT. Moreover, certain clinical and demographic characteristics were predictive of omission of PMRT. Increasing age and omission of systemic chemotherapy were both predictive of omission of PMRT, suggesting that patients who may have been less likely to benefit from PMRT due to either comorbid conditions or an inability to tolerated the toxicities of treatment may have not received PMRT. The presence of negative surgical margins was predictive of a decreased likelihood of PMRT use as well, which is in line with data that demonstrates that positive surgical margins lead to a higher chance of local recurrence.

No difference in OS was observed with the use of PMRT in patients with pT1, pT2, or pT4 disease. While local control is not recorded in the NCDB, the OS information is valuable and suggests

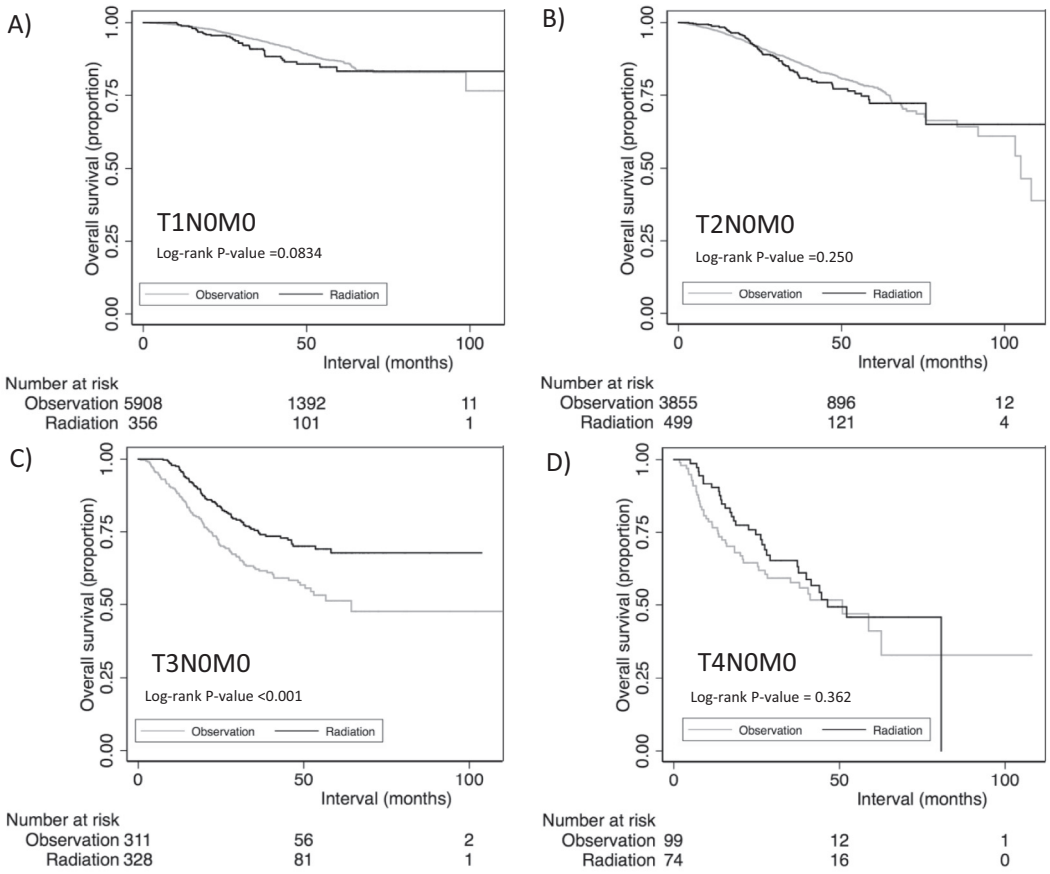


**Fig. 3.** Kaplan–Meier's curves comparing overall survival for patients with (A) T1 disease; (B) T2 disease; (C) T3 disease; (D) T4 disease.

a lack of benefit to PMRT in patients with node-negative, early stage TNBC. The significant OS gain observed in patients with pT3 disease undergoing PMRT suggests that tumor size may be an important indicator of biologic aggressiveness, and patients with tumors >5 cm may require PMRT to eradicate microscopic residual disease that persists following a mastectomy. The lack of observed benefit with use of PMRT among patients with pT4 disease is curious, but may be a result of the relatively small sample size of the pT4 cohort. Alternatively, it may be due to the lack of benefit of local treatment in patients who may already have distant micrometastatic disease.

The present results are discordant with a randomized trial that demonstrated significant OS improvements with use of PMRT for patients with stage I–II TNBC [12]. There are a number of possible reasons for the differences in outcomes observed in the aforementioned trial and those observed in the present study. First, the trial randomized patients diagnosed with TNBC between 2001 and 2006, an earlier era in which systemic therapy may not have been as comprehensively efficacious. PMRT may have thus compensated for inadequate systemic treatment. Second, while over 80% of patients included in the trial had N0 disease, about 20% of patients did have node-positive disease. It is possible that most of the OS benefit with the use of PMRT was limited to the node-positive patients; since the present study did not include any patients with node-positive disease, no OS benefit was observed for T1-2 patients. Third, it is possible that there was a selection bias present in the present observational study, and patients at higher risk for recurrence due to factors not present within the NCDB may have been preferentially selected for PMRT. Consequently, the patients receiving PMRT with T1-2 disease in the present study may not have had an OS benefit due to more biologically aggressive disease, whereas the randomized study design of the aforementioned trial by Wang et al. was able to eliminate clinical differences between the two cohorts of patients and was thus able to demonstrate differences in outcome with the use of PMRT. Finally, nearly 60% of patients included in the trial were $\leq$50 years of age, whereas only about 33% of patients in the present observational study were $\leq$50 years old. PMRT may have a greater benefit among younger, premenopausal patients.

Two recent retrospective reviews have demonstrated a benefit with the addition of PMRT in patients with TNBC. In a review of 104 patients with Stage II–III TNBC treated with neoadjuvant chemotherapy and modified radical mastectomy, Chen et al. showed that patients treated with PMRT had improved local control and distant disease control, regardless of whether or not these patients has positive lymph nodes [21]. In another retrospective review from a single institution, Shen et al. demonstrated that out of 167 patients with TNBC and T1-2N1 disease, the addition of PMRT resulted in decreased locoregional failure [22]. Due to the limitations of the NCDB, the present study was not able to report on potential local control benefits with PMRT, and this is an area that requires further exploration.

Though the NCDB offers a unique platform to study national practice patterns of PMRT use among patients with node-negative TNBC, there are several known limitations inherent to this dataset [14,23]. NCDB studies are characteristically retrospective and consequently, can never eliminate selection biases, including but not limited to judgment by individual providers, nature of follow-up management, and referral patterns. Therefore, the results of this study should be interpreted with caution, given that the specific

**Table 3**
Univariate and multivariate analysis for factors predictive of overall survival.

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| Characteristic | Hazard ratio | 95% Confidence interval | *P* value | Hazard ratio | 95% Confidence interval | *P* value |
| Group | | | | | | |
| Radiation | 1 (reference) | | | 1 (reference) | | |
| Observation | 0.622 | 0.541–0.715 | <0.001 | 0.883 | 0.754–1.033 | 0.119 |
| Age | | | | | | |
| ≤50 | 1 (reference) | | | 1 (reference) | | |
| 51–60 | 1.149 | 0.969–1.362 | 0.109 | 1.079 | 0.896–1.299 | 0.424 |
| 61–70 | 1.571 | 1.331–1.855 | <0.001 | 1.241 | 1.014–1.519 | 0.036 |
| 71+ | 3.625 | 3.140–4.184 | <0.001 | 2.179 | 1.759–2.698 | <0.001 |
| Race | | | | | | |
| White | 1 (reference) | | | – | – | – |
| African American | 1.150 | 0.999–1.323 | 0.051 | – | – | – |
| Other | 0.762 | 0.572–1.014 | 0.06 | – | – | – |
| Charlson–Deyo's Score | | | | | | |
| 0 | 1 (reference) | | | 1 (reference) | | |
| 1 | 1.682 | 1.475–1.918 | <0.001 | 1.425 | 1.248–1.628 | <0.001 |
| ≥2 | 3.610 | 3.022–4.313 | <0.001 | 2.525 | 2.107–2.038 | <0.001 |
| Insurance status | | | | | | |
| Medicaid | 1 (reference) | | | 1 (reference) | | |
| Private | 0.509 | 0.419–0.619 | <0.001 | 0.661 | 0.542–0.805 | <0.001 |
| Medicare | 1.479 | 1.226–1.783 | <0.001 | 0.957 | 0.766–1.196 | 0.698 |
| Not insured | 0.915 | 0.635–1.319 | 0.634 | 0.881 | 0.611–1.271 | 0.498 |
| Other | 0.614 | 0.391–0.965 | 0.034 | 0.668 | 0.424–1.052 | 0.082 |
| Median Income | | | | | | |
| ≤$62999 | 1 (reference) | | | 1 (reference) | | |
| ≥$63000 | 0.682 | 0.603–0.771 | <0.001 | 0.835 | 0.737–0.946 | 0.005 |
| Not recorded | 2.451 | 1.271–4.724 | 0.007 | 2.817 | 1.459–5.438 | 0.002 |
| Facility type | | | | | | |
| Non academic | 1 (reference) | | | 1 (reference) | | |
| Academic | 0.847 | 0.751–0.956 | 0.007 | 0.986 | 0.873–1.113 | 0.817 |
| Not recorded | 0.535 | 0.423–0.675 | <0.001 | 0.928 | 0.710–1.213 | 0.585 |
| T stage | | | | | | |
| 1 | 1 (reference) | | | 1 (reference) | | |
| 2 | 2.061 | 1.831–2.320 | <0.001 | 2.144 | 1.900–2.420 | <0.001 |
| 3 | 4.568 | 3.869–5.393 | <0.001 | 4.162 | 3.468–5.00 | <0.001 |
| 4 | 7.578 | 5.966–9.644 | <0.001 | 6.202 | 4.827–7.967 | <0.001 |
| Systemic chemotherapy | | | | | | |
| Yes | 1 (reference) | | | 1 (reference) | | |
| No | 1.779 | 1.578–2.006 | <0.001 | 1.472 | 1.287–1.682 | <0.001 |
| Not recorded | 2.098 | 1.125–3.911 | 0.020 | 1.620 | 0.865–3.034 | 0.132 |
| Surgical margins | | | | | | |
| Positive | 1 (reference) | | | 1 (reference) | | |
| Negative | 0.597 | 0.449–0.794 | <0.001 | 0.708 | 0.531–0.944 | 0.019 |
| Not reported | 0.478 | 0.226–1.009 | 0.053 | 0.654 | 0.309–1.384 | 0.267 |

reason for the selection patients to receive PMRT could not be ascertained. Second, the NCDB does not record information regarding the chemotherapy agents used, which may have been a source of confounding. Third, as mentioned above, important information regarding clinical outcomes including local control or distant metastasis free survival, all potential indicators for benefit of PMRT use, are not included in the NCDB. Fourth, this investigation has a limited follow up time. It is possible that with longer follow up worse outcomes may have been recorded in patients not receiving PMRT. Finally, the NCDB does not contain detailed information regarding the radiation fields, including whether or not the supraclavicular nodes and internal mammary nodes were included, for a majority of patients.

This study using a large, contemporary data base of national practice patterns, demonstrates that the use of PMRT for node-negative TNBC is low for early stage patients, and the use of PMRT is greater for pT3-4 patients as well as patients with positive surgical margins. Additionally, use of PMRT is associated with an OS advantage in pT3 patients. These results suggest PMRT should not be used routinely in patients with pT1-2N0 disease, but may be indicated in patients with pT3 disease.

## Disclaimers

None. This has never been presented/published before in any form. All authors declare that conflicts of interest do not exist.

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Waqar Haque was responsible for the statistical analysis.

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