Original Investigation

Temporal Trends in Postmastectomy Radiation Therapy and Breast Reconstruction Associated With Changes in National Comprehensive Cancer Network Guidelines

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IMPORTANCE Evolving data on the effectiveness of postmastectomy radiation therapy (PMRT) have led to changes in National Comprehensive Cancer Network (NCCN) recommendations, counseling clinicians to "strongly consider" PMRT for patients with breast cancer with tumors 5 cm or smaller and 1 to 3 positive nodes; however, anticipation of PMRT may lead to delay or omission of reconstruction, which can have cosmetic, quality-of-life, and complication implications for patients.

OBJECTIVE To determine whether revised guidelines have increased PMRT and affected receipt of breast reconstruction. We hypothesized that (1) PMRT rates would increase for women affected by the revised guidelines while remaining stable in other cohorts and (2) receipt of breast reconstruction would decrease in these women while increasing in other groups.

DESIGN, SETTING, AND PARTICIPANTS Retrospective, population-based cohort study of Surveillance, Epidemiology, and End Results (SEER) data on women with stage I to III breast cancer undergoing mastectomy from 2000 through 2011. Our analytic sample (N = 62 442) was divided into cohorts on the basis of current NCCN radiotherapy recommendations: "radiotherapy recommended" (tumors >5 cm or ≥4 positive lymph nodes), "strongly consider radiotherapy" (tumor ≤5 cm, 1-3 positive nodes), and "radiotherapy not recommended" (tumors ≤5 cm, no positive nodes).

MAIN OUTCOMES AND MEASURES We used Joinpoint regression analysis to evaluate temporal trends in receipt of PMRT and breast reconstruction.

RESULTS The 3 cohorts comprised 15 999 in the "radiotherapy recommended" group, 15 0006 in the "strongly consider radiotherapy" group, and 31 837 in the "radiotherapy not recommended" group. Rates of PMRT were unchanged in the radiotherapy recommended (29.9%) and radiotherapy not recommended (7.4%) cohorts over the study period. Receipt of PMRT for the strongly consider radiotherapy cohort was unchanged at 26.9% until 2007. At that time, a significant change in the APC was observed (P=.01) with an increase in APC from 2.1% to 9.0% (P = .02) through the end of the study period, for a final rate of 40.5%. Breast reconstruction increased across all cohorts. Despite increasing receipt of PMRT, the strongly consider radiotherapy cohort maintained a consistent increase in reconstruction (annual percentage change, 7.4%) throughout the study period. This is similar to the increase in reconstruction observed for the radiotherapy recommended (10.7%) and radiotherapy not recommended (8.4%) cohorts.

CONCLUSIONS AND RELEVANCE Changes in NCCN guidelines have been associated with an increase in PMRT among patients with tumors 5 cm or smaller and 1 to 3 positive nodes without an associated decrease in receipt of reconstruction. This may represent increasing clinician comfort with irradiating a new breast reconstruction and may have cosmetic and quality-of-life implications for patients.

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Invited Commentary

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In the past decade, indications for the use of postmastectomy radiation therapy (PMRT) have expanded. Prior to the year 2000, several trials demonstrated decreased locoregional recurrence, as well as improved survival, in patients with breast cancer with tumors larger than 5 cm, positive lymph nodes, and/or invasion of skin or pectoral fascia who received PMRT plus mastectomy and axillary clearance vs mastectomy and axillary clearance alone,[1-3] establishing a standard of care for who should be considered for PMRT. In subgroup analyses of these initial studies, the observed benefits of PMRT persisted in patients with 1 to 3 positive lymph nodes, with a decrease in locoregional recurrence from 27% to 4% ($P < .001$) and a corresponding increase in overall survival from 48% to 57% ($P = .03$).[4] Further data supporting the benefit of PMRT for patients with 1 to 3 positive lymph nodes was presented by the Early Breast Cancer Trialists' Collaborative Group in 2005. Although the magnitude of the absolute reduction in locoregional recurrence was lower in this meta-analysis (11.6%) than in the randomized clinical trials, similar results were observed, with a 4.1% improvement in 15-year breast cancer survival for patients who underwent mastectomy, axillary clearance, and PMRT compared with surgery alone ($P < .01$).[5] On the basis of these findings, the National Comprehensive Cancer Network (NCCN) expanded its treatment guidelines to "strongly consider" PMRT for patients with tumors 5 cm or smaller and 1 to 3 positive lymph nodes.[6] However, the role of PMRT for patients with 1 to 3 positive lymph nodes remains controversial because of the relatively high rate of local recurrence observed in these trials combined with advances in systemic and targeted therapies since completion of the trial.

Concurrently, there has been a rapid expansion in the use of immediate breast reconstruction over the past 2 decades.[7,8] Breast reconstruction appears to significantly improve quality of life,[9,10] and immediate reconstruction reduces the adverse psychosocial effects associated with mastectomy,[11] can streamline treatment by reducing the number of necessary surgical procedures, and is favored by women compared with delayed reconstruction.[12] However, for patients who anticipate receiving PMRT, reconstruction decision making becomes more complicated: prior studies suggest that both radiation oncologists and plastic surgeons have reservations about the use of immediate reconstruction in patients who receive PMRT. The majority of radiation oncologists believe that immediate breast reconstruction challenges their ability to effectively deliver radiotherapy to the chest wall,[13] and the majority of reconstructive surgeons would prefer to delay reconstruction in the setting of anticipated PMRT.[14] Postmastectomy radiation therapy appears to be associated with increased risk of reconstruction-related complications such as implant removal[15,16] and fat necrosis of autologous tissue reconstructions[16]; however, there is no clear association between PMRT and reduced patient satisfaction.[15,17] Currently, there is no consensus on optimal management and timing of breast reconstruction in the setting of possible PMRT. Consequently, whereas the new NCCN guidelines urging strong consideration of PMRT in patients with tumors 5 cm or smaller with 1 to 3 positive lymph nodes have the potential to significantly affect oncologic outcomes, they may also lead clinicians to discourage immediate breast reconstruction, resulting in poorer patient satisfaction and quality of life.

At a Glance

- Revised guidelines recommend consideration of postmastectomy radiation therapy (PMRT) for patients with breast cancers 5 cm or smaller and 1 to 3 positive nodes; we evaluated the effect on receipt of PMRT and breast reconstruction.
- We created cohorts based on current guidelines: "radiotherapy recommended" (tumors >5 cm or ≥4 positive lymph nodes), "strongly consider radiotherapy" (≤5 cm, 1-3 nodes), and "radiotherapy not recommended" (≤5 cm, 0 nodes).
- Rates of PMRT were unchanged in the radiotherapy recommended and radiotherapy not recommended cohorts. Rates of PMRT were unchanged in the strongly consider radiotherapy cohort until 2007, then significantly increased ($P = .01$).
- Rates of breast reconstruction increased across all radiation recommendation cohorts at a similar rate.
- Increasing rates of reconstruction despite increased PMRT may represent growing clinician comfort with irradiating a new breast reconstruction and may have cosmetic and quality-of-life implications for patients.

We therefore sought to determine whether changing guidelines have increased receipt of PMRT in patients with tumors 5 cm or smaller and 1 to 3 positive lymph nodes, and whether any changes in receipt of PMRT have affected rates of breast reconstruction. We hypothesized that (1) PMRT would increase in the cohort of patients for whom NCCN guidelines have changed (ie, patients with tumors ≤5 cm and 1-3 positive lymph nodes) while use of PMRT in those with clear indications for (tumors >5 cm or ≥4 positive lymph nodes) or against (tumors ≤5 cm with negative lymph nodes) would remain stable, and (2) new guidelines would result in a decrease in the receipt of breast reconstruction in patients for whom NCCN guidelines for PMRT have changed relative to those for whom the NCCN PMRT guidelines have remained the same.

Methods

Patients who underwent mastectomy for stage I to III breast cancer from 2000 through 2011 were identified in the Surveillance, Epidemiology, and End Results (SEER) database (n = 104 433). Patients were excluded if they were male (n = 2003), had prior cancers (including prior breast cancer) (n = 37 214), or had previously received radiotherapy (n = 2774). The final sample size was 62 442 patients. This project fell under an institutional review board exemption due to its use of deidentified data and does not constitute research involving human subjects.

Patients were grouped into 3 cohorts on the basis of current NCCN recommendations for receipt of PMRT (**Table 1**). The "radiotherapy recommended" cohort (n = 15 599) represents patients with 4 or more positive lymph nodes, regardless of tumor size, and patients with tumors larger than 5 cm, regardless of nodal status. The "strongly consider radiotherapy" cohort (n = 15 006) represents patients for whom NCCN guidelines have changed over the study period: those with tumors

Table 1. Cohort Creation Based on National Comprehensive Cancer Network Guidelines for Receipt of Postmastectomy Radiation Therapy

Study Cohort	Tumor Characteristics	No.
Radiotherapy recommended	Tumor >5 cm in size (regardless of nodal status) with ≥4 positive lymph nodes (regardless of primary tumor size)	15 599
Strongly consider radiotherapy	Tumor ≤5 cm with 1-3 positive lymph nodes	15 006
Radiotherapy not recommended	Tumor ≤5 cm with 0 positive lymph nodes	31 837

5 cm or smaller and 1 to 3 positive lymph nodes. The last cohort, "radiotherapy not recommended" (n = 31 837), represents patients with tumors 5 cm or smaller and negative lymph nodes. Sociodemographic data (age, race/ethnicity, marital status), tumor characteristics (tumor size, number of positive lymph nodes, estrogen and progesterone receptor status), and receipt of PMRT and immediate reconstruction as reported by SEER were evaluated for the overall sample and by cohort using Stata, version 12.1 (StataCorp). As defined by SEER guidelines, nodal status and tumor size are coded according to the most advanced stage (pathologic or clinical) identified for a given patient. Breast reconstruction included any reconstruction within 4 months of mastectomy, as defined by SEER.

Outcomes

The aim of our study was to investigate rates of receipt of PMRT and breast reconstruction in women for whom NCCN guidelines regarding PMRT changed over the study period, relative to that of women for whom NCCN guidelines for PMRT have remained unchanged.

Statistical Analysis

Differences between the 3 cohorts in sociodemographic and tumor characteristics were assessed with the Pearson χ^2 test. A 2-tailed $P < .05$ was considered statistically significant. Exploratory analyses using logistic regression were performed to evaluate associations between demographic and tumor characteristics with receipt of reconstruction and PMRT.

Temporal trends in receipt of PMRT and breast reconstruction were evaluated for our cohorts using Joinpoint regression software (National Cancer Institute). Joinpoint regression analysis is increasingly used[18,19] to evaluate temporal trends in an outcome of interest by evaluating changes in the rates of that outcome over time. Joinpoint regression analysis determines whether multiple regression lines provide a better fit for the data than a single straight line, suggestive of changing trends in the data. If a multisegmented line represents a better fit, this means that the rate of change (the slope of the line) is different before and after 1 or more points in time, and the program provides statistical estimation of when the change(s) in slope occurred, with $P < .05$ considered statistically significant. It also calculates the slope of all line segments, called the annual percentage change (APC), and the likelihood that this APC is significantly different from 0, or represents a statistically significant trend ($P < .05$). The APC represents the change in rate on an annual basis—for example, an APC of 0 would reflect no change over time and would be represented by a horizontal line on the graph. An APC of any value would not be considered significant if the software is unable to definitively identify a trend in the data. For these reasons, a small APC associated with a definitive trend (for example, 0.4%) may be considered statistically significant while a larger APC (for example, 10%) associated with more variable data may not.

Sensitivity Analyses

Older women are less likely to undergo breast reconstruction[7,20] and tend to have less aggressive and lower stage tumors, making them overrepresented in our radiotherapy not recommended cohort. Because we were interested in the relationship between radiotherapy and reconstruction, we wanted to ensure that age was not confounding our results. We therefore performed a sensitivity analysis evaluating changes in rates of both PMRT and breast reconstruction, considering only those patients younger than 65 years.

Results

Table 2 provides a summary of differences in sociodemographic and tumor characteristics for our overall cohort and by NCCN PMRT recommendations. Approximately half of patients were in the radiotherapy not recommended cohort, with the remaining half split nearly equally between the radiotherapy recommended and strongly consider radiotherapy cohorts. Patients in the radiotherapy not recommended cohort were more likely to be older ($P < .001$). In addition to the expected differences in tumor size and lymph node status between the radiotherapy recommendation cohorts, patients in the radiotherapy recommended cohort were more likely to be estrogen and progesterone receptor negative.

Radiotherapy was received by 67.6% of patients in the radiotherapy recommended cohort, 29.9% in the strongly consider radiotherapy cohort, and 7.4% in the radiotherapy not recommended cohort. Age was significantly associated with receipt of radiotherapy for both the radiotherapy recommended and strongly consider radiotherapy cohorts. For example, in the radiotherapy recommended cohort, patients aged 55 to 64 years (odds ratio [OR], 0.77 [0.69-0.87]) and 65 years or older (OR, 0.44 [95% CI, 0.40-0.50]) were significantly less likely to receive PMRT than patients younger than 45 years ($P < .001$). Tumor characteristics also influenced receipt of radiotherapy. In the radiotherapy recommended cohort, patients who were recommended PMRT on the basis of tumor size alone (ie, T3N0) were less likely to receive PMRT than those with 4 or more positive nodes (OR, 0.43 [95% CI, 0.39-0.47]). In the strongly consider radiotherapy cohort, patients with smaller tumors (<2 vs 2-5 cm) and lower tumor grade (grade 1 vs 2/2) were less likely to receive PMRT ($P < .001$).

Postmastectomy Radiation Therapy

Use of PMRT increased over the study period from 24.7% in 2000 to 30.0% in 2011. Results of the Joinpoint regression analysis of receipt of PMRT indicated that the radiotherapy rec-

Table 2. Demographic and Tumor Characteristics for Women Undergoing Mastectomy for Invasive Breast Cancer, Surveillance, Epidemiology, and End Results Database, 2000 Through 2011

Characteristic	%[a]			
		NCCN Radiotherapy Recommendation Cohort[b]		
	All Patients (N = 62 442)	Recommended (n = 15 599)	Strongly Consider (n = 15 006)	Not Recommended (n = 31 837)
Demographic Characteristics				
Age, y				
<45	17.2	19.8	19.5	14.5
45-54	25.8	27.5	28.1	24.0
55-64	22.5	22.8	22.3	22.5
≥65	34.5	29.9	30.2	38.8
Race				
White	80.4	77.9	81.0	81.4
Black	9.1	12.2	9.4	7.5
Other	9.9	9.6	9.1	10.5
Marital status				
Married	57.4	55.6	59.3	57.5
Single	12.9	14.7	12.4	12.1
Divorced, separated, or widowed	25.7	26.0	24.6	26.0
Tumor Characteristics				
Tumor size, cm				
0-2.0	43.0	9.3	37.5	62.2
2.1-5.0	43.4	36.4	62.5	37.8
>5.0 or diffuse/inflammatory	13.6	54.3	0	0
Positive lymph nodes				
0	54.8	15.4	0	100
1-3	28.1	16.3	100	0
≥4	17.1	68.3	0	0
Estrogen receptor status				
Positive	73.3	68.8	76.1	74.2
Negative	21.5	26.5	19.6	19.6
Progesterone receptor status				
Positive	62.4	57.0	65.7	63.4
Negative	32.0	37.9	29.7	30.3
Receipt of PMRT	27.1	67.6	29.9	7.6
Receipt of breast reconstruction	21.7	15.6	22.1	24.1

Abbreviations: NCCN, National Comprehensive Cancer Network; PMRT, postmastectomy radiation therapy.

[a] Data shown for all patients and for cohorts based on NCCN guidelines for receipt of PMRT. Percentages sum within columns for each category (age, race, marital status). Missing data not shown; percentages may not sum to 100%.

[b] All demographic and tumor characteristics were significantly different among the 3 cohorts ($P < .001$).

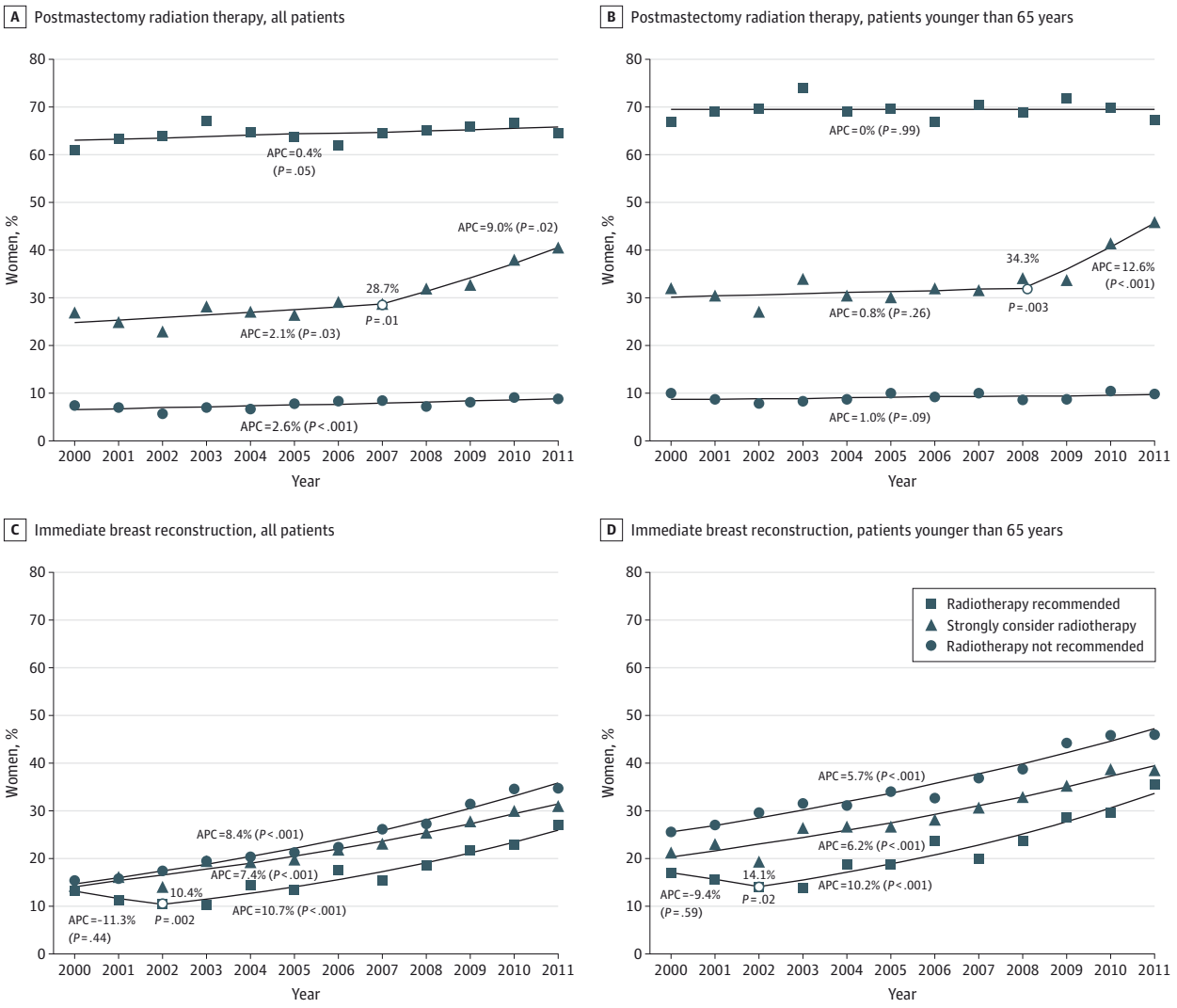
ommended and radiotherapy not recommended cohorts demonstrated small but steady increases in receipt of PMRT over the study period. This corresponds to an APC of 0.4% (increase in rate of PMRT from 60.8% to 64.4%; $P = .05$) and 2.6% (change from 7.5% to 8.8%; $P < .001$) over the study period, respectively (**Figure**, A). Receipt of PMRT in the strongly consider radiotherapy cohort was statistically unchanged until 2007. At that time, a significant change in the APC was observed ($P = .01$) with an increase in APC from 2.1% to 9.0% ($P = .02$) through the end of the study period (increase in rate of PMRT from 26.9% to 40.5%).

Given the observed difference in age between the radiotherapy cohorts, we assessed changes in rates of receipt of PMRT in a subgroup of women younger than 65 years (n = 30 605), with similar findings observed (Figure, B). Receipt of PMRT for the radiotherapy recommended and radiotherapy not recommended cohorts was stable throughout the study period. The strongly consider radiotherapy cohort demonstrated a statistically unchanged rate of PMRT (32.0%) until 2008, followed by a change in slope ($P = .003$) and a subsequent APC of 12.6% ($P < .001$) until the end of the study period when the rate of PMRT was 45.9%.

Breast Reconstruction

The receipt of breast reconstruction increased during the study period from 14.8% to 31.9% overall. Younger age, white race, smaller tumor size, negative lymph node status, and later year of diagnosis were all associated with receipt of reconstruction ($P < .001$). Results from the Joinpoint regression analysis (Figure, C) indicate that the radiotherapy not recommended and strongly consider radiotherapy cohorts experienced steadily increasing rates of breast reconstruction throughout the study period. This corresponds to APCs of 8.4% (increase in reconstruction rate from 15.4% to 34.7%; $P < .001$) and 7.4% (increase from 14.8% to 30.9%; $P < .001$), respectively. The radiotherapy recommended cohort experi-

Figure. Joinpoint Regression Analysis of Postmastectomy Radiation Therapy and Immediate Breast Reconstruction



A, Postmastectomy radiation therapy, all patients (N = 62 442). B, Postmastectomy radiation therapy, patients younger than 65 years (n = 30 605). C, Immediate breast reconstruction, all patients (N = 62 442). D, Immediate breast reconstruction, patients younger than 65 years (n = 30 605). Annual percentage change (APC) represents the change in rate on a yearly basis. An APC of 0 would mean no change in the rate, represented by a horizontal line. Open circle indicates that a change in slope has occurred; associated *P* value indicates the statistical significance associated with that change in slope.

enced an unchanged rate of receipt of reconstruction between 2000 and 2002 at 13.4%, at which point there was a change in slope (P = .002) and the APC increased to 10.7% for the remainder of the study period for a final rate of 27.0%. Results were similar when the sample was restricted to patients younger than 65 years old (n = 30 605) (Figure, D).

Discussion

This study used national patient data to examine temporal changes in the rates of receipt of PMRT and breast reconstruction based on current NCCN guidelines for PMRT. As expected, receipt of PMRT by women for whom guideline recommendations did not change (ie, the radiotherapy not recommended and radiotherapy recommended cohorts) demonstrated minimal changes in receipt of PMRT over time, while women for whom the guidelines changed (ie, strongly consider radiotherapy cohort) initially demonstrated statistically unchanged rates of PMRT, followed by a significant increase in PMRT after 2007. This would suggest that, as expected, guidelines are affecting clinical practice patterns, with increased use of PMRT in this group.

Rates of breast reconstruction increased significantly over the study period overall. The rates observed were consistent with findings of other population-based studies, especially when taking into consideration our inclusion of older patients (who are less likely to receive reconstruction) and ex-

clusion of patients with ductal carcinoma in situ (who are more likely to receive reconstruction).[20-23] Although rates of breast reconstruction increased for all 3 cohorts, the baseline and final rates of reconstruction differed on the basis of likelihood of receiving PMRT. This suggests that surgeons may be using anticipated receipt of PMRT to guide decision making regarding recommendations for immediate reconstruction. This is supported by previous literature showing receipt of PMRT to be a negative predictor for both immediate[24] and overall[25] breast reconstruction. However, in contrast to our expectations, rates of breast reconstruction for women in the strongly consider radiotherapy cohort (those with tumors ≤5 cm and 1-3 positive lymph nodes) did not have a change in rate of breast reconstruction to correspond to the observed increase in PMRT. Instead, breast reconstruction continued to increase over time, at a rate similar to that of women in both the radiotherapy not recommended and radiotherapy recommended cohorts (for whom receipt of PMRT was stable).

Patients with locally advanced tumors have an overall poorer prognosis from their cancer and are likely to be recommended PMRT by their clinicians. Given concerns expressed by plastic surgeons and radiation oncologists about PMRT in patients undergoing reconstruction surgery, deferring or recommending against reconstruction in this clinical scenario may be reasonable. Similarly, patients with small, node-negative tumors are not likely to be offered the option of radiotherapy and clinicians may be more comfortable recommending immediate reconstruction. However, how these clinical factors influence decision making for patients who fall into the strongly consider radiotherapy cohort is difficult to determine. The majority of these women likely have clinically node-negative disease at the time of surgery and are identified as eligible for PMRT postoperatively, after reconstruction decision making has already occurred. This may explain why the dramatic changes in rates of PMRT observed in this cohort did not translate into changes in the rate of breast reconstruction.

In the radiotherapy recommended cohort, the first few years of the study demonstrated statistically flat rates of breast reconstruction prior to a statistically significant increase. Although graphically the rate of reconstruction appears to decrease over these years, the increase was not considered significant in our analysis. This finding may represent the tail end of a tendency for women with more advanced tumors to be less likely to be offered or undergo breast reconstruction. The reversal of this tendency could be related to the introduction of new therapies, such as trastuzumab, which significantly improved prognosis and made consideration of reconstruction more relevant for these women. Additionally, introduction of new techniques for reconstruction may have provided surgeons with alternative options for patients who anticipate receiving PMRT. This latter explanation would also help to explain the observed stable increase in rates of reconstruction despite a significant increase in the use of PMRT for the strongly consider radiotherapy cohort.

Although there are a number of strengths to the present study, including a nationally representative sample of breast cancer cases with validated assessments of treatment received, a few limitations should be noted. Underascertainment of radiation therapy is an acknowledged weakness of SEER registry data.[26] However, this should not affect evaluation of temporal trends within each cohort, which is the focus of this article. The SEER registry data do not allow us to determine the proportion of patients undergoing immediate vs early-delayed reconstruction, as all reconstructive procedures within 4 months of initiation of treatment are captured together. Some patients may be receiving early-delayed reconstruction, in which surgeons defer reconstruction at the time of mastectomy to await results of pathologic analysis, and then return to the operating room after a short interval for definitive reconstruction if PMRT is not indicated. This clinical scenario may be especially true for the strongly consider radiotherapy cohort, leading to an underestimation of the effect of current NCCN guidelines for PMRT on decision making surrounding reconstruction. However, recent literature indicates that the majority of reconstructions performed in the United States are immediate (>75%).[20-23,27,28] Therefore, despite our inability to separate immediate from early-delayed reconstruction captured in SEER data, we are confident that the majority of the reconstructions identified in SEER represent immediate reconstruction. Additionally, the present analysis did not include an examination of temporal trends in the types of reconstruction (autologous tissue flap, implant, or combination procedures) or whether type of reconstruction varied by a patient's likelihood of receiving PMRT. It is possible that surgeons are offering different reconstruction options to patients who may be candidates for PMRT (ie, less likely to offer tissue expander and implant reconstruction); this may have implications on patients' out-of-pocket costs of reconstruction, cosmesis, and overall satisfaction with their reconstruction, and our study may therefore underestimate the influence of changes to PMRT recommendations on the experience of patients who undergo breast reconstruction. However, to fully assess trends in the type of reconstruction received, it would be important to have complete information on all reconstructions, including those that occur in a delayed fashion. Given that SEER does not capture delayed reconstruction, we were unable to assess this in this study. Finally, these data cannot assess the contributions of surgeon practice patterns and patients' values and preferences to decision making for breast reconstruction.

Conclusions

The multidisciplinary treatment of women with breast cancer is complex and continues to evolve. Numerous factors influence the receipt of breast reconstruction, including nonclinical factors such as the availability of reconstructive surgeons, institutional and physician practice patterns, and patients' values and preferences. We examined 1 important clinical component, the expanded use of PMRT, as the decision for PMRT requires breast cancer clinicians and patients to weigh improved cancer outcomes (local-regional recurrence and survival) associated with PMRT against the potential for negative implications on breast reconstruction. It is encouraging that the national increases in PMRT that we observed

were not accompanied by declining use of breast reconstruction, despite prior evidence that reconstructive surgeons would prefer to delay reconstruction in patients who anticipate receiving PMRT. Further research is needed to understand how patients and clinicians reach consensus on this topic, and how receipt of PMRT may be affecting type of reconstruction received and patient-centered outcomes including cosmesis and quality of life.

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Study concept and design: Frasier, Greenberg, Neuman.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Frasier, Greenberg, Neuman.
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