Original Study

Adjuvant Radiation Therapy for T3N0 Breast Cancer Patients Older Than 75 Years After Mastectomy: A SEER Analysis

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Abstract

Current trends seek to identify low-risk breast cancer patients who can forego adjuvant radiation therapy (RT), including elderly patients with stage T3N0 who have undergone mastectomy. The present analysis of 635 such patients in the Surveillance, Epidemiology, and End Results database found decreasing use of post-mastectomy RT (PMRT) with increasing age. We found a trend toward an overall survival benefit with adjuvant RT but no disease-specific survival benefit. However, age could have been a major confounder. These data support continuing efforts to identify which subset of these patients, if any, will benefit from PMRT.

Introduction: Breast cancer patients with tumors > 5 cm but without nodal disease who undergo mastectomy present a clinical challenge regarding the appropriate adjuvant treatment. Traditionally, postmastectomy radiation therapy (PMRT) was the standard of care. However, recent studies have suggested local failure rates without PMRT might be low enough to omit RT. This might be especially true in the elderly. **Patients and Methods:** Women aged ≥ 75 years with a diagnosis of T3N0 breast cancer who had undergone mastectomy were identified from the Surveillance, Epidemiology, and End Results (SEER) 18 database. The study period was limited to 2006 to 2009 for more modern sampling. Multivariable proportional hazards modeling was used to examine the association of treatment and mortality, adjusting for demographic and clinicopathologic factors. **Results:** A total of 635 patients were identified. The median follow-up period was 43 months. PMRT was given to 31.2% of the patients aged 75 to 79 years, 21.5% of those aged 80 to 84 years, and 11.7% of the patients aged ≥ 85 years ($P < .001$). The receipt of PMRT showed a trend toward improved overall survival on bivariable analysis (hazard ratio [HR], 0.58; $P < .001$) and multivariable analysis (HR, 0.78; $P = .14$). The 5-year overall survival was 64.2% for those who had received PMRT and 44.8% for those who had not. A nonsignificant trend was seen toward improved breast cancer-specific survival at 5 years on bivariable analysis (HR, 0.63; $P = .09$) but not on multivariable analysis. The interaction of age and PMRT receipt could have confounded the results. Patient age and tumor grade were significant indicators of the survival prognosis in these patients. **Conclusion:** The results of the present analysis of the SEER database suggest that PMRT might still be beneficial in women aged > 75 years with T3N0 disease but also supports continuing efforts to confirm whether it could be safe to omit. It is likely that efforts to subdivide this population using other factors (eg, comorbidity) will be important. The search for refined inclusion and exclusion criteria for adjuvant RT remains an important field of research both clinically and economically.

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Introduction

An important and growing trend in oncology is that of "less is more," which seeks to identify the patients who will benefit the most and those who will benefit the least from treatment, because all interventions have potential toxicities and costs. This is especially true for diseases such as early-stage breast cancer for which the outcomes are good and the incremental benefit of certain treatments might be outweighed by their risks. Recent trends have seen a shift

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from standard fractionation to hypofractionation,[1,2] from whole breast to partial breast irradiation,[3] and from the inclusion to the omission of adjuvant radiation therapy (RT), at least for carefully selected patients. Significant research has been undertaken to carefully delineate the optimal patient criteria for each treatment decision.

Multiple studies have suggested that women older than a certain age with small estrogen receptor-positive (ER^+) breast cancer who take tamoxifen might not need adjuvant RT after lumpectomy.[4-6] Although a local control benefit was still realized in these studies, no difference was seen in survival. Although the studies included slightly different patients, with age thresholds of 60, 65, or 70 years and tumor size thresholds of 1.0, 2.0, or 3.0 cm, they suggested that elderly patients with small tumors might realize little to no survival benefit from adjuvant RT.

The question regarding elderly women with larger tumors remains. Although currently few debate the need for adjuvant RT for T3N0 patients after lumpectomy, controversy exists regarding whether to offer postmastectomy RT (PMRT) to patients with tumors $>$ 5 cm but no lymph node involvement. The original landmark trials showing a survival benefit of PMRT included T3N0 patients; however, a closer look at the data from the Danish 82c postmenopausal trial showed a 10-year OS in T3 patients of 30% with RT versus 29% without and in N0 patients of 56% with RT versus 55% without.[7] Taghian et al performed a subset meta-analysis of 5 National Surgical Adjuvant Breast and Bowel Project postmastectomy chemotherapy trials and found that the 10-year locoregional recurrence (LRR) rate in T3N0 patients after mastectomy (without RT) was 7.1% overall.[8] This rate was 12.6% without systemic therapy, 5.6% with adjuvant chemotherapy, 4.6% with adjuvant tamoxifen, and 5.3% with chemotherapy and tamoxifen. A caveat of their study was that the average tumor size was 5.5 cm. A similar study from Massachusetts General Hospital showed a 5-year LRR rate of 7.6% in this population with adjuvant systemic therapy.[9] Both of these studies suggested an acceptable LRR rate without PMRT. Also, some concern exists that PMRT might be detrimental in these patients. The Early Breast Cancer Trialists' Collaborative Group 2005 meta-analysis reported that PMRT for node-negative patients reduced the 5-year LRR from 6% to 2% but also increased the incidence of contralateral breast cancer and non–breast cancer mortality (albeit older RT techniques were used).[10]

The current National Comprehensive Cancer Network (NCCN) guidelines, version 3.2017, have recommended considering PMRT with or without regional nodal irradiation for all T3N0 patients. The NCCN guidelines have only recommended the strong consideration of PMRT with 1 to 3 positive lymph nodes and have definitively recommended PMRT only with $\geq$ 4 positive lymph nodes.

The cited studies and others[11,12] have considered factors that might be important in the delineation of patients who will benefit from PMRT, including nodal status, age, surgical margins, histologic grade, lymphovascular invasion (LVI), hormone receptor status, hormonal therapy, and tumor size. The NCCN guidelines currently have only incorporated margin status into their recommendations regarding PMRT and have noted age and LVI, but ongoing trials and reports might add to this.

Unnecessary RT does have disadvantages, including cost, inconvenience, and toxicities. However, the risks might be greater with omission of RT for patients who would benefit. The uncertainty of clinicians regarding the optimal course of action is perhaps reflected in a Surveillance, Epidemiology, and End Results (SEER) analysis that found that PMRT usage increased steeply from 37% in 1996 to 58% in 1998 but then remained relatively flat at $\sim$50% from 1999 to 2005, despite multiple guidelines endorsing its use.[13] Therefore, we studied patient outcomes in the SEER database for elderly women with T3N0 breast cancer after mastectomy, a controversial group concerning the need for adjuvant RT.

Patients and Methods

Patient data were taken from the SEER 18 Registry Research Data set, including Hurricane Katrina–impacted cases, with cases diagnosed from 1973 to 2012, using SEER*Stat, version 8.2.1 (National Cancer Institute, Bethesda, MD). Only cases with malignant tumor behavior, known patient age, and cases in the research database were considered. The eligibility criteria were age at diagnosis of $\geq$ 75 years, female sex, year of diagnosis 2006 through 2009, site and morphology (defined as "breast"), and American Joint Committee on Cancer, 6th edition (2004+), classification of T3, T3a, T3b, T3c, T3, NOS, with N0 and M0 status. The following variables were used in the analysis: age, race, grade, prescription summary, surgical primary Site (1998+), RT, ER status recode breast cancer (1990+), PR status recode breast cancer (1990+), SEER cause-specific death, SEER other cause of death, and survival in months. A total of 964 cases were included in the present analysis.

We calculated the summary statistics using frequencies and proportions for categorical variables. The demographic data and clinical characteristics were compared between the patients who received RT and those did not using the χ^2 test. To evaluate the effect of RT on all-cause and breast cancer-specific death, we first plotted Kaplan-Meier curves and evaluated the differences in survival using log-rank tests. We then constructed Cox proportional hazards regression models for all-cause and breast cancer-specific mortality (ie, separate models), estimating the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the demographic and clinical factors of interest. Multivariable models were adjusted for age at diagnosis, race, grade, and ER and PR status. The proportional hazards assumption was examined using Schoenfeld residuals, and it was not violated in either model. All statistical tests were 2-sided, with statistical significance evaluated at the 0.05 α level. All analyses were conducted with SAS, version 9.4 (SAS Institute, Inc, Cary, NC).

Results

A total of 635 patients were identified from the SEER 18 Registry Research Data set who met all the inclusion criteria. Of the 635 patients, 477 had complete data available for all covariates and were included in the multivariable regression model. Of the included patients, 36.4% were aged 75 to 79 years, 30.1% were aged 80 to 84 years, and 33.5% were aged $\geq$ 85 years. White patients constituted 81.3% of the data set. Of the remaining patients, 12.4% were black and 6.3% were other or unknown. The histologic grade was grade 1 in 16.5%, grade 2 in 35.1%, grade 3 in

36.4%, grade 4 in 1.9%, and unknown in 10.1%. ER status was positive for 65.8%, negative for 24.9%, and unknown for 9.3%. Progesterone receptor (PR) status was positive for 49.6%, negative for 39.8%, and unknown for 10.6%. The full demographic information is listed in Table 1.

The receipt of PMRT was significantly associated with patient age. PMRT was given to 72 of 231 patients (31.2%) aged 75 to 79 years, 41 of 191 patients (21.5%) aged 80 to 84 years, and 25 of 213 patients (11.7%) aged ≥ 85 years ($P < .001$). Additionally, PMRT was given more often to patients with ER^- and PR^- tumors (Table 1).

The median follow-up for all patients was 43 months (range, 0-95 months). Overall, 47.2% of the patients were still alive at the last follow-up visit, 15.0% had died of cancer, and 37.8% had died of a reason other than cancer. Of the 635 patients in the present study, 497 had not received RT (78.3%) and 138 had received RT (21.3%).

The receipt of RT for these selected patients was associated with improved overall survival on bivariable analysis (HR, 0.58; Figure 1A; $P < .001$). The 5-year overall survival was 64.2% for those who had received RT and 44.8% for those who had not received RT. After multivariable adjustment, a nonsignificant trend was observed, suggesting that PMRT was protective (HR, 0.78; 95% CI, 0.55-1.09; $P = .14$). The receipt of PMRT was also associated with trend toward improvement in breast cancer-specific survival (CSS) at 5 years (HR, 0.63; Figure 1B; $P = .09$). The 5-year breast CSS was 86.5% for those who received RT and 80.6% for those who had not. However, this trend was not observed after multivariable analysis (HR, 0.94; 95% CI, 0.51-1.75; $P = .85$).

Age, grade, and ER and PR status were significant indicators of the survival prognosis on bivariable analysis. Patients aged 80 to 84 years had a HR of 1.48 for overall survival compared with patients aged 75 to 79 years ($P = .01$). Patients aged ≥ 85 years had a HR of 2.42 ($P < .001$). Patients with histologic grade 2 disease had a HR for overall survival of 1.27 ($P = .20$) compared with grade 1, and those with grade 3 had a HR of 2.41 ($P < .001$). ER^+ status conferred a HR of 0.55 for overall survival ($P < .001$) and PR^+ status conferred a HR of 0.61 ($P < .001$). Race did not have a significant effect on either overall survival or breast CSS. After multivariable adjustment, only age and histologic grade showed a significant correlation with survival. Patients aged ≥ 84 years had a HR of 1.88 (95% CI, 1.38-2.56; $P < .001$) for overall survival compared with patients aged 75 to 79 years. Patients with histologic grade 3 had a HR of 2.29 (95% CI, 1.52-3.43; $P < .001$) for overall survival compared with those with grade 1. The full results are listed in Tables 2 and 3.

Discussion

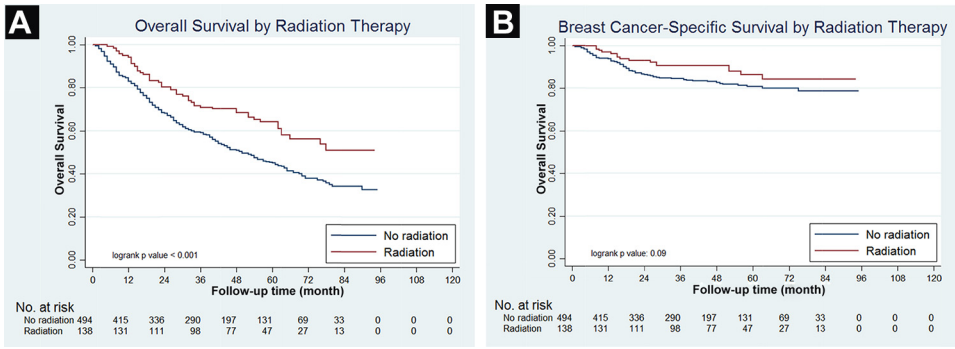
In breast cancer patients aged ≥ 75 years who underwent mastectomy for T3N0 disease, the use of PMRT correlated with

Table 1 Baseline Demographic and Tumor Characteristics Stratified by Radiation Status

Characteristic	Total (n = 635)	Receipt of RT		*P* Value
		Yes (n = 138l; 21.7)	No (n = 497; 78.3)	
Age, y				< .001
75-79	231 (36.4)	72 (52.2)	159 (32.0)	
80-84	191 (30.1)	41 (29.7)	150 (30.2)	
≥ 85	213 (33.5)	25 (18.1)	188 (37.8)	
Race				.04
White	516 (81.3)	108 (78.3)	408 (82.1)	
Black	79 (12.4)	15 (10.9)	64 (12.9)	
Other or unknown	40 (6.3)	15 (10.9)	25 (5.0)	
Grade				.07
1	105 (16.5)	29 (21.0)	76 (15.3)	
2	223 (35.1)	55 (39.9)	168 (33.8)	
3	231 (36.4)	36 (26.1)	195 (39.2)	
4	12 (1.9)	3 (2.2)	9 (1.8)	
Unknown	64 (10.1)	15 (10.9)	49 (9.9)	
ER status				< .001
ER^+	418 (65.8)	110 (79.7)	308 (62.0)	
ER^-	158 (24.9)	26 (18.8)	132 (26.6)	
Unknown	59 (9.3)	2 (1.5)	57 (11.5)	
PR status				< .001
PR^+	315 (49.6)	85 (61.6)	230 (46.3)	
PR^-	253 (39.8)	52 (37.7)	201 (40.4)	
Unknown	67 (10.6)	1 (0.7)	66 (13.3)	

Data presented as n (%).
Abbreviations: ER = estrogen receptor; PR = progesterone receptor; RT = radiation therapy.

Figure 1 Kaplan-Meier Survival Curves for T3N0 Breast Cancer Patients Age ≥ 75 Years. (A) Overall Survival Improved With Postmastectomy Radiation Therapy ($P < .001$). (B) Breast Cancer-Specific Survival Did Not Significantly Improve With Postmastectomy Radiation Therapy ($P = .09$). Median Follow-Up Was 43 Months



a trend toward increased overall survival at 5 years but not with breast-cancer specific survival. The threshold of $P < .05$ was met on bivariable analysis but not after multivariable adjustment. This lack of statistical significance might have resulted from the small number of outcome events in the multivariable model. Although $P < .05$ was not reached, the P values and 95% CIs might still be suggestive of an RT effect on survival. However, it is also possible that confounding effects were responsible for the apparent benefit of PMRT in the initial analysis. Age was a significant indicator of overall survival, and an imbalance was found in the age distribution of patients who had received PMRT (18% were aged ≥ 85 years) compared with those who had not (38% aged ≥ 85 years). It is possible that patients who received PMRT appeared to have longer survival because they were younger. In contrast, it could be concerning that a strong correlation was found between increasing age and decreasing use of

Table 2 Analysis of Overall Survival Rates Stratified by Demographic Data and Radiation Treatment

Characteristic	Patients, n	Events, n	Rate, %	Bivariable Analysis		Multivariable Analysis	
				HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, y							
75-79	231	88	38.1	Ref	Ref	Ref	Ref
80-84	191	99	51.8	1.48 (1.11-1.97)	.01	1.28 (0.92-1.77)	.14
≥ 85	213	148	69.5	2.42 (1.86-3.16)	< .001	1.88 (1.38-2.56)	< .001
Race							
White	516	278	53.9	Ref	Ref	Ref	Ref
Black	79	43	54.4	1.10 (0.80-1.52)	.57	0.89 (0.61-1.29)	.53
Grade							
1	105	41	39.1	Ref	Ref	Ref	Ref
2	223	100	44.8	1.27 (0.88-1.82)	.20	1.22 (0.83-1.82)	.32
3	231	152	65.8	2.41 (1.71-3.40)	< .001	2.29 (1.52-3.43)	< .001
4	12	6	50.0	1.78 (0.76-4.20)	.19	1.81 (0.74-4.42)	.20
RT							
No	497	281	56.5	Ref	Ref	Ref	Ref
Yes	138	54	39.1	0.58 (0.43-0.78)	< .001	0.78 (0.55-1.09)	.14
ER status							
ER^+	418	198	47.4	0.55 (0.44-0.70)	< .001	0.88 (0.61-1.25)	.47
ER^-	158	104	65.8	Ref	Ref	Ref	Ref
PR status							
PR^+	315	142	45.1	0.61 (0.49-0.77)	< .001	0.85 (0.62-1.17)	.32
PR^-	253	157	62.1	Ref	Ref	Ref	Ref

Abbreviations: CI = confidence interval; ER = estrogen receptor; HR = hazard ratio; PR = progesterone receptor; RT = radiation therapy.

Table 3 Analysis of Breast Cancer-specific Survival Rates Stratified by Demographic Data and Radiation Treatment

Characteristic	Patients, n	Events, n	Rate, %	Bivariable Analysis		Multivariable Analysis	
				HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, y							
75-79	231	27	11.7	Ref	Ref	Ref	Ref
80-84	191	32	16.8	1.54 (0.92-2.57)	.10	1.52 (0.85-2.69)	.16
≥ 85	213	36	16.9	1.77 (1.07-2.92)	.03	1.45 (0.80-2.62)	.22
Race							
White	516	78	15.1	Ref	Ref	Ref	Ref
Black	79	12	15.2	1.05 (0.57-1.93)	.87	0.54 (0.25-1.20)	.13
Grade							
1	105	5	4.8	Ref	Ref	Ref	Ref
2	223	19	8.5	1.96 (0.73-5.24)	.18	1.64 (0.60-4.50)	.33
3	231	54	23.4	6.66 (2.66-16.66)	< .001	6.36 (2.43-16.66)	< .001
4	12	4	33.3	9.79 (2.63-36.46)	< .001	9.52 (2.40-37.74)	.001
RT							
No	497	79	15.9	Ref	Ref	Ref	Ref
Yes	138	16	11.6	0.63 (0.37-1.08)	.09	0.94 (0.51-1.75)	.85
ER status							
ER^+	418	54	12.9	2.23 (1.46-3.39)	< .001	0.82 (0.42-1.59)	.55
ER^-	158	37	23.4	Ref	Ref	Ref	Ref
PR status							
PR^+	315	39	12.4	1.82 (1.20-2.77)	.005	1.10 (0.58-2.09)	.76
PR^-	253	50	19.8	Ref	Ref	Ref	Ref

Abbreviations: CI = confidence interval; ER = estrogen receptor; HR = hazard ratio; PR = progesterone receptor; RT = radiation therapy.

PMRT, because no definitive evidence of its lack of benefit in this population is available.

Elderly patients are thought to derive less benefit from adjuvant RT owing to their shorter life expectancy, the presence of comorbidities, and lower risk of LRR. Because the average life expectancy in the United States has continued to increase, the threshold for "elderly" could also continue to shift higher. We picked 75 years as our threshold in recognition of the use of 70 years of age in numerous previous studies and in accordance with the mention of age 75 years in the latest NCCN clinical practice guidelines for older adult oncology.

The SEER database started in 1973, and the version we used included patients up to 2012. However, to better capture more current trends, we started our data collection in 2006. To ensure a data analysis with ≥ 3 years of median follow-up data, we stopped collecting data after 2009. These start and stop points were fairly arbitrary and present a limitation of the present study. A broader view over time with specific subanalyses of different time periods would provide a more thorough perspective.

One interesting finding from these data was that most elderly T3N0 patients included in the present analysis did not receive PMRT from 2006 to 2009. Only 21.3% of patients received PMRT in this data set, lower than that from other reported data that were not restricted by age. At least 3 SEER analyses have been performed of PMRT for T3N0 breast cancer patients. One study found that 22% of these patients had received PMRT from 1988 to 1997, and this had increased to 41% from 1998 to 2002.[14] Another study of data from 2000 to 2010 reported that 42% of T3N0M0 female breast cancer patients had received PMRT.[15] A third study focusing on those aged < 50 years from 1998 to 2007 showed that 47% had received PMRT.[16] The percentage of patients receiving PMRT seemed lower compared with that in our study, potentially because of, primarily, the age restriction. This was supported by the decreasing percentage of patients receiving PMRT when stratified by the age group in the present study, from 31.2% for those aged 75 to 79 years to 21.5% for those aged 80 to 84 and 11.7% for those aged ≥ 85 years (Table 1). However, other factors could have also been influential, such as shifts in practice over time. The recommendation for PMRT in this patient population was almost certainly also very institution dependent. A report from the MD Anderson Cancer Center indicated that 73.5% of T3N0 patients received PMRT.[17] In contrast, at a similar time period, Jagsi et al[18] reported that 47.5% of T1N1, T2N1, or T3N0 patients in Detroit and Los Angeles received PMRT. One benefit of using the multi-institutional SEER database is the minimization of potential biases from single-institution reports.

One of the driving motivations behind the present study was the multitude of conflicting reports of T3N0 breast cancer patients and PMRT. Some investigators have reported that PMRT for T3N0 breast cancer patients significantly reduced LRR[17,19] and even improved survival.[15] Others, however, have reported that LRR is already very low in these patients (11%) and, thus, PMRT is not required.[20] To the best of our knowledge, the present study is the first large database analysis of elderly patients with T3N0 breast

cancer. A previous study examined younger T3N0 patients (< 50 years) in the SEER database and found no OS or CSS benefit from PMRT.[16]

One limitation of the present study was that clinical judgment considerations are not captured in databases such as the SEER databases. Patients with significant comorbidities or short life expectancies might be less likely to be offered adjuvant RT. Thus, the patient population we examined in the present study might have had a selection bias for which we could not fully account. This is an inherent limitation of retrospective database analyses. This selection bias might have been responsible for the improved OS but nonsignificant change in CSS in the present study. The aforementioned SEER analysis by McCammon et al[14] also showed an OS benefit with PMRT but no CSS benefit. They declared that this likely reflected a patient selection bias in the data set. However, we also found a trend in our study toward an improved breast CSS with PMRT, which might have resulted from an insufficient sample size given our restriction to a study period of 2006 to 2009. This selection bias might also have resulted in the loss of statistical significance for PMRT on OS on multivariable analysis. It is possible that patients who received PMRT had differences in age (as previously discussed), grade, or other pathologic criteria (eg, LVI, receptor status), or comorbidities that could explain their different survival, rather than the receipt of PMRT. However, the SEER data set we analyzed was lacking information on these factors, other than patient age. Furthermore, the SEER data set is limited by its lack of data on other endpoints such as local control and progression-free survival.

Another potential limitation of the present study was the risk of immortal time bias, because the survival time in the SEER database is calculated from the date of diagnosis. We did not perform specific analyses to counter this bias, because we believed it was unlikely that the typical delay from mastectomy to adjuvant RT would be clinically meaningful for the survival endpoints.

Another limitation of the present study was that we could not include systemic therapy data, which are not available from SEER. Some patients could have received systemic therapy in the neoadjuvant setting for T3N0 disease, and some might have received it after mastectomy. Including this modality of treatment for a patient would likely have an effect on the benefit and risks of PMRT.

Conclusion

At present, it remains controversial whether elderly T3N0 breast cancer patients will benefit from PMRT. Our results initially showed the suggestion of a survival benefit; however, definitive findings were not possible owing to limited events, confounding factors such as age, and the inherent limitations of retrospective database analyses. It could also be concluded from our data that PMRT is not needed for this patient population. Just as with many other issues in medicine, the answer is likely somewhere in between. As we move further toward personalized medicine, a multitude of variables will become available to help clinicians distinguish patient subsets. It is likely that studies in the future will establish some of these variables (eg, LVI, ER and PR status, histologic grade) and perhaps some new ones (ie, novel molecular, genetic markers) as key variables to accurately define which elderly T3N0 breast cancer patients will require PMRT and which will not.

Clinical Practice Points

- The concept of "less is more" has driven ongoing research to identify low-risk breast cancer patients who could omit adjuvant RT.
- One group under investigation is T3N0 female breast cancer patients after mastectomy.
- Reported studies have revealed conflicting data regarding the risk of recurrence and the benefit of RT for this population.
- Older age also confers a lower risk profile compared with that of younger patients; therefore, T3N0 female breast cancer patients undergoing mastectomy who are also aged $\geq$ 75 years presumably represent an even lower risk population.
- The present study analyzed the data from such patients in the SEER database from 2006 to 2009 and found a suggestion of an OS benefit with adjuvant RT.
- However, a greater number of younger women underwent RT, which could have confounded the results.
- Consequently, stronger evidence continues to be needed regarding whether adjuvant RT can be omitted for older patients with T3N0 breast cancer.
- Also, it is likely that further delineation into subgroups according to other factors (eg, comorbidities) will become important.

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Disclosure

The authors declare that they have no competing interests.

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