Original Article

Effectiveness of Radiation for Prevention of Mastectomy in Older Breast Cancer Patients Treated With Conservative Surgery

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BACKGROUND: A recent clinical trial concluded that radiation therapy (RT) does not lower the risk of mastectomy and, thus, may be omitted in older women with stage I, estrogen receptor (ER)-positive breast cancer who undergo conservative surgery (CS). However, it is not known whether this finding applies to patients outside of clinical trials. Accordingly, we used the Surveillance, Epidemiology, and End Results-Medicare observational cohort to determine the effect of RT on the risk of mastectomy among older women with stage I, ER-positive breast cancer. **METHODS:** The authors identified 7403 women ages 70 to 79 years who underwent CS between 1992 and 2002. Claims were used to determine RT status and to identify women who underwent mastectomy subsequent to initial treatment. The Kaplan-Meier method was used to estimate the risk of subsequent mastectomy, and Cox regression analysis was used to determine the effect of RT adjusted for clinical-pathologic covariates. **RESULTS:** At a median follow-up of 7.3 years, the risk of subsequent mastectomy within 10 years of diagnosis was 3.2% for patients who received RT versus 6.3% for patients who did not receive RT ($P<.001$). In adjusted analyses, RT was associated with a lower risk of mastectomy (hazard ratio, 0.33; 95% confidence interval, 0.22-0.48; $P<.001$). RT provided no benefit for patients ages 75 to 79 years without high-grade tumors who had a pathologic lymph node assessment ($P=.80$); however, for all other subgroups, RT was associated with an absolute reduction in risk of mastectomy that ranged from 4.3% to 9.8% at 10 years. **CONCLUSIONS:** Outside of a clinical trial, the receipt of RT after CS was associated with a greater likelihood of ultimate breast preservation for most older women with early breast cancer. ***Cancer*** **2012;118:4642-51.**

KEYWORDS: breast cancer, radiotherapy, elderly, comparative effectiveness.

INTRODUCTION

Following conservative surgery (CS) for invasive breast cancer, radiation therapy (RT) to the breast has been shown to improve survival and increase the likelihood of long-term breast preservation by preventing a local recurrence which would require salvage mastectomy.[1-7] However, because the risk of local recurrence is particularly low for older women,[5,6] several groups have investigated the viability of omitting RT in this patient population.[8-10] For example, Cancer and Leukemia Group B (CALGB) conducted a clinical trial, CALGB 9343, that included women aged ≥70 years with stage I, estrogen receptor (ER)-positive breast cancer who underwent CS and also received tamoxifen, and randomized patients into an RT group and a no RT group.[9] At 10 years of follow-up, the results indicated that RT lowered the risk of local recurrence but did not significantly lower the risk of subsequent mastectomy or death from breast cancer.[11] Those authors concluded that the omission of RT was an appropriate treatment option for these patients, because neither breast preservation rates nor survival rates were compromised.

Nevertheless, clinically meaningful differences with respect to treatment quality, patient compliance, and follow-up intensity likely exist between patients who are treated in routine practice and those who were treated on CALGB 9343.[12-19] For example, poor compliance with endocrine therapy is common,[15-18] and differences in compliance may exist between a motivated clinical trial population and the general population. It also has been suggested that compliance with breast cancer treatment standards of imaging, surgical specimen labeling, and pathologic assessment details may be lower

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in the community setting.[19] These differences may cause patients who are treated in routine practice to experience a greater risk of subsequent mastectomy and a greater benefit from RT than reported by CALGB 9343, or vice versa.

Accordingly, we used population-based data to quantify the risk of subsequent mastectomy and the associated benefit derived from RT for patients who were treated in routine practice and would have been eligible for CALGB 9343. We chose subsequent mastectomy as the primary outcome, because the primary objective of RT in this population is to maximize the likelihood of breast preservation through prevention of recurrence. We also sought to determine whether key clinical-pathologic factors could be used to guide treatment decisions by identifying those patients most likely and least likely to benefit from RT.

MATERIALS AND METHODS

Data Source

The study cohort was derived from the Surveillance, Epidemiology, and End Results (SEER)-Medicare data, which spans diagnosis years 1992 through 2002 with follow-up through 2007. In accordance with our previously described methods,[20] we defined the treatment interval as the first 9 months after diagnosis, and the follow-up interval was defined as the interval which began 10 months after diagnosis and continued until the first occurrence of the following: mastectomy, death, loss to follow-up, or completion of 10 years of follow-up.

Study Sample

The current analysis was limited to women ages $\leq$79 years, because our previous research suggested that RT rarely is beneficial for women aged $>$79 years because of the competing risk of death from comorbid illness.[20] Of 93,335 women ages 66 to 79 years who were diagnosed with breast cancer between 1992 and 2002 who had no previous history of cancer, we excluded those with nonepithelial histology, lobular carcinoma in situ, distant metastasis/unknown stage, no pathologic diagnosis, unknown tumor laterality/bilateral breast cancer, second breast/other cancer diagnosed or death during treatment interval, and those with fee-for-service Part A/B Medicare coverage from 12 months before to 9 months after diagnosis. This left 53,391 women with incident breast cancer, of whom 27,926 underwent CS.

From the CS cohort, we excluded 931 women who developed contralateral breast cancer during follow-up according to SEER, because a claim for mastectomy in the follow-up period could not discriminate between salvage treatment for the index cancer versus treatment of the contralateral cancer. We excluded 2595 patients who lost fee-for-service Part A or B Medicare coverage during follow-up, because claims data were incomplete and, thus, could not be used reliably to identify a mastectomy claim. This left 24,400 women who had adequate follow-up to measure the outcome. Of these, the study cohort consisted of 7403 women who met CALGB entry criteria (ages 70-79 years, ER-positive breast cancer, invasive tumor $\leq$2 cm, and negative lymph node status).

Outcome

The primary outcome was a subsequent mastectomy occurring at any time during the follow-up interval determined by billing claim codes, as previously described.[21]

Covariates

The type of breast surgery during the treatment interval was determined from SEER and Medicare claims, and the most extensive surgery reported by either source was considered the definitive surgery. Patients who had at least 1 pathologically sampled lymph node reported by SEER were considered to have undergone pathologic axillary assessment, whereas patients who had a SEER historic stage of "local" but no pathologically sampled lymph nodes were considered to have undergone clinical axillary assessment. Patients were considered to have received RT if SEER or Medicare claims indicated treatment with radiation. Patients were considered to have received chemotherapy if at least 1 claim for administration of chemotherapy was reported during the treatment interval. Information on endocrine therapy was not available in the SEER-Medicare data that were accessible at the time of this study.

Patient characteristics included age at diagnosis, year of diagnosis, race, SEER registry, and Charlson comorbidity score, which was calculated using claims that spanned an interval of 1 to 12 months before diagnosis in accordance with our previously described methods.[20] Tumor characteristics included size, grade, and histology (ductal/lobular/other). Margin status is not reported.

Statistical Analysis

Associations between covariates and receipt of RT were tested using the Pearson chi-square test. The cumulative incidence of subsequent mastectomy at 5 years and at 10 years was calculated using the Kaplan-Meier method, and differences were assessed using the log-rank test. A Cox proportional hazards model adjusted for relevant covariates was used to test whether receipt of RT was associated with a reduced risk of subsequent mastectomy. The proportionality assumption was assessed using nonparametric

smoothing to plot the magnitude of the scaled Schoenfeld residuals versus time for the predictor variable (receipt of RT). Visual inspection confirmed that this line was parallel to the x-axis, indicating that the proportionality assumption was satisfied.[22] Prespecified interactions of RT with type of lymph node assessment, age, histology, and grade tested whether the effect size of RT differed across the strata of these covariates. A sensitivity analysis was performed using the method proposed by Lash and Fink[23] to determine how the presence of an unmeasured confounder would alter the observed effect size of RT.

Clinically relevant patient subgroups were defined using the key clinical-pathologic predictors identified in the Cox model. For each subgroup, the association of RT with the outcome was tested using the log-rank test, and the absolute risk of mastectomy with and without RT at 5 years and at 10 years was calculated using the Kaplan-Meier method. Finally, 5-year and 10-year overall survival rates for each age and comorbidity strata were calculated using the Kaplan-Meier method. All statistical analyses were 2-tailed with $\alpha = .05$ using SAS statistical software (version 9.3; SAS Inc., Cary, NC). This project was granted exempt status by our Institutional Review Board.

RESULTS

Patient Characteristics and Follow-Up

Of 7403 patients who were identified, 6484 (87.6%) received RT. The median follow-up was 7.3 years. Complete follow-up (until 10 years, mastectomy, or death) was available for 3771 patients (50.9%); for the remaining patients, the minimum follow-up was 5.0 years, and the median was 6.9 years.

Baseline clinical-pathologic characteristics are reported in Table 1. In this cohort, 52.3% of patients were ages 70 to 74 years, and 47.7% were ages 75 to 79 years. Grade was low in 32.2% of tumors, intermediate in 43.6% of tumors, and high in 13.4% of tumors. Lymph node status was assessed pathologically in 73.6% of patients and clinically in 26.4% of patients (Table 1).

Radiation Therapy and the Risk of Mastectomy

In total, 174 patients (2.4%) underwent subsequent mastectomy, which we defined as a mastectomy performed at least 9 months after diagnosis. Treatment with RT was associated with a decreased risk of subsequent mastectomy; the 10-year risk of mastectomy was 6.3% (95% confidence interval [CI], 4.6%-8.6%) in patients who did not receive RT and 3.2% (95% CI, 2.6%-3.9%) in patients who did receive RT ($P < .001$) (Table 2, Fig. 1a). The association of receipt of RT with lower risk of subsequent mastectomy remained intact across nearly all key covariate strata (Table 2). For example, RT was associated 10-year absolute reduction in mastectomy risk of 3.8% (=7.6%-3.8%) for women ages 70-74 (P<0.001) and 2.9% (=5.4%-2.5%) for women ages 75-79 (P<0.001). RT also was associated with a 2.5% (=5.4%-2.9%), 2.2% (=5.5%-3.3%), and 6.7% (=11.2%-4.5%) absolute reduction in 10-year risk of mastectomy for patients with low, intermediate, and high grade breast cancer, respectively (P=0.01, 0.001, and 0.002). In adjusted analysis, receipt of RT retained a significant association with a decreased risk of subsequent mastectomy (hazard ratio [HR], 0.33; 95% CI, 0.22-0.48; $P < .001$). Younger age (ages 70-74 years), black race, and high tumor grade also were associated independently with a greater risk of mastectomy (Table 3).

A sensitivity analysis was performed to determine whether the presence of an unmeasured, unbalanced confounder would alter the observed effect size of RT. Inclusion of such a confounder reduced the effect size of RT (Table 4). An unmeasured confounder yielded an effect size of RT that was not statistically significant under the following conditions: 1) prevalence of 15% for the group that received RT and 70% for the group that did not receive RT and a 3.2-fold associated increase in event risk, and 2) prevalence of 15% for the group that received RT and 85% for the group that did not receive RT and a 3.3-fold associated increase in event risk. An unmeasured confounder that was more balanced between the 2 groups or that was associated with a smaller effect size did not negate the statistical significance of the observed relation between RT and a reduced risk of mastectomy (Table 4).

Axillary Lymph Node Assessment and Benefit From Radiation Therapy

In the multivariate model for the risk of subsequent mastectomy, the interaction of type of lymph node assessment with RT was significant ($P = .04$), but interactions of grade ($P = .56$), age ($P = .99$), and histology ($P = .19$) with RT were not. RT was associated with a more substantial reduction in the risk of mastectomy for patients who had clinically assessed lymph node status (adjusted HR, 0.21; 95% CI, 0.11-0.37; $P < .001$) compared with patients who had pathologically assessed lymph node status (adjusted HR, 0.49; 95% CI, 0.27-0.87; $P = .015$). For patients who had clinically assessed lymph nodes, the 10-year absolute risk of mastectomy was 6.8% for those who did not receive RT compared with 1.9% for those who did receive RT, yielding a 4.9% absolute risk

Table 1. Baseline Characteristics and Receipt of Radiation Therapy

Clinical Variable	No. of Patients (%)			P^a
	All Patients	No RT	RT	
Entire cohort	7403	919 (12.4)	6484 (87.6)	
Demographic characteristics				
Age, y				<.001
70-74	3869	359 (39.1)	3510 (54.1)	
75-79	3534	560 (60.9)	2974 (45.9)	
Race				<.001
White	6766	818 (89)	5948 (91.7)	
Black	301	70 (7.6)	231 (3.6)	
Other/unknown[b]	336	31 (3.4)	305 (4.7	
No. of comorbidities				<.001
0	4505	425 (46.2)	4080 (62.9)	
1	1752	243 (26.4)	1509 (23.3)	
≥2	926	160 (17.4)	766 (11.8)	
Unknown	220	91 (9.9)	129 (2)	
Year of diagnosis				<.001
1992-1995	1611	280 (30.5)	1331 (20.5)	
1996-1999	2432	292 (31.8)	2140 (33)	
2000-2002	3360	347 (37.8)	3013 (46.5)	
Tumor characteristics				
Tumor histology				<.001
Invasive ductal	5314	609 (66.3)	4705 (72.6)	
Invasive lobular	597	70 (7.6)	527 (8.1)	
Other/unknown	1492	240 (26.1)	1252 (19.3)	
Tumor grade				<.001
Low	2385	341 (37.1)	2044 (31.5)	
Intermediate	3231	345 (37.5)	2886 (44.5)	
High	989	96 (10.4)	893 (13.8)	
Unknown	798	137 (14.9)	661 (10.2)	
Treatment characteristics				
Axillary lymph node status				<.001
Clinically negative lymph nodes	1954	587 (63.9)	1367 (21.1)	
Pathologically negative lymph nodes	5449	332 (36.1)	5117 (78.9)	
Receipt of chemotherapy				<.001
No	7034	898 (97.7)	6136 (94.6)	
Yes	369	21 (2.3)	348 (5.4)	

Abbreviations: RT (Radiation therapy).
[a] *P* values were determined with the Pearson chi-square test.
[b] The other/unknown race group includes Asian and Hispanic individuals. These groups have been combined in this table in accordance with Surveillance, Epidemiology, and End Results-Medicare guidelines to suppress cell sizes <11.

reduction ($P < .001$) (Table 2, Fig. 1b). In comparison, for patients who had pathologically assessed lymph nodes, the 10-year absolute risk of mastectomy was 5.6% for those who did not receive RT compared with 3.6% for those who did receive RT, yielding a 2% absolute risk reduction ($P = .017$) (Table 2, Fig. 1c).

Subset Analyses by Tumor Grade, Age, and Type of Lymph Node Assessment

Because tumor grade and patient age were associated with the risk of mastectomy in multivariate analysis, subset analyses were performed for these 2 variables and were stratified by type of lymph node assessment (Fig. 2). A group of 2076 patients (28% of the cohort) ages 75 to 79 years who had pathologic lymph node assessment and without high-grade histology appeared to derive no benefit from RT, with a 10-year risk of mastectomy of 1.3% (95% CI, 0.3%-5.3%) in among those who did not receive RT and 2.7% (95% CI, 1.8%-4.1%) in those w ho did receive RT ($P = .80$). For all other subgroups, patients who received RT experienced a numerically lower risk of subsequent mastectomy than patients who did not receive RT, and the 10-year absolute risk reduction associated with receipt of RT ranged from 4.3% to 9.8% (Fig. 2a,b).

Survival by Severity of Comorbidity

Because life expectancy is an important consideration when evaluating the potential benefits of adjuvant

Table 2. The Risk of Subsequent Mastectomy at 5 Years and at 10 Years With and Without Radiation Therapy

Clinical Variable	Cumulative Incidence of Mastectomy (95% CI), %				P^a
	No RT Group		RT Group		
	5-Year	10-Year	5-Year	10-Year	
Entire cohort	3.5 (2.5-5.1)	6.3 (4.6-8.6)	0.94 (0.73-1.2)	3.2 (2.6-3.9)	<.001
Demographics					
Age, y					
70-74	4.3 (2.5-7.1)	7.6 (5-11.5)	1.2 (0.85-1.6)	3.8 (3-4.7)	<.001
75-79	3.1 (1.9-5)	5.4 (3.4-8.6)	0.68 (0.43-1.1)	2.5 (1.7-3.5)	<.001
Race					
White	3.2 (2.1-4.7)	5.6 (4.0-7.9)	0.95 (0.73-1.2)	3.1 (2.6-3.8)	<.001
Hispanic	9.1 (1.3-49.2)	9.1 (1.3-49.2)	0 (0-0)	4.2 (1.1-16.1)	.206
Black	6.5 (2.5-16.3)	14.8 (7.0-29.5)	1.8 (0.70-4.8)	6.8 (3.4-13.1)	.030
Asian	8.3 (1.2-46.1)	8.3 (1.2-46.1)	0 (0-0)	0 (0-00)	.001
Other/unknown	0 (0-0)	0 (0-0)	0 (0-0)	1.9 (0.26-12.4)	.739
No. of comorbidities					
0	4.1 (2.5-6.6)	7.1 (4.7-10.6)	0.99 (0.72-1.3)	2.9 (2.3-3.7)	<.001
1	2.6 (1.2-5.7)	4.5 (2.1-9.3)	0.93 (0.54-1.6)	3.4 (2.2-5.2)	.077
≥2	4.5 (2-9.7)	10.2 (5.4-19.1)	0.71 (0.29-1.7)	4.9 (2.7-8.8)	.001
Unknown	1.4 (0.20-9.5)	1.4 (0.20-9.5)	0.84 (0.12-5.8)	4.6 (1.7-12.2)	.432
Tumor characteristics					
Tumor histology					
Invasive ductal	3.8 (2.4-5.8)	6.8 (4.7-9.8)	0.98 (0.73-1.3)	3.5 (2.8-4.3)	<.001
Invasive lobular	4.5 (1.5-13.3)	4.5 (1.5-13.3)	0.40 (0.10-1.6)	1.0 (0.38-2.8)	.005
Other/unknown	2.7 (1.2-5.9)	5.4 (2.9-10)	1 (0.57-1.8)	3.0 (1.9-4.6)	.021
Tumor grade					
Low	2.4 (1.1-4.9)	5.4 (2.9-9.7)	0.76 (0.46-1.3)	2.9 (1.9-4.2)	.010
Intermediate	3.2 (1.7-5.8)	5.5 (3.3-9.1)	0.85 (0.56-1.3)	3.3 (2.5-4.3)	.001
High	8.8 (4.3-17.6)	11.2 (5.6-21.7)	1.8 (1.1-2.9)	4.5 (3.0-6.6)	.002
Unknown	4.0 (1.7-9.3)	7.6 (3.8-14.9)	0.80 (0.33-1.9)	2.3 (1.2-4.4)	.001
Treatment characteristics					
Axillary lymph node status					
Clinically negative lymph nodes	4.1 (2.7-6.2)	6.8 (4.7-9.8)	0.62 (0.31-1.2)	1.9 (1.1-3)	<.001
Pathologically negative lymph nodes	2.6 (1.3-5.1)	5.6 (3.2-9.7)	1.0 (0.78-1.3)	3.6 (2.9-4.5)	.017
Receipt of chemotherapy					
No	3.6 (2.5-5.2)	6.4 (4.7-8.7)	0.96 (0.74-1.2)	3.2 (2.6-3.9)	<.001
Yes	0 (0-0)	0 (0-0)	0.60 (0.15-2.4)	3.5 (1.6-7.6)	.566

Abbreviations: CI, confidence interval; HR, hazard ratio; RT, radiation therapy.
[a] *P* values were determined with the log-rank test comparing the risk of mastectomy for the RT group versus the no RT group through 10 years of follow-up.

therapies, we determined survival rates for this cohort. The 5-year and 10-year overall survival rates were correlated with age at diagnosis and baseline comorbidity scores. For women ages 70 to 74 years, the 10-year overall survival rate ranged from 46% for those with moderate-severe comorbidity to 78% for those without comorbidity. For women ages 75 to 79 years, the 10-year overall survival rate ranged from 41% for those with moderate-severe comorbidity to 67% for those without comorbidity (Table 5).

DISCUSSION

In this population-based cohort representative of older women with stage I, ER^+ breast cancer treated in routine practice, receipt of RT was associated with a statistically significant two-thirds relative reduction in the risk of subsequent mastectomy, with an absolute risk at 10-years of 6.3% for patients not treated with RT compared to 3.2% for patients treated with RT. In contrast, in the CALGB 9343 trial, RT resulted in a statistically nonsignificant 50% relative reduction in the risk of subsequent mastectomy, with an absolute risk at 10 years of 4% for those who did not receive RT compared with 2% for patients who did receive RT.[11] Findings from our analyses support our hypothesis that the risk of subsequent mastectomy and the absolute reduction in risk conferred by RT appear slightly greater in routine practice than in the clinical trial setting.

Our findings further suggest that baseline clinical-pathologic features may help to identify patients who are

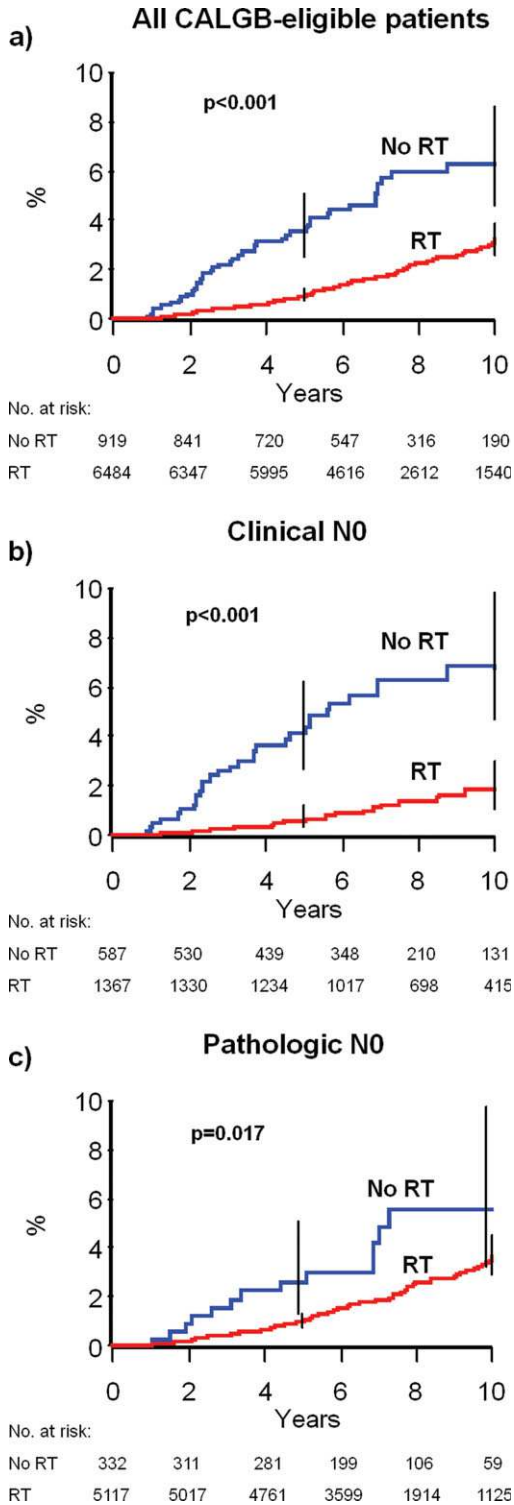

Figure 1. The cumulative risk of mastectomy is illustrated for (a) all patients who would be eligible for Cancer and Leukemia Group B (CALGB) trial 9343, (b) patients with clinically lymph node-negative (N0) disease, and (c) patients with pathologically N0 disease. Error bars represent 95% confidence intervals for the risk of mastectomy at 5 years and 10 years. *P* values were determined by using the log-rank test. RT indicates radiation therapy.

Table 3. Multivariate Model for Risk of Mastectomy

Variable	HR	95% CI	*P*
Receipt of RT			
No	1.00		
Yes	0.33	0.22-0.48	<.001
Age, y			
70-74	1.00		
75-79	0.61	0.45-0.84	.002
Race			
White	1.00		
Hispanic	1.63	0.52-5.12	.404
Black	2.32	1.39-3.86	.001
Asian	0.27	0.04-1.95	.196
Other/unknown	0.46	0.07-3.31	.442
No. of comorbidities			
0	1.00		
1	0.92	0.63-1.34	.651
≥2	1.24	0.79-1.93	.348
Unknown	0.69	0.28-1.72	.425
Year of diagnosis			
1992-1995	1.0		
1996-1999	0.87	0.60-1.26	.460
2000-2002	0.93	0.63-1.39	.728
Tumor histology			
Invasive ductal/other	1.00		
Invasive lobular	0.49	0.23-1.05	.067
Tumor grade			
Low/intermediate/unknown	1.00		
High	1.79	1.24-2.58	.002
Receipt of chemotherapy			
No	1.00		
Yes	0.90	0.42-1.91	.775
Axillary lymph node status			
Clinically negative lymph nodes	1.00		
Pathologically negative lymph nodes	1.28	0.88-1.85	.195

Abbreviations: CI, confidence interval; HR, hazard ratio; RT, radiation therapy.

most and least likely to benefit from RT. For example, women ages 75 to 79 years who did not have tumors with high-grade histology and who underwent pathologic lymph node assessment (28% of the cohort) derived no benefit from RT. We believe that these results, coupled with those from the CALGB 9343 trial, strongly justify CS plus endocrine therapy, without RT to the breast, as the standard of care for the vast majority of such patients. Considering the morbidity,[9] cost,[25] and inconvenience of RT for older patients, this robust finding has the potential to simplify and improve care for a sizeable group of patients and also may lead some older women who otherwise would have chosen mastectomy to opt for CS without RT instead.

Table 4. Sensitivity Analysis to Determine the Effect of an Unmeasured Confounder on the Observed Effect Size of Radiation Therapy[a]

Prevalence of Unmeasured Confounder in Patients Who Did Not Have the Outcome (Range), %		Unadjusted Association Between Unmeasured Confounder and Outcome, HR	Effect Size of RT After Accounting for Unmeasured Confounder, HR					
			Systematic Error			Systematic and Random Error		
RT	No RT		2.50%	50%	97.50%	2.50%	50%	97.50%
5 (0-10)	70 (60-80)	1.92	0.24	0.32	0.44	0.17	0.32	0.60
5 (0-10)	50 (40-60)	1.75	0.27	0.32	0.40	0.20	0.32	0.54
5 (0-10)	85 (80-90)	2.07	0.20	0.33	0.51	0.16	0.33	0.66
15 (10-20)	70 (60-80)	3.23	0.46	0.66	0.92	0.34	0.66	1.22
15 (10-20)	50 (40-60)	3.14	0.40	0.51	0.66	0.30	0.52	0.89
15 (10-20)	85 (80-90)	3.32	0.59	0.86	1.21	0.43	0.86	1.60

Abbreviations: HR, hazard ratio; RT, radiation therapy.
[a] The format for this table was adapted from Smith BD, Haffty BG, Buchholz TA, et al. Effectiveness of radiation therapy in older women with ductal carcinoma in situ. *J Natl Cancer Inst.* 2006;98:1302-1310.[24]

In contrast, our findings also help to identify patient groups for which the receipt of RT is associated with a measurable reduction in the risk of mastectomy that may be clinically relevant. For example, RT was associated with a 6.7% absolute reduction in the 10-year risk of mastectomy for all patients with high-grade breast cancer, a 4.9% absolute reduction for all patients who underwent clinical lymph node assessment, and a 3.8% absolute reduction for all patients ages 70 to 74 years. The benefit associated with RT for these subgroups is comparable in magnitude to the benefits of other well accepted medical therapies, such as antihypertensive treatment for the prevention of cardiac events or bisphosphonate therapy for the prevention of fracture.[26,27] Because the primary goal of RT in this population is to maximize the likelihood of long-term breast preservation, our data suggest that RT incrementally improves the likelihood of achieving this goal for these subgroups of women, thus decreasing the likelihood that such patients will be exposed to the morbidity, costs, and potential complications associated with undergoing subsequent mastectomy for local recurrence. Therefore, these results suggest that patients with any of these factors should be informed of the potential benefit derived from RT and should be given an opportunity to consider it.

Demographic shifts in the United States are expected to result in a 57% increase in the number of breast cancers diagnosed in older women over the next 20 years.[28] For older patients in particular, the benefits of adjuvant therapies intended to prevent a future recurrence must be weighed against the competing risk of noncancer death before recurrence. We observed that 61% of patients in our current cohort had no major comorbid illness, and at least 66% of such patients survived for at least 10 years after diagnosis. The life expectancy of such patients, thus, is sufficiently long to justify consideration of RT.

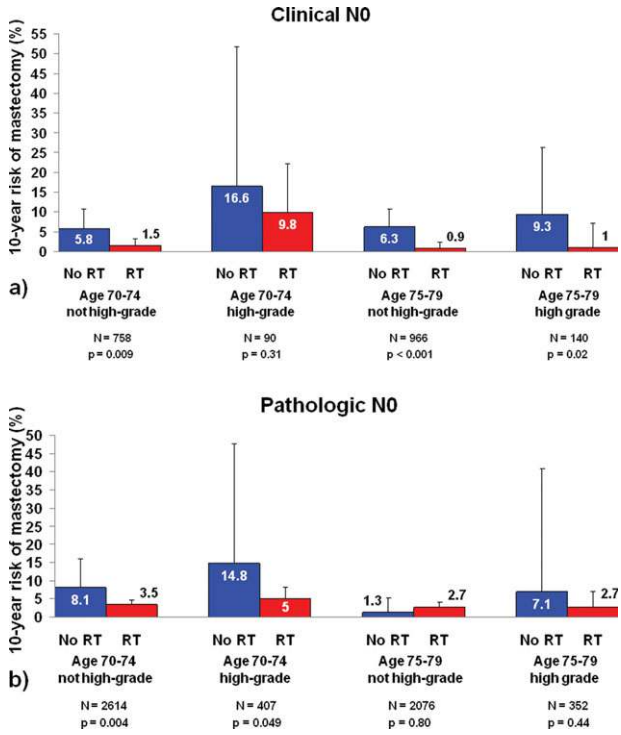

Figure 2. The 10-year risk of mastectomy is illustrated for subgroups according to tumor grade, age, and type of lymph node assessment for (a) patients with clinically lymph node-negative (N0) disease and (b) patients with pathologically N0 disease. Error bars represent 95% confidence intervals for the risk of mastectomy at 10 years. *P* values were determined with the log-rank test. RT indicates radiation therapy.

Table 5. Overall Survival by Severity of Comorbidity

No. of Comorbidities	Survival Rate, %				P^a
	5-Year	95% CI	10-Year	95% CI	
Ages 70-74 y					<.001
0	93.5	92.4-94.4	78.2	76.1-80.2	
1	87.2	84.8-89.3	66.3	62.3-70	
2	77.1	72.9-80.8	46.3	40.2-52.1	
Ages 75-79 y					<.001
0	90.9	89.6-92	67.4	64.7-70	
1	81.8	79.1-84.2	49.3	44.7-53.7	
2	72.9	68.7-76.7	40.8	34.7-46.8	

Abbreviations: CI, confidence interval.
[a] *P* values were determined with the log-rank test.

Although randomized controlled trials are considered the gold standard of clinical evidence, clinical trial data are not always available to guide every clinical decision. For example, even well designed studies like CALGB 9343 often do not have sufficient power to permit meaningful subgroup analyses, making it difficult to determine which subgroups of patients may be more or less likely to benefit from the therapy under consideration. In addition, despite the rapidly growing number of older patients with cancer, relatively few older patients enroll in clinical trials.[14] Fortunately, it has been demonstrated that high-quality observational studies can play a valuable role in comparative-effectiveness research, helping to fill gaps in the knowledge available from clinical trials.[29-32]

A limitation of this study is its retrospective nature, which results in some imbalances in the treatment groups that, theoretically, may have an impact on the choice of surgical management at the time of local recurrence. For example, if patients who underwent CS alone were more likely to opt for mastectomy at the time of recurrence than patients who underwent CS and also received RT, then the association between CS alone and increased mastectomy risk may not be causal. However, given the fact that prior treatment with CS plus RT generally mandates mastectomy at the time of recurrence, it is unlikely that local recurrences would be treated preferentially with mastectomy in patients who previously underwent CS alone compared with those who underwent CS and also received RT. In addition, recurrence details are not captured by SEER. Therefore, there is no way to know whether patients who underwent salvage mastectomy for local recurrence after CS alone may have been candidates for repeat lumpectomy with RT. Because mastectomy is the only viable salvage option for patients who receive upfront CS plus RT, our data may overestimate the benefit from RT for centers that have experience with salvaging local recurrences after CS alone with repeat lumpectomy and RT. Nevertheless, our data highlight the potential benefit of RT given existing practice patterns.

Another limitation to the current study is that treatment with endocrine therapy could not be determined. It has been demonstrated that endocrine therapy lowers the risk of local recurrence by approximately 50%[33,34] and, thus, may be an important confounder if its use varies dramatically by treatment group. However, several observations argue against this possibility. First, previous literature has suggested that adherence to endocrine therapy does not vary dramatically by type of local therapy.[35,36] Second, the RT effect size of 0.33 reported in this study is nearly identical to the effect size of 0.31 reported in a meta-analysis of 51,958 women who were treated on 11 clinical trials that compared CS with CS plus RT.[1] Third, previously, we used SEER-Medicare data to demonstrate that RT also is beneficial for women with ER-negative breast cancer.[20] If the effect of RT measured in this study was because of confounding with endocrine therapy, then we would expect to observe no benefit from RT in ER-negative patients, for whom endocrine therapy is not effective. Regardless, to address this limitation, we performed a sensitivity analysis to determine whether an unmeasured imbalance in the use of endocrine therapy could account for the study findings. We observed that the use of endocrine therapy could negate the observed effect of RT under conditions in which 85% of patients who did receive RT and 15% of patients who did not receive RT received endocrine therapy, and the receipt of endocrine therapy conferred a 3-fold reduction in the risk of mastectomy. However, based on published literature, endocrine therapy use varies little based on the receipt of RT and yields an approximate 2-fold reduction in the risk of local recurrence,[33,34] suggesting that subtle

imbalances in the use of endocrine therapy in this cohort are insufficient to explain the observed benefit of RT.

Lack of data regarding adherence to endocrine therapy, although a limitation of the current study, mirrors actual clinical practice, because treating physicians who make decisions regarding a recommendation for or against RT are not able to accurately predict the extent to which any given patient will adhere to endocrine therapy. Prior literature suggests that nearly 75% of patients will not fully comply with 5 years of adjuvant endocrine therapy,[15-18,37] indicating that failure to comply with endocrine therapy is a common event but is difficult to predict at the outset of therapy.[16,17,38] A strength of the current study, therefore, is that the outcomes reported reflect the average outcome that can be expected given current patterns of adherence to endocrine therapy among older patients with breast cancer. Thus, these outcomes can be used to inform clinical decision making for the average patient, whose adherence to endocrine therapy will likely mirror the general population.

In summary, outside of a clinical trial, the receipt of RT after CS is associated with a greater likelihood of ultimate breast preservation for most women ages 70 to 79 years who have early breast cancer. This benefit should be considered by patients and physicians when evaluating choices for local treatment. However, RT does not appear to be beneficial for the subset of women defined by ages 75 to 79 years who undergo pathologic lymph node assessment and do not have high-grade tumor histology.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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