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ORIGINAL REPORT

Patient Prognostic Score and Associations With Survival Improvement Offered by Radiotherapy After Breast-Conserving Surgery for Ductal Carcinoma In Situ: A Population-Based Longitudinal Cohort Study

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Y.S. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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ABSTRACT

Purpose
Radiotherapy (RT) after breast-conserving surgery (BCS) is a standard treatment option for the management of ductal carcinoma in situ (DCIS). We sought to determine the survival benefit of RT after BCS on the basis of risk factors for local recurrence.

Patients and Methods
A retrospective longitudinal cohort study was performed to identify patients with DCIS diagnosed between 1988 and 2007 and treated with BCS by using SEER data. Patients were divided into the following two groups: BCS+RT (RT group) and BCS alone (non-RT group). We used a patient prognostic scoring model to stratify patients on the basis of risk of local recurrence. We performed a Cox proportional hazards model with propensity score weighting to evaluate breast cancer mortality between the two groups.

Results
We identified 32,144 eligible patients with DCIS, 20,329 (63%) in the RT group and 11,815 (37%) in the non-RT group. Overall, 304 breast cancer–specific deaths occurred over a median follow-up of 96 months, with a cumulative incidence of breast cancer mortality at 10 years in the weighted cohorts of 1.8% (RT group) and 2.1% (non-RT group; hazard ratio, 0.73; 95% CI, 0.62 to 0.88). Significant improvements in survival in the RT group compared with the non-RT group were only observed in patients with higher nuclear grade, younger age, and larger tumor size. The magnitude of the survival difference with RT was significantly correlated with prognostic score ($P < .001$).

Conclusion
In this population-based study, the patient prognostic score for DCIS is associated with the magnitude of improvement in survival offered by RT after BCS, suggesting that decisions for RT could be tailored on the basis of patient factors, tumor biology, and the prognostic score.

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INTRODUCTION

Ductal carcinoma in situ (DCIS) of the breast is a lesion consisting of an abnormal proliferation of epithelial cells within breast ducts. The incidence of DCIS has increased dramatically since the implementation of breast screening protocols in the 1980s, and it is estimated that approximately 60,000 patients will be diagnosed with DCIS in the United States during 2015.[1,2] Although DCIS is not an invasive carcinoma, it displays a broad spectrum of tumor biology and is considered a premalignant lesion.[3] A standard surgical option for the local management of both DCIS and invasive disease is breast-conserving surgery (BCS) often followed by postoperative radiation therapy (RT). The benefit of postoperative RT is well established in patients with invasive disease, with large randomized data demonstrating reduced local recurrence rates and improved breast cancer–specific mortality (BCM) for RT-treated patients.[4] However, the survival benefit for RT has not yet been clearly established for patients with DCIS.

Given the favorable breast cancer–specific survival of DCIS compared with invasive

carcinoma (the 10-year breast cancer–specific survival of DCIS approaches 96% to 98%), prior research efforts have had difficulty achieving adequate sample size and power to examine the survival benefit of RT in the context of in situ disease.[5] Whereas prior research for DCIS has shown that mortality risk increases after the development of a second ipsilateral primary invasive breast cancer, prevention of recurrence using RT has not been definitely shown to diminish BCM.[6]

Many studies have attempted to determine which, if any, patient subgroups may be able to safely avoid RT after BCS.[2,7-15] Several clinical factors including age, tumor size, grade, and surgical margin status have been identified as predictive factors that increase the risk for ipsilateral breast tumor recurrence (IBTR) after BCS, suggesting that certain high-risk patients may be most apt to benefit from RT. Prognostic score systems have been developed to help identify this cohort of patients, including the University of Southern California/Van Nuys prognostic index and the patient prognostic score.[16-20] We sought to determine the specific survival benefit of RT after BCS among variable risk subpopulations of patients with DCIS. We hypothesized that the addition of RT to BCS may confer a survival benefit to patients with DCIS with clinicopathologic features associated with higher local recurrence risk.

PATIENTS AND METHODS

Study Design and Data Source

After receiving an exemption from the Partners HealthCare Institutional Review Board, we performed a retrospective longitudinal cohort study using data obtained from the SEER Program of the National Cancer Institute. The SEER database includes incidence and survival data routinely collected from multiple population-based cancer registries.[21] For this study, we identified 76,110 women over the age of 20 years who received BCS (site-specific surgery code: 10, 20) after being diagnosed with a first case of DCIS in SEER 17 General Health Service Areas between January 1, 1988, and December 31, 2007 (Appendix Fig A1, online only). Given that DCIS has a good prognosis, we opted for a cohort with a longer median follow-up period and, therefore, excluded patients diagnosed after 2008. Among these patients, 34,676 patients had known nuclear grade and tumor size. Patients with unknown RT status or method or source of RT unspecified and those who received radioisotopes or radioactive implants were excluded. We also excluded patients without information on known prognostic characteristics, including grade, tumor size, and race. Additional exclusion criteria included patients with Paget disease or DCIS with microinvasion, patients registered as multiple cases during the same year, and patients with ipsilateral or contralateral recurrence after breast surgery. The final cohort included 32,144 patients.

Assembly of Key Variables

Using SEER*Stat version 8.2.1, we generated a data table including individual cancer records and patient characteristics and included the following variables: patient identification number, year of diagnosis, age, race, tumor size, nuclear grade, estrogen receptor (ER) status, progesterone receptor (PgR) status, RT, cause-specific death classification, other cause of death classification, survival month, family income, marital status, and SEER registry. All variables were categorized as outlined in Table 1. We used RT codes to classify patients with the code of "beam radiation" into the BCS+RT group (RT group) and those with the code of "none" and "refused" into the BCS alone group (non-RT group).

To investigate the benefit of RT on the basis of the risk of IBTR after BCS, we used a patient prognostic score, which was proposed by Smith et al[20] (Fig 1), to define an ordinal factor where patients with a score of 0 have the lowest risk and those with a score of 6 have the highest risk of local recurrence.

Table 1. Patient Characteristics by Receipt of RT

Characteristic	No. of Patients (%)		*P*
	Non-RT Group (n = 11,815)	RT Group (n = 20,329)	
Year of diagnosis			< .001
1988-1992	151 (1.3)	128 (0.6)	
1993-1997	1,195 (10.1)	1,299 (6.4)	
1998-2002	4,536 (38.4)	7,140 (35.0)	
2003-2007	5,933 (50.2)	11,762 (57.9)	
Age, years			< .001
20-39	329 (2.8)	567 (2.8)	
40-44	878 (7.4)	1,885 (9.3)	
45-49	1,403 (11.9)	2,920 (14.4)	
50-54	1,536 (13.0)	3,186 (15.7)	
55-59	1,469 (12.4)	3,145 (15.5)	
60-64	1,304 (11.0)	2,568 (12.6)	
65-69	1,207 (10.2)	2,336 (11.5)	
70-74	1,220 (10.3)	1,817 (8.9)	
75-79	1,126 (9.5)	1,221 (6.0)	
80+	1,343 (11.4)	684 (3.4)	
Race			< .001
White	9,687 (82.0)	16,261 (80.0)	
Black	951 (8.1)	1,630 (8.0)	
Other	1,177 (10.0)	2,438 (12.0)	
Marital status			< .001
Married	6,580 (55.7)	13,015 (64.0)	
Single	4,705 (39.8)	6,816 (33.5)	
Unknown	530 (4.5)	498 (2.5)	
Tumor size, mm			< .001
1-9	7,078 (60.0)	9,856 (48.5)	
10-19	2,844 (24.1)	6,453 (31.7)	
20-49	1,570 (13.3)	3,582 (17.6)	
50+	323 (2.7)	438 (2.2)	
Grade			< .001
1	2,626 (22.2)	2,549 (12.5)	
2	5,594 (47.4)	7,923 (39.0)	
3	3,595 (30.4)	9,857 (48.5)	
Estrogen receptor status			< .001
Negative	549 (4.7)	1,714 (8.4)	
Positive	3,449 (29.1)	7,947 (39.1)	
Unknown	7,817 (66.2)	10,668 (52.5)	
Progesterone receptor status			< .001
Negative	867 (7.3)	2,521 (12.4)	
Positive	2,779 (23.5)	6,522 (32.1)	
Unknown	8,169 (69.1)	11,286 (55.5)	

Abbreviation: RT, radiotherapy.

Outcome of Interest

The primary outcome of interest was breast cancer–specific death after BCS in patients with DCIS. SEER defines mortality data on the basis of the International Classification of Diseases Revisions 8 to 10. The SEER cause of death recode was used to categorize the cause of death as breast cancer–specific death, other cancer death, death as a result of heart disease, or noncancer cause of death. The time to overall death and breast cancer specific death (overall mortality [OM] and BCM) was calculated as the time period from the date of diagnosis until the last date for which completed vital status data were available (last follow-up date: December 31, 2012). The data regarding deaths were ascertained from death certificates that are coded by state health departments and/or state vital records for each SEER region.[22]

Statistical Analysis

For this study, we used the same statistical analytic approach as reported in our earlier study that examined the benefit of breast surgery for DCIS.[23] In brief, we compared clinicopathologic factors between RT groups

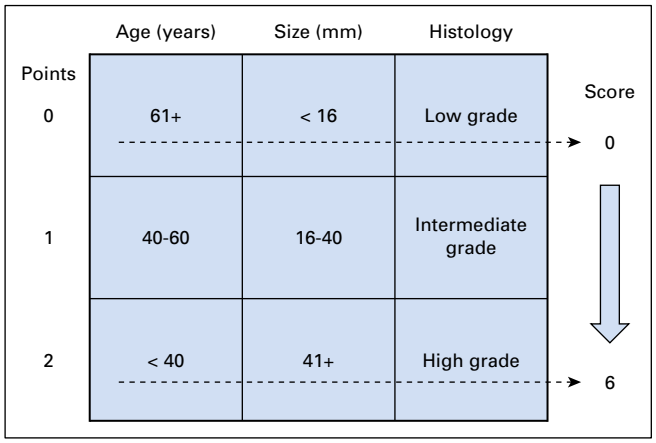

Fig 1. Patient prognostic score: risk stratification. Modified from Smith et al.[20]

and non-RT groups using Pearson or Mantel-Haenszel χ^2 tests for categorical and ordinal factors, respectively. For inferring missing values of marital status (n = 1,028; 3.2%), ER status (n = 18,485; 57.5%), and PgR status (n = 19,455; 60.5%), we applied a multiple imputation procedure using IVEware macro version 0.2 (University of Michigan, Ann Arbor, MI) with the following variables: patient age (continuous), race (white, black, or other), nuclear grade, tumor size classification (0.1 to 0.5, 0.6 to 10, 11 to 50, or ≥ 51 mm), receipt of RT, and SEER registry.[24,25] To stabilize the results, the procedure was repeated for 10 cycles to produce a single imputed data set (Appendix Table A1, online only). For analysis, the classification of all variables remained consistent in this study except for patient age (5-year age bands) to allow for a nonlinear effect in regression models.

We then used inverse probability propensity score weighting to balance patient characteristics between the RT and non-RT groups.[26,27] To calculate propensity scores, baseline characteristics of patient age, year of diagnosis (categorical, 5-year intervals), race, tumor size, nuclear grade, ER status, PgR status, marital status (single or married), and SEER registry were applied to a logistic regression model for receipt of RT.

BCM and OM were compared between RT and non-RT groups using propensity score–weighted log-rank tests and Cox proportional hazards models. Hazard ratios (HRs) of BCM and OM were reported from multivariable models that adjusted for patient age, year of diagnosis, race, tumor size, nuclear grade, and marital status. Because family income was not significant, we did not include it in the models. Interaction tests were performed to explore whether any survival benefit conferred by RT varied across subgroups. Treatment effect modification of RT was evaluated using categorical factors and interaction tests in bivariable weighted Cox models. In addition, we performed a secondary analysis by using a proportional subdistribution hazard model to confirm the HRs of BCM, which was adjusted by competing events such as death from other cancer, death as a result of heart disease, death from other noncancer causes, or death as a result of unknown reasons.[28]

To assess the consistency of our findings, we conducted four types of sensitivity analyses. First, we repeated analyses after excluding variables for marital, ER, and PgR status, with the missing data exchanged by multiple imputation. Second, we performed the analysis after restriction to patients in the SEER 9 registry, because the RT data in the SEER 9 registry are more accurate than the data in newer SEER registries.[29] Third, we repeated analyses after excluding patients without overlapped propensity score between RT group and non-RT group.[26,29,30] Last, we performed an additional analysis for the 57,101 patients diagnosed with DCIS during the 20-year period between 1992 and 2011 by using the same multivariable Cox regression hazard model.

We assessed proportional hazard assumption by using a method of Kernel estimation and a time-varying covariate in the Cox regression model. All *P* values presented are from two-sided tests that use $\alpha = .05$ to assess the statistical significance of survival benefit by RT. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics in Full SEER Cohort

We identified 32,144 eligible patients with DCIS on the basis of our inclusion and exclusion criteria (Appendix Fig A1). Of this initial cohort, 11,815 patients (36.8%) were stratified into the non-RT group, and 20,329 patients (63.2%) were stratified into the RT group. Patient clinicopathologic factors and SEER cancer registries according to receipt of RT are listed in Table 1 and Appendix Table A2 (online only). Balance in patient characteristics was achieved after multiple imputations and propensity score adjustments for estimating average treatment effect, as shown in Table 2. All clinicopathologic factors were statistically related to the receipt of RT. Patients diagnosed during earlier years, older patients, unmarried patients, patients with low income, patients with

Table 2. Patient Characteristics Weighted by Propensity Score

Characteristic	No. of Patients (%)	
	Non-RT Group (n = 11,815)	RT Group (n = 20,329)
Year of diagnosis		
1988-1992	105 (0.9)	178 (0.9)
1993-1997	922 (7.8)	1,569 (7.7)
1998-2002	4,298 (36.2)	7,376 (36.1)
2003-2007	6,561 (55.2)	11,320 (55.4)
Age, years		
20-39	345 (2.9)	578 (2.8)
40-44	1,010 (8.5)	1,744 (8.5)
45-49	1,582 (13.3)	2,740 (13.4)
50-54	1,730 (14.6)	2,997 (14.7)
55-59	1,711 (14.4)	2,924 (14.3)
60-64	1,433 (12.1)	2,445 (12.0)
65-69	1,306 (11.0)	2,242 (11.0)
70-74	1,146 (9.6)	1,936 (9.5)
75-79	863 (7.3)	1,488 (7.3)
80+	760 (6.4)	1,349 (6.6)
Race		
White	9,597 (80.7)	16,532 (80.9)
Black	967 (8.1)	1,641 (8.0)
Others	1,322 (11.1)	2,270 (11.1)
Marital status		
Married	7,440 (62.6)	12,820 (62.7)
Single	4,446 (37.4)	7,623 (37.3)
Tumor size, mm		
1-9	6,200 (52.2)	10,760 (52.6)
10-19	3,442 (29.0)	5,892 (28.8)
20-49	1,933 (16.3)	3,267 (16.0)
50+	311 (2.6)	524 (2.6)
Grade		
1	1,906 (16.0)	3,285 (16.1)
2	4,901 (41.2)	8,564 (41.9)
3	5,079 (42.7)	8,594 (42.0)
Estrogen receptor status		
Negative	2,082 (17.5)	3,469 (17.0)
Positive	9,804 (82.5)	16,974 (83.0)
Progesterone receptor status		
Negative	3,158 (26.6)	5,302 (25.9)
Positive	8,728 (73.4)	15,141 (74.1)

Abbreviation: RT, radiotherapy.

small tumor size, and patients with low nuclear grade were less likely to receive RT ($P < .001$)

Survival Benefit of RT

With a median follow-up time of 96 months from diagnosis (interquartile range, 69 to 127 months), there were 304 breast cancer–specific deaths (0.9%), 827 deaths from other cancer causes (2.6%), 837 deaths from heart disease (2.6%), 1,575 deaths from other noncancer causes (4.9%), and 97 deaths from unknown causes (0.3%; Table 3 lists data for cohort weighted by propensity score; Appendix Table A3, online only, lists data for original patient cohort). The 10-year BCM rate weighted by inverse propensity score was 1.8% in the RT group and 2.1% in the non-RT group (absolute difference, 0.3%; log-rank test, $P = .003$; HR, 0.73; 95% CI, 0.62 to 0.88). There was no statistically significant departure from the proportional hazard assumption in the Cox regression hazard model ($P = .59$). After adjusting for other clinical factors, age ($P = .004$), nuclear grade ($P = .007$), and tumor size ($P = 0.02$) were each identified as statistically significant effect modifiers of RT for BCM.

Survival Benefit of RT According to Patient Prognostic Score

When examining the benefit of RT stratified by factors associated with a risk of local recurrence used in the patient prognostic score, we found that the survival for the RT group was significantly better than that observed in the non-RT group for patients with higher nuclear grade, younger age, and larger tumor size. A statistically significant reduction in BCM with RT was not observed among patients without these prognostic factors (Appendix Tables A4 and A5, online only). Moreover, the magnitude of improved survival among patients treated with RT was significantly correlated with the patient prognostic score ($P < .001$), whereby patients with low scores demonstrated no significant difference in BCM (score 0: absolute difference, −0.4%; HR, 1.2; 95% CI, 0.67 to 2.06; $P = .58$; score 1: absolute difference, −0.5%; HR, 1.0; 95% CI, 0.70 to 1.47; $P = .95$, respectively) compared with patients with higher scores of 4 or 5, who saw a near 70% reduction in BCM (score 4: absolute difference, 1.9%; HR, 0.31; 95% CI, 0.16 to 0.58; $P < .001$; score 5: absolute difference, 4.0%; HR, 0.29; 95% CI, 0.09 to 0.91; $P = .03$; Figs 2 and 3). These findings were comparable with those in the secondary analysis through the proportional subdistribution hazards model (Appendix Table A6, online only).

In sensitivity analyses performed after the exclusion of variables for hormone receptor status and marital status, after restriction of patients within SEER 9, and after exclusion of patients without overlapped propensity score, we observed similar findings. In an additional analysis of the patients diagnosed between 1992 and 2011, the results were consistent with the primary analysis.

Table 3. Cause of Death With Patient Cohort Weighted by Propensity Score

Cause of Death	No. of Patients (%)		Total No. of Patients (%)
	Non-RT Group	RT Group	
Alive	10,278 (87)	18,222 (89.6)	28,500 (88.7)
Cause of death			
Breast cancer	153 (1.3)	164 (0.8)	317 (1.0)
Other cancer	328 (2.8)	512 (2.6)	840 (2.6)
Heart disease	356 (3.0)	470 (2.3)	826 (2.6)
Other noncancer	654 (5.5)	912 (4.5)	1,566 (4.9)
Unknown reason	46 (0.4)	49 (0.2)	95 (0.3)
Total	11,815	20,329	32,144

Abbreviation: RT, radiotherapy.

DISCUSSION

In our large population-based cohort study, we observed low BCM in women with DCIS, a reassuring finding that is consistent with prior reports.[5,6] However, our findings suggest a possible heterogeneous treatment effect of RT that may be most important when certain risk factors (ie, large tumor size, young age, and high nuclear grade) are present. These clinicopathologic factors have been used together to produce a recurrence risk scoring system called the patient prognostic score.[16-19,31] Our findings suggest that patients with low prognostic scores experienced a small difference in breast cancer–specific survival outcome when RT was combined with BCS, whereas patients with high prognostic scores treated with RT and BCS demonstrated a statistically significant difference in outcome compared with those in whom only BCS was used. In addition, overall BCM was only approximately 1%, whereas mortality from other causes was approximately 10% in our study. These results, when taken together with our earlier findings on DCIS, suggest that further research investigating the overdiagnosis and overtreatment of breast cancer is warranted and that a less invasive and more individualized local treatment strategy on the basis of one's probability of local recurrence should be considered.[23,32-35]

Local recurrence after BCS for DCIS is significant, because nearly half of patients with IBTR are diagnosed with invasive ductal carcinoma, which is associated with the potential for distant recurrence and an increased risk of death.[2,6] In observational studies and in a randomized clinical trial, several investigators have attempted to identify a cohort of patients with DCIS with a low probability of local recurrence for whom RT could be safely avoided after BCS.[11,16-20] Smith et al[20] proposed the patient prognostic score, which was designed to predict one's risk of IBTR using well-known predictive factors including patient age, tumor size, and grade. They investigated 14,202 patients with DCIS in the SEER database and found that the likelihood of IBTR increases by 22% with every 1-point increase in the prognostic score.

Although the National Comprehensive Cancer Network clinical guidelines do not mandate RT for low-risk DCIS,[36] RT after BCS is widely recognized as an acceptable treatment option and has become a standard approach for DCIS management in the United States.[37-39] Recent studies have sought to determine which subgroups of patients may be able to avoid RT, using IBTR as the primary end point to assess whether RT should be used. Young patient age, large tumor size, and high nuclear grade have been reported as predictive factors of IBTR after BCS,[7-12,14-20] yet data have been lacking on whether RT portends an improved survival in the treatment of DCIS. One randomized clinical trial investigated

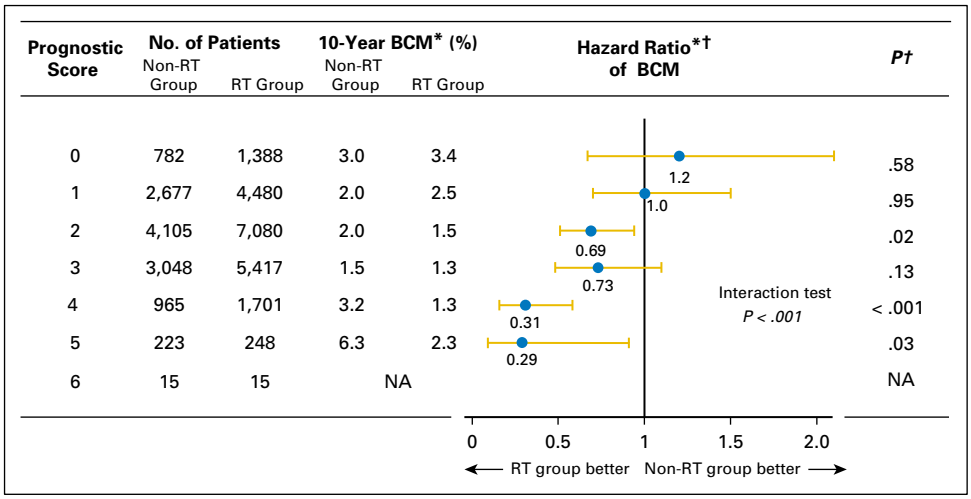

Fig 2. Hazard ratio comparing breast cancer mortality (BCM) between radiotherapy (RT) group and non-RT group according to prognostic score. (*) Weighted by inverse propensity score. (†) Multivariate analysis adjusted by age of patients, year of diagnosis, race, tumor size, nuclear grade, and marital status. NA, not applicable.

the efficacy of RT for DCIS with low recurrence risk features. The rate of local failure of patients with BCS alone was 6.7% during 7 years of follow-up and was significantly reduced by RT, whereas distant recurrence–free survival and overall survival remained identical between RT and non-RT groups.[11] Our results suggest that the omission of RT for patients with low prognostic scores is safe, given that it does not seem to improve survival compare with BCS alone.

Several researchers have investigated whether a gene profiling tool, the DCIS Score Assay, can predict local recurrence risk after BCS for DCIS.[40,41] In a cohort of patients from the Eastern Cooperative Oncology Group 5194 study, nuclear grade, margin width, and Van Nuys prognostic index were not significant predictive factors of an ipsilateral breast event.[41] However, the number of patients for this analysis was small (n = 327), possibly precluding the detection of small differences in recurrence rates. In addition, it is possible that the DCIS score maintains a collinear relationship with nuclear grade, such that the score inappropriately reduces the explanatory power of nuclear grade in the Cox regression model. The patient prognostic score uses classic clinical factors that have been established for predicting IBTR, whereas the DCIS score needs further validation to confirm how much additional prognostic information could be derived from its use.

There are several limitations in our study. Because unmeasured confounders such as surgical margin status, endocrine therapy, patient comorbidities, and reasons for treatment selection were not available in the SEER database and may have influenced overall results, our results should be interpreted with some caution. If surgical margins were positive, a physician would be more likely to recommend RT and the benefit would be underestimated in this study. In contrast, if RT was selectively avoided in patients with medical comorbidities, the survival benefit associated with its use would be overestimated. In view of this limitation, it is reassuring to note that one previous National Comprehensive Cancer Network study demonstrated no significant relationship between the presence of patient comorbidities and receipt of RT after BCS in the setting of DCIS.[39] Regarding the agreement of RT implementation between Medicare and the SEER database, substantial agreement was reported in one study ($\kappa = 0.77$), and almost perfect agreement was observed in another study ($\kappa = 0.87$).[42,43] Finally, we recognize that it may be more straightforward to use the prognostic score to select high-risk patients in whom the RT benefit is clear, as opposed

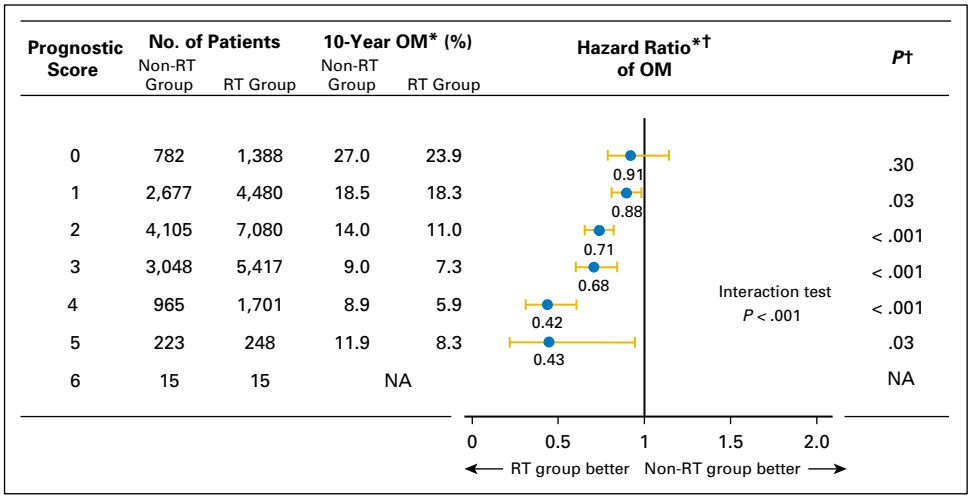

Fig 3. Hazard ratio comparing overall mortality (OM) between radiotherapy (RT) group and non-RT group according to prognostic score. (*) Weighted by inverse propensity score. (†) Multivariate analysis adjusted by age of patients, year of diagnosis, race, tumor size, nuclear grade, and marital status. NA, not applicable.

to the more challenging scenario of selecting lower risk patients, in whom RT provides negligible absolute benefit despite the significant reduction in local recurrence. Therefore, thorough counseling on the risk-benefit profile should be required for informed decision making.

The strength of our study is that it is the first to investigate the survival benefit of RT after BCS for DCIS according to individualized patient risk factors. By using a large population-based registry, it was possible to detect the absolute difference of survival rates between the RT and non-RT groups. Furthermore, our results provide information to guide individual treatment options according to prognostic scores that will predict the survival benefit of RT.

In conclusion, our study validates the prognostic score of DCIS, which can be used to predict not only local recurrence but also the magnitude of survival benefit offered by RT after BCS. As an oncology community, we must be cognizant of overtreatment for this disease process that has low BCM. Further prospective studies will be needed to confirm our findings and tailor RT for DCIS.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Patient Prognostic Score and Associations With Survival Improvement Offered by Radiotherapy After Breast-Conserving Surgery for Ductal Carcinoma In Situ: A Population-Based Longitudinal Cohort Study

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Appendix

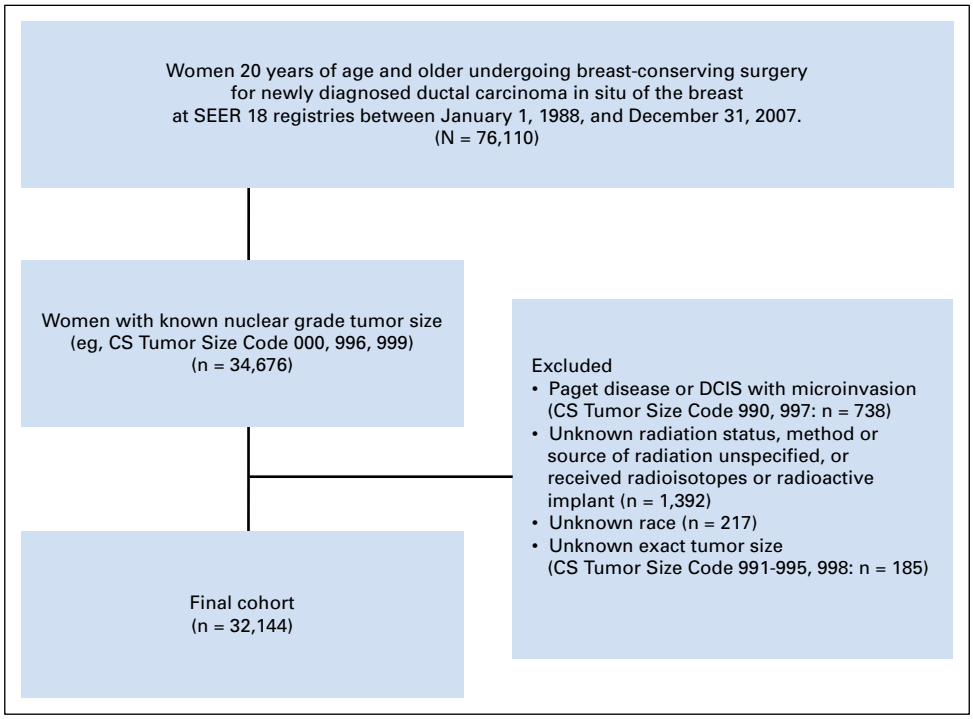

Fig A1. Flow diagram of patient population. CS, collaborative stage; DCIS, ductal carcinoma in situ.

Table A1. Patient Characteristics After Multiple Imputation for Unknown Data

Characteristic	No. of Patients (%)		*P*
	Non-RT Group (n = 11,815)	RT Group (n = 20,329)	
Marital status			< .001
Married	6,940 (58.4)	13,427 (65.7)	
Single	4,946 (41.6)	7,016 (34.3)	
Estrogen receptor status			< .001
Negative	1,684 (14.2)	3,794 (18.6)	
Positive	10,202 (85.8)	16,649 (81.4)	
Progesterone receptor status			< .001
Negative	2,639 (22.2)	5,721 (28.0)	
Positive	9,247 (77.8)	14,722 (72.0)	

Abbreviation: RT, radiotherapy.

Table A2. Original Registries Data

Registry	No. of Patients (%)		*P*
	Non-RT Group (n = 11,886)	RT Group (n = 20,443)	
Alaska Natives, 1992+	25 (0.2)	16 (0.1)	< .001
Atlanta (metropolitan), 1975+	383 (3.2)	971 (4.8)	
California excluding SF/SJM/LA	2,347 (19.8)	3,637 (17.8)	
Connecticut, 1973+	904 (7.6)	1,528 (7.5)	
Detroit (metropolitan), 1973+	797 (6.7)	2,041 (10.0)	
Hawaii, 1973+	200 (1.7)	963 (4.7)	
Iowa, 1973+	267 (2.3)	837 (4.1)	
Kentucky, 2000+	249 (2.1)	574 (2.8)	
Los Angeles, 1992+	2,371 (20.0)	2,299 (11.3)	
Louisiana, 2000+	203 (1.7)	450 (2.2)	
New Jersey, 2000+	981 (8.3)	1,572 (7.7)	
New Mexico, 1973+	272 (2.3)	379 (1.9)	
Rural Georgia, 1992+	18 (0.2)	19 (0.1)	
San Francisco-Oakland SMSA, 1973+	1,425 (12.0)	1,705 (8.3)	
San Jose-Monterey, 1992+	343 (2.9)	884 (4.3)	
Seattle (Puget Sound), 1974+	811 (6.8)	2,156 (10.6)	
Utah, 1973+	290 (2.4)	412 (2.0)	

Abbreviations: LA, Los Angeles; RT, radiotherapy; SF, San Francisco; SJM, San Jose-Monterey; SMSA, standard metropolitan statistical area.

Table A3. Cause of Death: Original Patient Cohort

Cause of Death	No. of Patients (%)		Total No. of Patients (%)
	Non-RT Group	RT Group	
Alive	9,850 (83.4)	18,657 (91.8)	28,507 (88.7)
Cause of death			
Breast cancer–specific death	151 (1.3)	153 (0.8)	304 (0.9)
Other cancer cause of death	378 (3.2)	449 (2.2)	827 (2.6)
Death from heart disease	506 (4.3)	328 (1.6)	837 (2.6)
Other noncancer cause of death	876 (7.4)	699 (3.4)	1,575 (4.9)
Death from unknown reason	54 (0.5)	43 (0.2)	97 (0.3)
Total	11,815	20,329	32,144

Abbreviation: RT, radiotherapy.

Table A4. HRs Comparing BCM Between Non-RT Group and RT Group According to Clinicopathologic Factors

Subgroup	No. of Patients		Weighted 10-Year BCM Rate (%)		Weighted Multivariable* HR	95% CI*	*P**
	Non-RT Group	RT Group	Non-RT Group	RT Group			
Age, years							
< 40	329	567	2.8	1.2	0.34	0.11 to 1.06	.06
40-60	5,545	11,697	1.4	0.9	0.51	0.38 to 0.69	< .001
> 60	5,941	8,065	3.0	3.0	0.94	0.75 to 1.2	.59
Tumor size, mm							
< 16	9,493	15,255	1.9	1.7	0.81	0.65 to 1.00	.05
16-40	1,919	4,484	2.7	2.1	0.64	0.45 to 0.92	.02
> 40	403	590	3.4	1.5	0.43	0.17 to 1.1	.08
Grade							
1	2,626	2,549	1.5	1.9	0.91	0.58 to 1.43	.67
2	5,594	7,923	1.9	2.0	0.87	0.66 to 1.16	.35
3	3,595	9,857	2.6	1.6	0.52	0.39 to 0.68	< .001
Total patients	11,815	20,329	2.1	1.8	0.74	0.62 to 0.88	< .001

Abbreviations: BCM, breast cancer mortality; HR, hazard ratio; RT, radiotherapy.
*Multivariable analysis adjusted by age of patients, year of diagnosis, race, tumor size, nuclear grade, and marital status.

Table A5. HRs Comparing OM Between Non-RT Group and RT Group According to Clinicopathologic Factors

Subgroup	No. of Patients		Weighted 10-Year OM Rate (%)		Weighted Multivariable* HR	95% CI*	*P**
	Non-RT Group	RT Group	Non-RT Group	RT Group			
Age, years							
< 40	329	567	4.5	1.8	0.30	0.12 to 0.74	.009
40-60	5,545	11,697	4.6	3.7	0.68	0.58 to 0.80	< .001
> 60	5,941	8,065	26.6	23.1	0.78	0.73 to 0.84	< .001
Tumor size, mm							
< 16	9,493	15,255	13.5	12.0	0.81	0.74 to 0.87	.05
16-40	1,919	4,484	16.4	12.1	0.64	0.56 to 0.74	< .001
> 40	403	590	18.2	18.0	0.58	0.41 to 0.82	.003
Grade							
1	2,626	2,549	14.4	13.8	1.01	0.93 to 1.27	.29
2	5,594	7,923	14.4	12.6	0.79	0.71 to 0.88	< .001
3	3,595	9,857	14.0	11.1	0.66	0.59 to 0.73	< .001
Total patients	11,815	20,329	14.2	12.2	0.76	0.71 to 0.81	< .001

Abbreviations: HR, hazard ratio; OM, overall mortality; RT, radiotherapy.
*Multivariable analysis adjusted by age of patients, year of diagnosis, race, tumor size, nuclear grade, and marital status.

Table A6. Patient Prognostic Score and HR Comparing BCM Between RT Group and Non-RT Group: HR From Cox Regression Model and Proportional Subdistribution Hazards Model

Patient Prognostic Score	Weighted Multivariable* HR of BCM (95%CI)	
	Cox Regression Model	Proportional Subdistribution Hazards Model
0	1.2 (0.67 to 2.1)	0.76 (0.33 to 1.8)
1	1.0 (0.70 to 1.5)	0.93 (0.57 to 1.5)
2	0.69 (0.51 to 0.94)	0.66 (0.46 to 0.96)
3	0.73 (0.48 to 1.1)	0.70 (0.43 to 1.1)
4	0.31 (0.16 to 0.58)	0.22 (0.10 to 0.49)
5	0.29 (0.09 to 0.91)	0.29 (0.09 to 0.91)
6	NA	NA

Abbreviations: BCM, breast cancer mortality; HR, hazard ratio; NA, not applicable; RT, radiotherapy.
*Multivariable analysis adjusted by age of patients, year of diagnosis, race, tumor size, nuclear grade, and marital status.