Original Investigation

Survival Benefit of Breast Surgery for Low-Grade Ductal Carcinoma In Situ
A Population-Based Cohort Study

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IMPORTANCE While the prevalence of ductal carcinoma in situ (DCIS) of the breast has increased substantially following the introduction of breast-screening methods, the clinical significance of early detection and treatment for DCIS remains unclear.

OBJECTIVE To investigate the survival benefit of breast surgery for low-grade DCIS.

DESIGN, SETTING, AND PARTICIPANTS A retrospective longitudinal cohort study using the Surveillance, Epidemiology, and End Results (SEER) database from October 9, 2014, to January 15, 2015, at the Dana-Farber/Brigham Women's Cancer Center. Between 1988 and 2011, 57 222 eligible cases of DCIS with known nuclear grade and surgery status were identified.

EXPOSURES Patients were divided into surgery and nonsurgery groups.

MAIN OUTCOMES AND MEASURES Propensity score weighting was used to balance patient backgrounds between groups. A log-rank test and multivariable Cox proportional hazards model was used to assess factors related to overall and breast cancer–specific survival.

RESULTS Of 57 222 cases of DCIS identified in this study, 1169 cases (2.0%) were managed without surgery and 56 053 cases (98.0%) were managed with surgery. With a median follow-up of 72 months from diagnosis, there were 576 breast cancer–specific deaths (1.0%). The weighted 10-year breast cancer–specific survival was 93.4% for the nonsurgery group and 98.5% for the surgery group (log-rank test, $P < .001$). The degree of survival benefit among those managed surgically differed according to nuclear grade ($P = .003$). For low-grade DCIS, the weighted 10-year breast cancer–specific survival of the nonsurgery group was 98.8% and that of the surgery group was 98.6% ($P = .95$). Multivariable analysis showed there was no significant difference in the weighted hazard ratios of breast cancer–specific survival between the surgery and nonsurgery groups for low-grade DCIS. The weighted hazard ratios of intermediate- and high-grade DCIS were significantly different (low grade: hazard ratio, 0.85; 95% CI, 0.21-3.52; intermediate grade: hazard ratio, 0.23; 95% CI, 0.14-0.42; and high grade: hazard ratio, 0.15; 95% CI, 0.11-0.23) and similar results were seen for overall survival.

CONCLUSIONS AND RELEVANCE The survival benefit of performing breast surgery for low-grade DCIS was lower than that for intermediate- or high-grade DCIS. A prospective clinical trial is warranted to investigate the feasibility of active surveillance for the management of low-grade DCIS.

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D uctal carcinoma in situ (DCIS) is a breast lesion defined as a proliferation of monoclonal epithelial cells in breast ducts without evidence of invasion in the basement membranes. Because the prevalence of breast cancer screening has increased, early detection has contributed to a dramatic increase in the incidence of DCIS, which has risen from 5.83 per 100 000 women in 1973 to 35.54 per 100 000 women in 2011.[1] Assuming constant incidence and survival rates, it is estimated that by 2020, more than 1 million women living in the United States will have a diagnosis of DCIS.[2]

Ductal carcinoma in situ displays a wide spectrum of histological diversity along a continuum, ranging from very well to very poorly differentiated, and nuclear grade has accurately conveyed this diversity.[3] Approximately 25% to 50% of DCIS cases will likely progress to invasive ductal carcinoma.[4-6] Ozanne et al[7] established a simulation model to predict the progression rate of DCIS to clinically significant invasive breast cancer. Ozanne et al[7] estimated that the rate of progression from DCIS to invasive cancer across a 10-year period is 60% for high-grade DCIS (for patients younger than 45 years with lesions larger than 1 cm) and 16% for low-grade DCIS (for patients older than 45 years with lesions larger than 2.5 cm). After local therapy for DCIS, nuclear grade was a proven predictive factor of ipsilateral breast cancer recurrence in a randomized clinical trial and meta-analysis.[8-10]
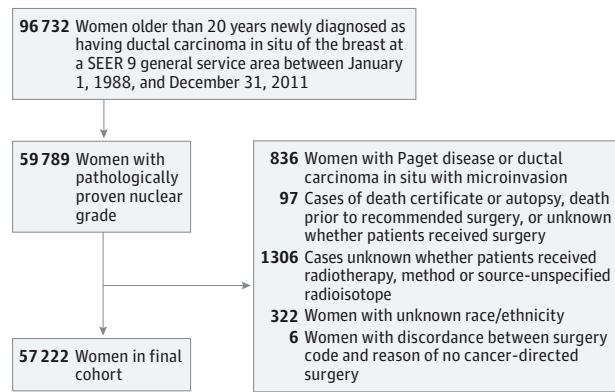
An optimal strategy for DCIS management would be based on individual risk factors that predict subsequent invasive ductal carcinoma to avoid overtreatment. Although surgical management is the current standard of care for all grades of DCIS, to our knowledge, the survival benefit of surgical resection has not been examined.[11,12] Therefore, we investigated the survival benefit conferred by surgical treatment in patients with DCIS using survival data in the Surveillance, Epidemiology, and End Results (SEER) database. We hypothesized that breast cancer–specific survival (BCSS) for patients with low-grade DCIS is independent from surgical treatment at the time of diagnosis.

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 from the SEER database of the National Cancer Institute, which has incidence and survival data routinely collected from population-based cancer registries. We used the SEER 9 general health service, which includes cases followed up from 1973 to 2011. The SEER 9 includes data from Atlanta, Georgia, Connecticut, Detroit, Michigan, Hawaii, Iowa, New Mexico, San Francisco, California and Oakland, California, Seattle, Washington, and the Puget Sound area, and Utah. Between January 1, 1988, and December 31, 2011, 96 732 patients who were older than 20 years were diagnosed as having DCIS of the breast (**Figure 1**). Among these patients, we identified 59 789 cases with a nuclear grade that was available based on pathology results. We excluded patients with Paget disease or ductal carcinoma with microinvasion, patients whose treatment pathway (surgery vs no surgery) was

Figure 1. Patient Population

| 96 732 | Women older than 20 years newly diagnosed as having ductal carcinoma in situ of the breast at a SEER 9 general service area between January 1, 1988, and December 31, 2011 |

| 59 789 | Women with pathologically proven nuclear grade |

836	Women with Paget disease or ductal carcinoma in situ with microinvasion
97	Cases of death certificate or autopsy, death prior to recommended surgery, or unknown whether patients received surgery
1306	Cases unknown whether patients received radiotherapy, method or source-unspecified radioisotope
322	Women with unknown race/ethnicity
6	Women with discordance between surgery code and reason of no cancer-directed surgery

| 57 222 | Women in final cohort |

SEER indicates Surveillance, Epidemiology, and End Results.

unknown, patients who were listed as deceased prior to recommended surgery, patients in whom it remained unclear whether a surgical procedure was performed owing to a discrepancy in coding, patients with unknown race/ethnicity, patients with unknown radiation status, patients with an unknown method of radiotherapy, and patients with isotope only–based radiotherapy.

Assembly of Key Variables

Using the case listing sessions in SEER*Stat software, version 8.1.5, a data table including individual cancer records and patient characteristics was created that was composed of the following variables: patient identification, year of diagnosis, age, race/ethnicity, histology, tumor size, nuclear grade, estrogen receptor (ER), progesterone receptor (PgR), adjusted American Joint Committee on Cancer 6th tumor node metastasis staging classification, surgery type, reason for no cancer-directed surgery, radiation therapy, cause-specific death classification, other cause of death classification, and survival month. The tumor size was primarily measured according to American Joint Committee on Cancer pathologic staging criteria; however, when pathologic data were not available, the tumor size was measured based on physical or imaging examinations. The hormone receptor status was coded as positive, negative, or unknown based on the records of highest value.

We queried the database using both surgery and therapy codes to determine which patients underwent surgical management of their DCIS. The surgery codes 00 and 02 were used to determine patients who did not have definitive therapy. Agreement between surgery codes and the reasons why a patient did not have cancer-directed therapy were confirmed prior to performing our analysis (Figure 1).

Main Outcome Measure

The SEER database defines mortality data based on the *International Classification of Diseases*, Eighth to Tenth revisions. In this study, the periods of BCSS and overall survival (OS) were calculated by measuring from the date of diagnosis to the last date for which completed vital status data were available (censored on

December 31, 2011). The data for deaths were ascertained from central cancer registries or from state, province, and national registries.

Statistical Analysis

Clinicopathologic factors were compared between the surgery groups and nonsurgery groups using Pearson χ^2 tests. For the missing values for covariates including tumor size (n = 14 160; 24.7%), ER (n = 26 274; 45.9%), and PgR status (n = 28 186; 49.2%), we applied a multiple imputation procedure using IVEware macro, version 0.2 (http://www.isr.umich.edu/src/smp/ive)[13,14] with the following variables: patient age (continuous), year of diagnosis, race/ethnicity (white, black, or other), ER (positive or negative), PgR (positive or negative), surgery (partial mastectomy, total mastectomy, or nonsurgery), nuclear grade, tumor size classification (0.1-0.5 mm, 0.6-10 mm, 11-50 mm, or <51 mm), and radiation therapy. To stabilize results, the procedure was repeated for 10 cycles to produce a single imputed data set (eTable 1 in the Supplement).[15,16]

Propensity score weighting was then used to balance patient characteristics between the surgery and nonsurgery groups.[17,18] A logistic regression model was used to calculate the probability of receiving surgery, baseline characteristics of patient age (categorical, 5-year interval), year of diagnosis (categorical, 5-year interval), race/ethnicity, tumor size classification, nuclear grade, ER, and PgR. From the model, the inverse predicted probability of breast surgery assignment was used to define weights for patients who received surgery (1/probability) and for those who did not receive surgery (1/[1 − probability]). Patient characteristics after propensity score adjustment are shown to be balanced in eTable 2 in the Supplement.

The hazard ratios for the BCSS and OS of patients in the surgery group compared with patients in the nonsurgery group were evaluated using propensity score weights for log-rank tests and Cox regression models. Adjusted hazard ratios were reported from multivariable Cox proportional hazards models with patient age (categorical, 5-year interval), year of diagnosis (categorical, 5-year interval), tumor size classification, radiation therapy, and African American race/ethnicity. An interaction test was performed to examine whether there was a difference in the survival benefit conferred by surgical treatment according to nuclear grade. To assess the consistency of our findings, we conducted the following 2 types of sensitivity analyses: one by excluding variables of tumor size and hormonal receptor status, with the missing data exchanged by multiple imputation, and another by performing a stratified propensity score analysis after excluding beyond the 2.5th and 97.5th percentiles of the propensity score distribution.[19,20]

All P values presented were from 2-sided tests that used α = .05 to assess statistical significance. Statistical analyses were performed using SAS, version 9.4 (SAS Institute).

Results

Patient Characteristics in Original Data Set

We identified 57 222 patients with DCIS who were eligible for this study based on our predefined inclusion and exclusion cri-

teria. There were 1169 cases (2.0%) managed without surgery and 56 053 cases (98.0%) managed with surgery. Patient characteristics according to surgery status are shown in **Table 1**. The proportion of elderly patients, patients with a recent year of diagnosis, African American race/ethnicity, and low-grade DCIS was larger for the nonsurgery group compared with the surgery group.

In the surgery group, partial mastectomy was performed in 34 439 patients (61%), mastectomy was performed in 16 334 patients (29%), and the type of surgery was not known in 5280 patients (9.4%). Among the patients who received partial mastectomy, 23 129 patients (67.2%) underwent radiotherapy of the breast. In the nonsurgery group, the reasons why patients did not receive cancer-directed surgery included the following reasons: a physician did not recommend surgery (n = 547; 46.8%), a physician did not recommend surgery owing to other contradicted conditions (n = 29; 1.7%), a physician recommended surgery but it was not performed because the patient refused (n = 115; 9.8%), and a physician recommended surgery but it was not performed owing to unknown reasons (n = 478; 40.9%).

Survival Benefit of Breast Surgery

During a median follow-up period of 72 months from the date of diagnosis (interquartile range, 34-120 months), there were 576 breast cancer–specific deaths (1.0%) and 3652 deaths from other causes (6.4%). Kaplan-Meier curves of BCSS comparing the surgery and nonsurgery groups in the total patient cohort weighted by inverse propensity scores are shown in **Figure 2** (see eTable 3 in the Supplement for analyses of unweighted BCSS). The weighted 10-year BCSS of all patients was 98.5% in the surgery group and 93.4% in the nonsurgery group (absolute difference, 5.1%; log-rank test, P < .001). After adjusting for other clinical factors, nuclear grade remained a statistically significant effect modifier for surgery in BCSS (P = .003).

Survival Benefit of Breast Surgery According to Nuclear Grade

Kaplan-Meier curves of BCSS comparing the surgery and the nonsurgery groups according to nuclear grade are shown in Figure 2. The weighted 10-year BCSS of the surgery and nonsurgery groups were 98.6% and 98.8% in low-grade DCIS (absolute difference, −0.2%), 98.6% and 94.6% in intermediate-grade DCIS (absolute difference, 4.0%), and 98.4% and 90.5% in high-grade DCIS (absolute difference, 7.9%), respectively (**Table 2**). Multivariate analysis showed that while there was no statistical difference in the weighted hazard ratios of BCSS and OS between the surgery and nonsurgery groups for low-grade DCIS, the weighted hazard ratios of intermediate- and high-grade DCIS were significantly different (Table 2 and **Table 3**). In the sensitivity analyses, consistent results were observed when excluding variables of tumor size and hormonal receptor status and when performing a stratified propensity score analysis.

Discussion

Low-grade DCIS is an indolent lesion of epithelial cells in breast ducts. It typically exhibits a slow growth pattern and, in many

Table 1. Patient Characteristics by Receipt of Cancer-Directed Surgery

Characteristic	Cancer-Directed Surgery, No. (%)		P Value
	Not Performed	Performed	
Age, y			
≤39	23 (2.0)	1809 (3.2)	
40-44	94 (8.0)	4809 (8.6)	
45-49	120 (10.3)	7259 (13.0)	
50-54	145 (12.4)	8148 (14.5)	
55-59	141 (12.1)	7660 (13.7)	<.001
60-64	133 (11.4)	6871 (12.3)	
65-69	109 (9.3)	6207 (11.1)	
70-74	89 (7.6)	5181 (9.2)	
75-79	133 (11.4)	4873 (8.7)	
≥80	182 (15.6)	3236 (5.8)	
Year of diagnosis			
1988-1993	7 (0.6)	1052 (1.9)	
1994-1999	161 (13.8)	9389 (16.8)	<.001
2000-2005	463 (39.6)	20 268 (36.2)	
2006-2011	538 (46.0)	25 344 (45.2)	
Race/ethnicity			
White	914 (78.2)	44 494 (79.4)	
Black	178 (15.2)	5295 (9.4)	<.001
Other	77 (6.6)	6264 (11.2)	
Tumor size, mm			
0.1-0.5	129 (31.2)	12 558 (29.5)	
0.6-10	97 (23.5)	10 344 (24.3)	
11-50	164 (14.0)	17 804 (31.8)	.60
≥51	23 (2.0)	1943 (3.5)	
Unknown	756 (64.7)	14 160 (25.3)	
Grade			
1	230 (19.7)	8820 (15.7)	
2	477 (40.8)	21 579 (38.5)	<.001
3	462 (39.5)	25 654 (45.8)	
ER			
Negative	67 (5.7)	5040 (9.0)	
Positive	409 (35.0)	25 432 (45.4)	.15
Unknown	693 (59.3)	25 581 (45.6)	
PgR			
Negative	125 (10.7)	7787 (13.9)	
Positive	317 (27.1)	20 807 (37.1)	.62
Unknown	727 (62.2)	27 459 (49.0)	
Radiation therapy			
Performed	159 (13.6)	30 707 (54.8)	<.001
Not performed	1010 (86.4)	25 346 (45.2)	
Total	1169	56 053	

Abbreviations: ER, estrogen receptor;
PgR, progesterone receptor.

cases, never fully develops into a clinically significant invasive carcinoma.[4-7,21,22] Although the natural history of low-grade DCIS is poorly understood, the current standard therapy is either partial mastectomy followed by whole-breast radiation therapy or a total mastectomy. The choice of local treatments does not currently take the biology of DCIS into consideration. As such, DCIS management principles may benefit from incorporating information regarding the biologic behavior of DCIS based on nuclear grade.[21-24]

In our analysis of a large population-based cohort, we saw a statistically significant survival benefit of breast surgery for intermediate- and high-grade cases of DCIS while no significant survival benefit was appreciated for cases of low-grade DCIS. The weighted BCSS curves of both groups were identical and the prognosis for patients treated nonoperatively was favorable (weighted 10-year BCSS, 98.8%) during the median 72-month follow-up period. From these results, we could consider recommending a strategy of nonoperative management

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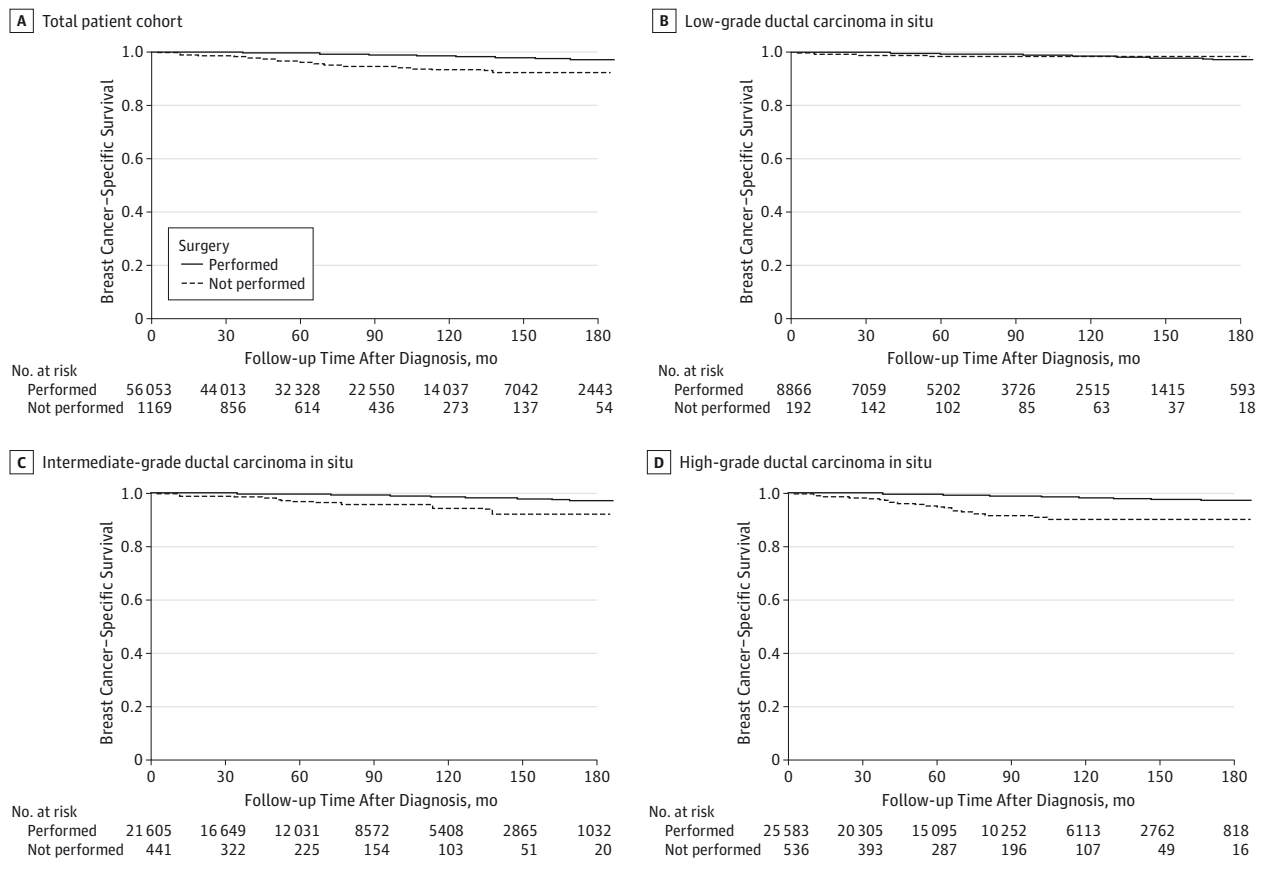**Figure 2. Kaplan-Meier Curves for Breast Cancer–Specific Survival Among a Propensity-Weighted Cohort of Patients**

A Total patient cohort

No. at risk
Performed	56 053	44 013	32 328	22 550	14 037	7042	2443
Not performed	1169	856	614	436	273	137	54

B Low-grade ductal carcinoma in situ

No. at risk
Performed	8866	7059	5202	3726	2515	1415	593
Not performed	192	142	102	85	63	37	18

C Intermediate-grade ductal carcinoma in situ

No. at risk
Performed	21 605	16 649	12 031	8572	5408	2865	1032
Not performed	441	322	225	154	103	51	20

D High-grade ductal carcinoma in situ

No. at risk
Performed	25 583	20 305	15 095	10 252	6113	2762	818
Not performed	536	393	287	196	107	49	16

Table 2. Effect of Surgery on BCSS According to Nuclear Grade

Grade	Cancer-Directed Surgery	Weighted BCSS, %		Analysis[a]				
				Univariate		Multivariate		
		5 Year	10 Year	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	
1	Performed	99.5	98.6	1.05 (0.26-4.23)	.95	0.85 (0.21-3.52)	.83	
	Not performed	98.8	98.8					
2	Performed	99.6	98.6	0.23 (0.14-0.39)	<.001	0.25 (0.14-0.42)	<.001	
	Not performed	96.8	94.6					
3	Performed	99.5	98.4	0.15 (0.10-0.22)	<.001	0.15 (0.11-0.23)	<.001	
	Not performed	94.8	90.5					

Abbreviation: BCSS, breast cancer–specific survival.

[a] Weighted by inverse propensity score.

with active surveillance similar to that used in the management of prostate cancer.[22,25] In addition, by integrating both conventional pathologic and molecular factors, such as human epidermal growth factor receptor 2, prostaglandin-endoperoxide synthase 2, and Ki67, it may be possible to identify subpopulations of low-grade DCIS with more favorable prognoses.[26-29] The results from ongoing clinical trials (NCT00290745 and NCT01439711) looking at the role of neoadjuvant therapy for DCIS may provide more information that could help identify optimal biology-based DCIS treatment strategies.[30]

We used multiple imputation to infer missing data pertaining to tumor size and ER status in the multivariable analysis because it characteristically yields less biased results than other methods. We viewed absent variables in the SEER database as being missing at random, meaning that the systematic difference between the missing and observed values could be explained by differences in observed data.[13,31,32] Furthermore, to ensure our study had enough power to detect the survival benefit offered by breast surgery, it was necessary for us to include such patient characteristics. A sensitivity analysis performed by excluding vari-

Table 3. Effect of Surgery on OS According to Nuclear Grade

Grade	Cancer-Directed Surgery	Weighted OS, %		Analysis[a]				
				Univariate		Multivariate		
		5 Year	10 Year	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	
1	Performed	95.8	87.9	1.14 (0.70-1.86)	.60	0.88 (0.54-1.44)	.60	
	Not performed	95.6	91.0					
2	Performed	96.4	89.3	0.68 (0.50-0.91)	.009	0.73 (0.54-0.99)	.04	
	Not performed	90.7	84.7					
3	Performed	96.6	90.0	0.45 (0.35-0.57)	<.001	0.40 (0.32-0.51)	<.001	
	Not performed	89.4	79.1					

Abbreviation: OS, overall survival.

[a] Weighted by inverse propensity score.

ables, which were exchanged using multiple imputations, confirmed the robustness of our results.

Propensity score weighting is an effective way of removing overt indication biases for the purpose of investigating treatment effects seen in observational studies.[17-20] Using this method, we attempted to balance the background characteristics of patients between the treatment (surgery) and nontreatment groups (eTable 2 in the Supplement). However, without the performance of a randomized clinical trial, we cannot account for unmeasured confounders that may have influenced the prognosis of DCIS. Our findings justify a subsequent prospective study aimed at investigating new approaches for the management of low-grade DCIS. Such a study may include active surveillance with an imaging arm that includes recommendations for delayed surgery only after confirming progression of the disease.

There were limitations to this study. First, we used population-based cancer registries with limited information regarding patient and tumor characteristics. Unavailable confounders, such as surgical margin status, comorbidity, endocrine therapy, and history of screening, could not be adjusted for this data set. We assumed that our results would have been minimally influenced by including information related to endocrine therapy because ER/PgR were not independent prognostic factors of DCIS in this study. Furthermore, the number of cases that did not receive surgery owing to other contraindicated conditions was much smaller than we expected (n = 29; 1.7%). An additional limitation to our study was that data abstraction was done in part by individuals who could have created information bias. However, it has been reported that there is good agreement between Medicare and SEER data with respect to whether or not patients underwent surgery; therefore, we anticipate that the possibility of misclassification was small.[33] There were 159 patients (14% of nonoperative group) who received radiation therapy without undergoing breast sur-

gery, which is not a standard treatment for DCIS. However, we believe these data are most likely accurate because we confirmed the concordance between the surgery code and reason of no cancer-directed surgery using the SEER database. Furthermore, the positive predictive values of receiving radiation therapy between the SEER database and Medicare data are as high as 97.5%, as reported by Noone et al.[34] In the SEER database, a biopsy that removes only a fragment or portion of the tumor is recorded as a noncancer-directed treatment. Therefore, we consider this is the group that had radiation therapy without cancer-directed surgery.

We sought to determine the prognosis of patients managed nonoperatively at the time of diagnosis. While we cannot conclude definitively based on the results of this study alone that we can avoid breast surgery for low-grade DCIS, our results do suggest that breast surgery performed at or shortly after the time of diagnosis does not significantly affect survival for low-grade DCIS.

To our knowledge, this study is the first to examine the survival benefit of surgical treatment for DCIS. From the SEER database, we identified more than 1000 cases of DCIS with known nuclear grade managed nonoperatively. The large number of nonoperative cases made it possible to investigate the survival benefit of surgery according to the grade of DCIS after adjusting for other clinicopathologic factors.

Conclusions

The survival benefit of breast surgery for low-grade DCIS was lower than that for intermediate- or high-grade DCIS, which raises concern regarding the necessity and benefit of surgery for patients with low-grade DCIS. A prospective clinical trial is warranted to investigate the feasibility of active surveillance for the management of low-grade DCIS.

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