Original Investigation

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

Yasuaki Sagara, MD; Melissa Anne Mallory, MD; Stephanie Wong, MD; Fatih Aydogan, MD; Stephen DeSantis, BS; William T. Barry, PhD; Mehra Golshan, MD

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.

◄ Invited Commentary

➕ Supplemental content at jamasurgery.com

Author Affiliations: Department of Surgery, Brigham and Women's Hospital, Boston, Massachusetts (Sagara, Mallory, Aydogan, Golshan); Department of Surgery, McGill University Health Centre, Montreal, Québec, Canada (Wong); Harvard Medical School, Boston, Massachusetts (Wong); Department of Breast Surgery, Cerrahpasa Medical School, Istanbul University, Istanbul, Turkey (Aydogan); Department of Breast Oncology Center, Dana-Farber Cancer Institute, Boston, Massachusetts (DeSantis); Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, Massachusetts (Barry).

Corresponding Author: Yasuaki Sagara, MD, Division of Surgical Oncology, Dana-Farber/Brigham and Women's Cancer Center, Harvard School of Public Health, 450 Brookline Ave, Yawkey Ste 1444, Boston, MA 02215 (ysagara@partners.org).

D uctal carcinoma in situ (DCIS) is a breast lesion de-
fined as a proliferation of monoclonal epithelial cells
in breast ducts without evidence of invasion in the
basement membranes. Because the prevalence of breast can-
cer 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 histo-
logical diversity along a continuum, ranging from very well to
very poorly differentiated, and nuclear grade has accurately con-
veyed 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 inva-
sive 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 le-
sions 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 duc-
tal carcinoma to avoid overtreatment. Although surgical man-
agement 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 sur-
vival 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 can-
cer-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 In-
stitutional Review Board, we performed a retrospective lon-
gitudinal cohort study using data from the SEER database of
the National Cancer Institute, which has incidence and sur-
vival 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 in-
cludes data from Atlanta, Georgia, Connecticut, Detroit, Michi-
gan, 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 diag-
nosed as having DCIS of the breast (Figure 1). Among these pa-
tients, 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, pa-
tients whose treatment pathway (surgery vs no surgery) was
unknown, patients who were listed as deceased prior to rec-

Figure 1. Patient Population
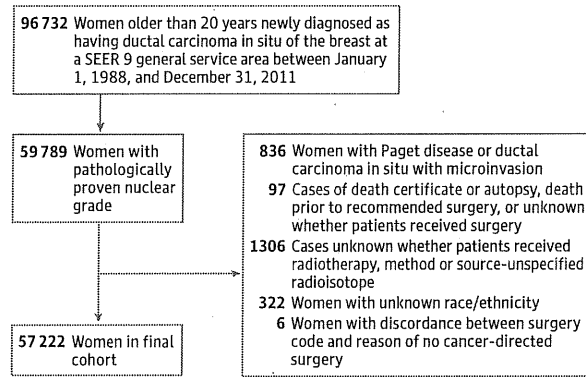
SEER indicates Surveillance, Epidemiology, and End Results.

ommended surgery, patients in whom it remained unclear
whether a surgical procedure was performed owing to a dis-
crepancy 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 pa-
tient characteristics was created that was composed of the fol-
lowing variables: patient identification, year of diagnosis, age,
race/ethnicity, histology, tumor size, nuclear grade, estrogen
receptor (ER), progesterone receptor (PgR), adjusted Ameri-
can Joint Committee on Cancer 6th tumor node metastasis stag-
ing classification, surgery type, reason for no cancer-directed
surgery, radiation therapy, cause-specific death classifica-
tion, other cause of death classification, and survival month.
The tumor size was primarily measured according to Ameri-
can Joint Committee on Cancer pathologic staging criteria; how-
ever, 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 man-
agement 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 pa-
tient 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 *Inter-
national 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 (cen-
sored on December 31, 2011). The data for deaths were ascer-

tained 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 criteria. 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 (Tables 2 and 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

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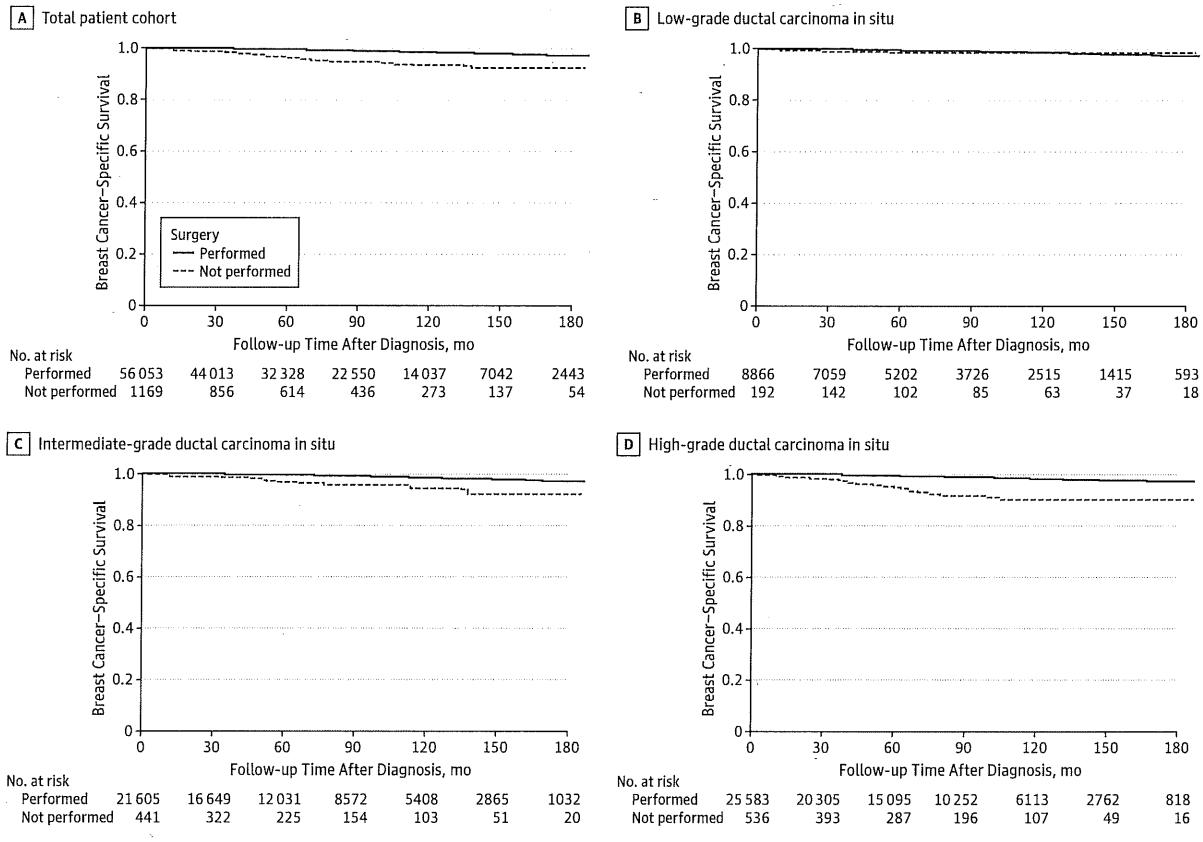

A | Total patient cohort

No. at risk

	0	30	60	90	120	150	180
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

	0	30	60	90	120	150	180
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

	0	30	60	90	120	150	180
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

	0	30	60	90	120	150	180
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]			
		5 Year	10 Year	Univariate		Multivariate	
				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.

management 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]				
		5 Year	10 Year	Univariate		Multivariate		
				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.

REFERENCE

1. Howlader N, Noone A, Krapcho M, et al. National Cancer Institute. SEER Cancer Statistics Review: 1975-2011. http://seer.cancer.gov/csr/1975_2012/. Accessed April 29, 2015.

2. Allegra CJ, Aberle DR, Ganschow P, et al. National Institutes of Health State-of-the-Science Conference statement: diagnosis and management of ductal carcinoma in situ September 22-24, 2009. *J Natl Cancer Inst*. 2010;102(3):161-169.

3. Allred DC, Mohsin SK, Fuqua SA. Histological and biological evolution of human premalignant breast disease. *Endocr Relat Cancer*. 2001;8(1):47-61.

4. Welch HG, Black WC. Using autopsy series to estimate the disease "reservoir" for ductal carcinoma in situ of the breast: how much more breast cancer can we find? *Ann Intern Med*. 1997;127 (11):1023-1028.

5. Page DL, Dupont WD, Rogers LW, Jensen RA, Schuyler PA. Continued local recurrence of carcinoma 15-25 years after a diagnosis of low grade ductal carcinoma in situ of the breast treated only by biopsy. *Cancer*. 1995;76(7):1197-1200.

6. Page DL, Dupont WD, Rogers LW, Landenberger M. Intraductal carcinoma of the breast: follow-up after biopsy only. *Cancer*. 1982;49(4):751-758.

7. Ozanne EM, Shieh Y, Barnes J, Bouzan C, Hwang ES, Esserman LJ. Characterizing the impact of 25 years of DCIS treatment. *Breast Cancer Res Treat*. 2011;129(1):165-173.

8. Benson JR, Wishart GC. Predictors of recurrence for ductal carcinoma in situ after breast-conserving surgery. *Lancet Oncol*. 2013;14(9):e348-e357.

9. Wapnir IL, Dignam JJ, Fisher B, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. *J Natl Cancer Inst*. 2011;103(6):478-488.

10. Wang S-Y, Shamliyan T, Virnig BA, Kane R. Tumor characteristics as predictors of local recurrence after treatment of ductal carcinoma in situ: a meta-analysis. *Breast Cancer Res Treat*. 2011; 127(1):1-14.

11. Virnig BA, Tuttle TM, Shamliyan T, Kane RL. Ductal carcinoma in situ of the breast: a systematic review of incidence, treatment, and outcomes. *J Natl Cancer Inst*. 2010;102(3):170-178.

12. Allegra CJ, Aberle DR, Ganschow P, et al. NIH state-of-the-science conference statement: diagnosis and management of ductal carcinoma in situ (DCIS). *NIH Consens State Sci Statements*. 2009;26(2):1-27.

13. Little RJA, Rubin DB. *Statistical Analysis With Missing Data*. 2nd ed. New York, NY: Wiley; 2002.

14. Horton NJ, Kleinman KP. Much ado about nothing: a comparison of missing data methods and software to fit incomplete data regression models. *Am Stat*. 2007;61(1):79-90.

15. Royston P, White IR. Multiple imputation by chained equations (MICE): implementation in Stata. *J Stat Softw*. 2011;45:1-20.

16. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Stat Med*. 1999;18(6): 681-694.

17. Rosenbaum PR. Model-based direct adjustment. *J Am Stat Assoc*. 1987;82:387-394.

18. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011; 46(3):399-424.

19. Patorno E, Grotta A, Bellocco R, Schneeweiss S. Propensity score methodology for confounding control in health care utilization databases. *Epidemiol Biostat Public Health*. 2013;10(3).

20. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. *J Am Stat Assoc*. 1984;79:516-524.

21. Esserman L, Shieh Y, Thompson I. Rethinking screening for breast cancer and prostate cancer. *JAMA*. 2009;302(15):1685-1692.

22. Esserman LJ, Thompson IM, Reid B, et al. Addressing overdiagnosis and overtreatment in cancer: a prescription for change. *Lancet Oncol*. 2014;15(6):e234-e242.

23. Welch HG, Black WC. Overdiagnosis in cancer. *J Natl Cancer Inst*. 2010;102(9):605-613.

24. Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. *N Engl J Med*. 2012;367(21):1998-2005.

25. Wilt TJ, Brawer MK, Jones KM, et al; Prostate Cancer Intervention vs Observation Trial (PIVOT) Study Group. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med*. 2012;367(3):203-213.

26. Kerlikowske K, Molinaro AM, Gauthier ML, et al. Biomarker expression and risk of subsequent tumors after initial ductal carcinoma in situ diagnosis. *J Natl Cancer Inst*. 2010;102(9):627-637.

27. Lazzeroni M, Guerrieri-Gonzaga A, Botteri E, et al. Tailoring treatment for ductal intraepithelial neoplasia of the breast according to Ki-67 and molecular phenotype. *Br J Cancer*. 2013;108(8): 1593-1601.

28. Vandenbussche CJ, Khouri N, Sbaity E, et al. Borderline atypical ductal hyperplasia/low-grade ductal carcinoma in situ on breast needle core biopsy should be managed conservatively. *Am J Surg Pathol*. 2013;37(6):913-923.

29. Bartlett JMS, Nofech-Moses S, Rakovitch E. Ductal carcinoma in situ of the breast: can biomarkers improve current management? *Clin Chem*. 2014;60(1):60-67.

30. Siziopikou KP, Anderson SJ, Cobleigh MA, et al. Preliminary results of centralized HER2 testing in ductal carcinoma in situ (DCIS): NSABP B-43. *Breast Cancer Res Treat*. 2013;142(2):415-421.

31. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393.

32. Howlader N, Noone AM, Yu M, Cronin KA. Use of imputed population-based cancer registry data as a method of accounting for missing information: application to estrogen receptor status for breast cancer. *Am J Epidemiol*. 2012;176(4):347-356.

33. Cooper GS, Virnig B, Klabunde CN, Schussler N, Freeman J, Warren JL. Use of SEER-Medicare data for measuring cancer surgery. *Med Care*. 2002; 40(8)(suppl):IV-43-IV-48.

34. Noone AM, Lund JL, Mariotto A, et al. Comparison of SEER treatment data with Medicare claims [published online March 15, 2014]. *Med Care*. 2014.