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Surgical Excision Without Radiation for Ductal Carcinoma in Situ of the Breast: 12-Year Results From the ECOG-ACRIN E5194 Study

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ABSTRACT

Purpose

To determine the 12-year risk of developing an ipsilateral breast event (IBE) for women with ductal carcinoma in situ (DCIS) of the breast treated with surgical excision (lumpectomy) without radiation.

Patients and Methods

A prospective clinical trial was performed for women with DCIS who were selected for low-risk clinical and pathologic characteristics. Patients were enrolled onto one of two study cohorts (not randomly assigned): cohort 1: low- or intermediate-grade DCIS, tumor size 2.5 cm or smaller (n = 561); or cohort 2: high-grade DCIS, tumor size 1 cm or smaller (n = 104). Protocol specifications included excision of the DCIS tumor with a minimum negative margin width of at least 3 mm. Tamoxifen (not randomly assigned) was given to 30% of the patients. An IBE was defined as local recurrence of DCIS or invasive carcinoma in the treated breast. Median follow-up time was 12.3 years.

Results

There were 99 IBEs, of which 51 (52%) were invasive. The IBE and invasive IBE rates increased over time in both cohorts. The 12-year rates of developing an IBE were 14.4% for cohort 1 and 24.6% for cohort 2 (P = .003). The 12-year rates of developing an invasive IBE were 7.5% and 13.4%, respectively (P = .08). On multivariable analysis, study cohort and tumor size were both significantly associated with developing an IBE (P = .009 and P = .03, respectively).

Conclusion

For patients with DCIS selected for favorable clinical and pathologic characteristics and treated with excision without radiation, the risks of developing an IBE and an invasive IBE increased through 12 years of follow-up, without plateau. These data help inform the treatment decision-making process for patients and their physicians.

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INTRODUCTION

The optimal clinical management for women with newly diagnosed ductal carcinoma in situ (DCIS; intraductal carcinoma) of the breast is controversial, with variable patterns of practice.[1-7] Although most women with DCIS of the breast present with an asymptomatic finding on routine screening mammography, population-based studies demonstrate a wide range of treatments.[4-7] Local treatment options for DCIS include surgical excision (lumpectomy) with or without radiation treatment, unilateral mastectomy, and even bilateral mastectomies. Systemic therapy options include adjuvant tamoxifen for hormone receptor–positive DCIS tumors. In randomized clinical trials, adding radiation treatment or tamoxifen after lumpectomy has been shown to reduce recurrence rates, with low rates of distant metastases and high rates of overall survival (OS), regardless of initial treatment.[8-19]

The Eastern Cooperative Oncology Group–American College of Radiology Imaging Network (ECOG-ACRIN; formerly the Eastern Cooperative Oncology Group) Cancer Research Group E5194 study prospectively enrolled onto a nonrandomized clinical trial those patients for whom surgical excision alone (without radiation) was thought to be a reasonable treatment option on the basis of low-risk clinical and pathologic characteristics. A previous analysis from the ECOG-ACRIN E5194 study reported 5- and 7-year outcomes.[20] The present report provides updated results from the ECOG-ACRIN E5194 study, including 10- and 12-year outcomes.

PATIENTS AND METHODS

Study Design

The ECOG-ACRIN E5194 study was a prospective, nonrandomized clinical trial. Patients were enrolled onto protocol through ECOG-ACRIN and the North Central Cancer Treatment Group (now part of the Alliance for Clinical Trials in Oncology) from April 1997 to October 2002. The study protocol was approved by the respective institutional review boards of the participating centers at which the patients were enrolled. All patients gave written informed consent.

Detailed information on the trial design and conduct has previously been reported.[20,21] A brief summary is as follows. The protocol study included two cohorts of patients (not randomly assigned) with low-risk clinical and pathologic characteristics: cohort 1: low- or intermediate-grade DCIS, tumor size 2.5 cm or smaller (cohort 1; n = 561 patients); or cohort 2: high-grade DCIS, tumor size 1 cm or smaller (cohort 2; n = 104 patients). Cohort assignment and study enrollment were based on clinical evaluation and pathology assessment from the treating institution.

All patients underwent surgical excision (lumpectomy) of the primary DCIS tumor. Protocol specifications included surgical excision with a minimum negative margin width of at least 3 mm or no tumor on re-excision. The surgical specimen was sequentially sectioned and completely embedded at the treating institution to determine the pathologic characteristics of the DCIS tumor. Hormone receptor status was not collected at the time of study entry. A negative postoperative mammogram was required for any patient presenting with suspicious calcifications on preoperative mammography. Radiation treatment was not allowed. In May 2000, the study was amended to allow treatment with adjuvant tamoxifen in an optional, nonrandomized fashion. In the event of disease recurrence or progression, treatment was given at the discretion of the treating physicians.

A total of 665 patients were evaluated for the present analysis (n = 561 patients in cohort 1; and n = 104 patients in cohort 2). After the first report of the E5194 study, subsequent central pathology review determined that five patients had invasive carcinoma, and these patients were excluded from the present analysis. Evaluation of the study results either with or without inclusion of these five patients did not differ substantially (data not shown).

Pathology Evaluation

Pathology findings have been scored in three ways. First, pathology findings were recorded from the institutional pathology assessment on entry into the parent study protocol. Second, in the parent study, central pathology review (also referred to as the first central pathology review) was performed using previously specified criteria.[22] Tumor size was evaluated on central pathology review of 601 patients (n = 501 for cohort 1; and n = 100 for cohort 2). Thereafter, the College of American Pathologists (CAP) published a new set of guidelines for reporting DCIS tumor specimens, now widely used in clinical practice.[23] Using the CAP guidelines, a second central pathology review was performed concurrently by two expert breast pathologists (S.S.B. and F.L.B.) to characterize the DCIS tumors of 500 patients (75% of the overall group) for whom pathology specimens were available (Appendix, online only).[24]

Statistical Methods

The primary end point of the study was an ipsilateral breast event (IBE). An IBE was defined as the first local recurrence of DCIS or invasive carcinoma in the treated (ipsilateral) breast. In addition to the primary end point of any IBE, separate analyses were also performed for the subsets of invasive IBE (with or without associated DCIS) and DCIS-only IBE. The time to an IBE was defined as the time from the last (definitive) surgery until the first evidence of an IBE.

The Kaplan-Meier method was used to estimate time to event distributions. SEs were estimated using the Greenwood formula. CIs were constructed using the normal approximation on the probability scale, and are given at the 95% level. Cox proportional hazard methods were used to estimate hazard ratios (HRs) and tests for significance for event times. All P values are two-sided. Tamoxifen use was considered as a time-dependent covariate.

Follow-up cutoff was at the time of last reported disease evaluation, ipsilateral mastectomy, initiation of chemotherapy, or death. The median follow-up time was 12.3 years, with 346 patients and 217 patients observed for at least 10 and 12 years, respectively.

RESULTS

Patient, Tumor, and Treatment Characteristics

Table 1 details patient, tumor, and treatment characteristics. The patients enrolled onto study showed generally more favorable clinical and pathologic characteristics than required by the study protocol. The median tumor size was 6 mm for cohort 1 and 7 mm for cohort 2. The minimum negative margin width was 5 mm or greater for 64% and 69% of the patients in each cohort, respectively, and 10 mm or greater for 21% and 24% of the patients, respectively. The median patient age was 60 years and 58 years, respectively. Tamoxifen was given in a nonrandomized fashion to 30% of the patients (31% for cohort 1% and 24% for cohort 2).

IBEs and Other Outcomes

Overall, there were 99 IBEs (n = 74 in cohort 1; n = 25 in cohort 2), of which 51 (52%) were an invasive IBE (n = 39 in cohort 1; n = 12 in cohort 2). The 12-year rates of developing an IBE were 14.4% for cohort 1 and 24.6% for cohort 2 (P = .003; Fig 1 and Table 2). The 12-year rates for developing an invasive IBE were 7.5% and 13.4%, respectively (P = .08; Fig 1 and Table 3). The risks of developing an IBE and an invasive IBE increased over time through 12 years of follow-up, without plateau. For cohort 1, the rate of developing an IBE was approximately 1.2% per year through year 12, and for an invasive IBE, approximately 0.6% per year through year 12. No differences were seen between the two cohorts for the 12-year rates of OS (84.0% v 82.8%; P = .96) or contralateral breast cancer events (6.7% v 12.0%; P = .16; Appendix Table A1, online only).

The rates of developing an IBE and an invasive IBE as a function of clinically relevant subsets of patients are shown in Tables 2 and 3, respectively. Tumor size was statistically significantly associated with developing an IBE (P = .01; Fig 2 and Table 2). The results of similar analyses restricted to the patients enrolled in cohort 1 are given in Appendix Tables A2 and A3 (online only).

We found that study cohort and tumor size were both statistically significantly associated with developing an IBE using multivariable Cox proportional hazards model. The hazard ratio (HR) for cohort 2 was 1.84 compared with cohort 1 (P = .009). Using a tumor size of 5 mm or less as the reference group, the HRs were 1.42 (95% CI, 0.88 to 2.29) for tumor size 6 to 10 mm and 2.11 (95% CI, 1.23 to 3.62) for tumor size greater than 10 mm (P = .03). Variables not statistically significant were age, menopausal status, minimum negative margin width, method of detection, bloody nipple discharge, tamoxifen use, and prior hormone therapy (all P > .25). The HR for tamoxifen use (compared with no tamoxifen use) was 0.66 (95% CI, 0.40 to 1.06; P = .09) with tamoxifen evaluated as a single variable in a proportional hazards model.

By using a multivariable Cox proportional hazards model for developing an invasive IBE, we found that only the study cohort was borderline significant (P = .08). No other factor was statistically significant (all P > .26).

Table 1. Patient, Tumor, and Treatment Characteristics

Characteristic	Cohort 1,[a] No. (%) (n = 561)	Cohort 2,[a] No. (%) (n = 104)
Age, years		
≤ 39	13 (2)	4 (4)
40-49	93 (17)	21 (20)
50-59	166 (30)	30 (29)
60-69	146 (26)	28 (27)
≥ 70	143 (25)	21 (20)
Race/ethnicity[b]		
White	519 (93)	95 (95)
Hispanic	8 (1)	1 (1)
Black	16 (3)	4 (4)
Other	14 (3)	0 (0)
Menopausal status[c]		
Premenopausal	134 (24)	29 (28)
Postmenopausal	427 (76)	75 (72)
Tumor size, mm[d]		
≤ 5	226 (40)	28 (27)
6-10	231 (41)	61 (59)
> 10	104 (19)	15 (14)
Minimum negative margin width, mm		
< 1[e]	9 (2)	2 (2)
1-2.9[e]	10 (2)	2 (2)
3-4.9	184 (33)	28 (27)
5-9.9	239 (43)	47 (45)
≥ 10[f]	119 (21)	25 (24)
Method of detection[b]		
Microcalcifications	399 (71)	88 (85)
Density or mass	93 (17)	4 (4)
Both	40 (7)	7 (7)
Incidental finding	19 (3)	5 (5)
Other	8 (1)	0 (0)
Bloody nipple discharge[b]		
Yes	12 (2)	1 (1)
No	541 (98)	102 (99)
Tamoxifen use		
Yes	174 (31)	25 (24)
No	387 (69)	79 (76)
Hormone replacement therapy before study entry[b]		
Yes	239 (43)	47 (45)
No	315 (57)	57 (55)
Treating institution grade[g]		
Low	281 (50)	0 (0)
Intermediate	280 (50)	0 (0)
High	0 (0)	104 (100)
CAP grade[h]		
Low	61 (15)	2 (2)
Intermediate	249 (59)	19 (24)
High	110 (26)	59 (74)

Abbreviation: CAP, College of American Pathologists.

[a]Cohort 1 defined as low- or intermediate-grade ductal carcinoma in situ (DCIS), tumor size 2.5 cm or smaller. Cohort 2 defined as high-grade DCIS, tumor size 1.0 cm or smaller. Cohort assignment was based on clinical evaluation and pathology assessment from the treating institution at the time of enrollment onto the study.

[b]Unknown cases and cases that were not evaluated were excluded.

[c]Patients younger than age 50 years were assumed to be premenopausal when menopausal status was not recorded.

[d]Tumor size was based on central pathology review, when this information was available.

[e]Cases with negative margin width less than 3 mm were determined on central pathology review.

[f]Cases with no tumor on re-excision are included.

[g]Grade as determined on pathology assessment from the treating institution at the time of enrollment onto study.

[h]Grade as determined on central pathology review using current CAP guidelines. Cases that were not evaluated were excluded.
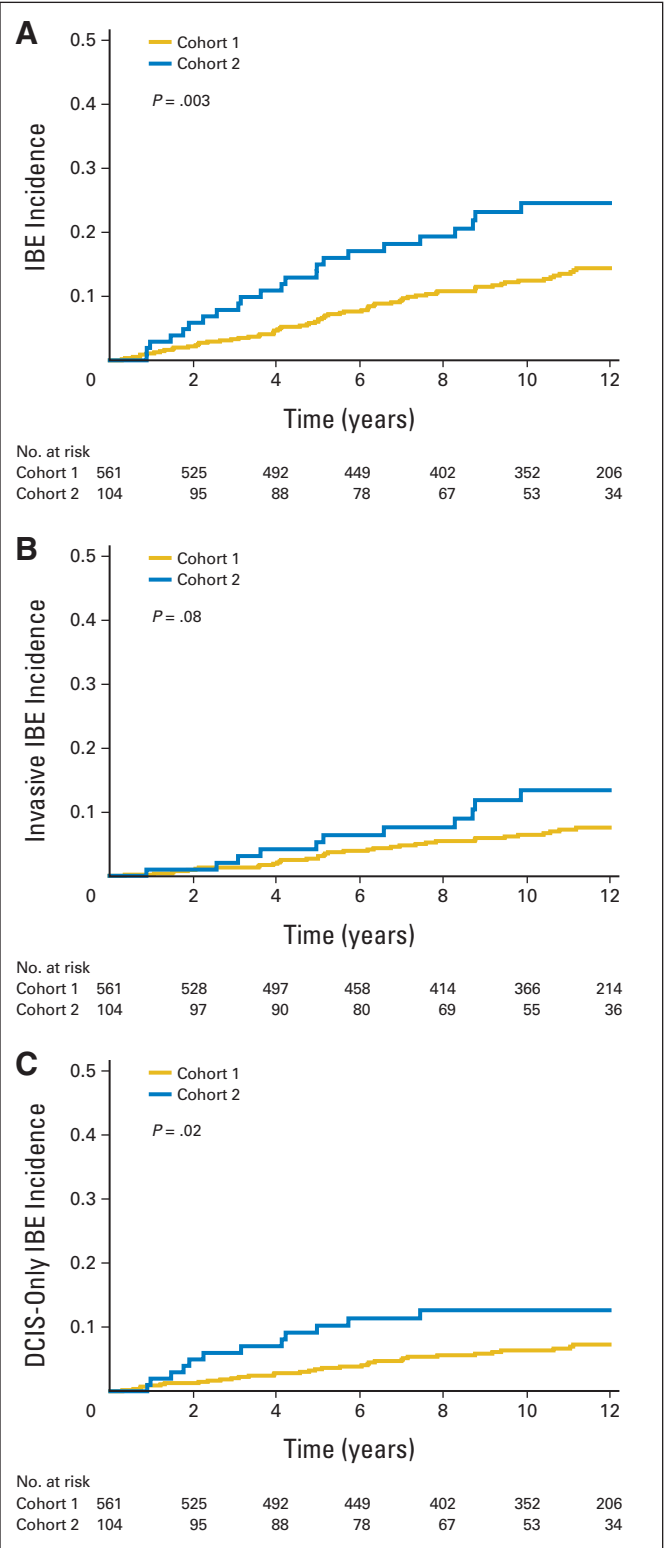
Fig 1. Ipsilateral breast events (IBEs) for cohort 1 and cohort 2. Cohort 1 was defined as low- or intermediate-grade ductal carcinoma in situ (DCIS), tumor size 2.5 cm or smaller. Cohort 2 was defined as high-grade DCIS, tumor size 1.0 cm or smaller. Cohort assignment was based on clinical evaluation and pathology assessment from the treating institution at the time of enrollment. The numbers at risk are given beneath the x-axis. (A) Any IBE. (B) Subset of invasive IBE. (C) Subset of DCIS-only IBE.

| Table 2. IBE Rates for Clinically Relevant Subsets of Patients | | | | | | | | | |
| | | 5 Years | | 10 Years | | 12 Years | | | |
Variable	No. of Patients	%	95% CI	%	95% CI	%	95% CI	P
Cohort 1	561	6.0	4.0 to 8.1	12.5	9.5 to 15.4	14.4	11.2 to 17.6	.003
Cohort 2	104	15.0	8.0 to 22.0	24.6	15.7 to 33.4	24.6	15.7 to 33.4	
Age, years									.51
≤ 49	131	11.7	6.2 to 17.3	16.8	10.3 to 23.4	18.9	11.9 to 26.0	
50-69	370	6.0	3.5 to 8.5	13.5	9.8 to 17.2	15.1	11.2 to 19.0	
≥ 70	164	7.1	3.1 to 11.2	14.1	8.1 to 20.1	15.7	9.0 to 22.3	
Minimum negative margin width, mm									.85
< 5	235	7.6	4.1 to 11.1	14.9	10.0 to 19.7	17.0	11.7 to 22.2	
5-9	286	7.1	4.0 to 10.1	13.5	9.2 to 17.8	15.2	10.6 to 19.8	
≥ 10	144	8.0	3.5 to 12.6	15.3	9.1 to 21.5	16.3	9.9 to 22.8	
Tumor size, mm*									.01
≤ 5	254	6.1	3.1 to 9.2	10.7	6.7 to 14.7	11.3	7.2 to 15.4	
6-10	292	6.6	3.7 to 9.6	15.5	11.0 to 20.0	17.8	12.9 to 22.7	
> 10	119	12.5	6.4 to 18.6	20.0	12.3 to 27.8	22.9	14.5 to 31.3	
CAP grade†									.16
Low	63	5.1	0 to 10.8	12.5	3.8 to 21.3	12.5	3.8 to 21.3	
Intermediate	268	6.3	3.3 to 9.4	13.2	8.9 to 17.6	15.1	10.4 to 19.9	
High	169	11.1	6.2 to 15.9	20.6	14.2 to 27.0	20.6	14.2 to 27.0	

Abbreviations: CAP, College of American Pathologists; IBE, ipsilateral breast event.
*Tumor size was based on central pathology review, when this information was available. Results are similar for tumor size on the basis of institutional pathology assessment at enrollment onto the study (P = .03; data not shown).
†Restricted to the subset of 500 cases for which a central pathology review was performed using current CAP guidelines.

Central Pathology Evaluation

For the subset of 500 patients for which central pathology review had been performed using current CAP guidelines for DCIS, the 12-year rates of developing an IBE were 12.5% for low-grade DCIS, 15.1% for intermediate-grade DCIS, and 20.6% for high-grade DCIS (P = .16; Table 2 and Appendix Fig A1, online only). The 12-year rates

of developing an invasive IBE were 5.5%, 6.7%, and 11.7%, respectively (P = .19; Table 3 and Appendix Fig A1). Comedo necrosis and the University of Southern California/Van Nuys Prognostic Index (USC/VNPI) were not significantly associated with developing an IBE or invasive IBE (all P > .13).[25] Appendix Tables A4 and A5 (online only) show analyses of IBE rates that compare current CAP grading

| Table 3. Invasive IBE Rates for Clinically Relevant Subsets of Patients | | | | | | | | | |
| | | 5 Years | | 10 Years | | 12 Years | | | |
Variable	No. of Patients	%	95% CI	%	95% CI	%	95% CI	P
Cohort 1	561	2.7	1.3 to 4.1	6.4	4.2 to 8.6	7.5	5.1 to 10.0	.08
Cohort 2	104	5.3	0.8 to 9.7	13.4	5.9 to 20.9	13.4	5.9 to 20.9	
Age, years									.43
≤ 49	131	4.8	1.1 to 8.6	8.5	3.4 to 13.5	9.6	4.1 to 15.0	
50-69	370	3.4	1.5 to 5.4	7.6	4.7 to 10.5	8.8	5.7 to 12.0	
≥ 70	164	0.7	0 to 2.1	6.2	1.7 to 10.8	6.2	1.7 to 10.8	
Minimum negative margin width, mm									.64
< 5	235	2.8	0.6 to 4.9	8.1	4.3 to 11.9	8.1	4.3 to 11.9	
5-9	286	3.4	1.2 to 5.5	7.8	4.4 to 11.3	9.6	5.7 to 13.4	
≥ 10	144	3.1	0.1 to 6.0	5.6	1.6 to 9.6	6.7	2.2 to 11.2	
Tumor size, mm*									.40
≤ 5	254	2.5	0.5 to 4.5	6.3	3.1 to 9.5	6.3	3.1 to 9.5	
6-10	292	2.9	0.9 to 4.9	8.5	5.0 to 12.0	10.3	6.3 to 14.3	
> 10	119	4.8	0.7 to 8.8	7.2	2.0 to 12.4	8.7	2.8 to 14.6	
CAP grade†									.19
Low	63	1.8	0 to 5.3	5.5	0 to 11.6	5.5	0 to 11.6	
Intermediate	268	2.0	0.3 to 3.8	5.4	2.4 to 8.4	6.7	3.2 to 10.1	
High	169	4.5	1.2 to 7.7	11.7	6.4 to 17.0	11.7	6.4 to 17.0	

Abbreviations: CAP, College of American Pathologists; IBE, ipsilateral breast event.
*Tumor size was based on central pathology review, when this information was available. Results are similar for tumor size on the basis of institutional pathology assessment at enrollment onto the study (P = .40; data not shown).
†Restricted to the subset of 500 cases for which a central pathology review was performed using current CAP guidelines.
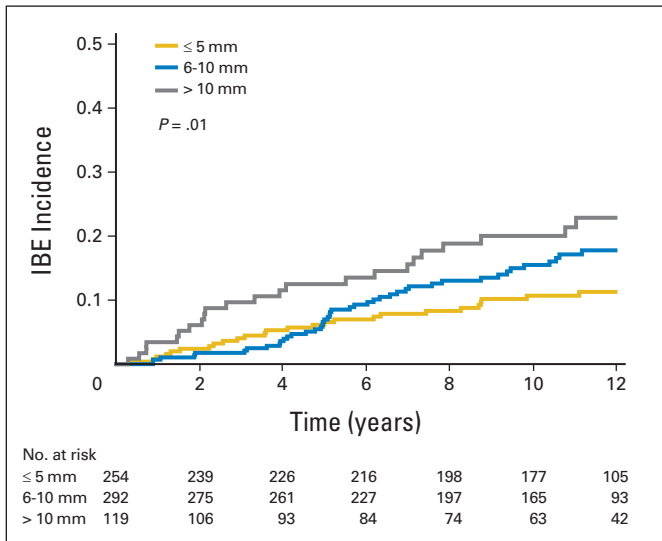
Fig 2. Ipsilateral breast events (IBEs) according to tumor size. The numbers at risk are given beneath the *x*-axis.

with older grading classifications. Fewer DCIS tumors were classified as low grade using CAP guidelines compared with older grading classifications.

DISCUSSION

This study has demonstrated that for patients with favorable DCIS who were selected on the basis of clinical and pathologic characteristics and treated with surgical excision without radiation, the risks of developing an IBE and an invasive IBE increased over time through 12 years of follow-up (Fig 1 and Tables 2 and 3). The 12-year rates of developing an IBE were 14.4% for cohort 1 and 24.6% for cohort 2 (*P* = .003; Fig 1 and Table 2), and the 12-year rates of developing an invasive IBE were 7.5% and 13.4%, respectively (*P* = .08; Fig 1 and Table 3). No clearly defined plateau was observed for either cohort of patients. Individual patients and their physicians will need to decide if these 12-year risks are acceptable, and whether or not to forego adding adjuvant treatment after surgical excision.

The ECOG-ACRIN E5194 study was a nonrandomized, prospective clinical trial for women with DCIS who were selected for low-risk clinical and pathologic features as identified at the time of enrollment. The majority of enrolled patients were postmenopausal and had small (tumor size ≤ 1 cm), mammographically detected DCIS excised with negative margins of resection (Table 1). These characteristics are similar to those of patients with DCIS in population-based studies.[4,5] Therefore, the findings in this study are relevant to contemporary practice.

The optimal treatment for women with newly diagnosed DCIS continues to be debated. National guidelines in the United States allow for a wide range of local treatment options, including surgical excision (lumpectomy) with or without radiation, unilateral mastectomy, and even bilateral mastectomies,[26,27] but no consensus approach has developed. For patients considered low risk, national guidelines include the option for surgical excision alone (without radiation) as acceptable local treatment, although what constitutes low risk is not well defined.

Five randomized clinical trials have consistently demonstrated that adding radiation treatment after surgical excision for patients with DCIS reduces the risk of local recurrence in the ipsilateral breast by approximately half.[8-16] The Early Breast Cancer Trialists' Collaborative Trial Group (EBCTCG) meta-analysis combined data from four of the randomized trials of radiation treatment after surgical excision.[17] Two randomized clinical trials have demonstrated that adding tamoxifen reduces the risk of all breast cancer events (ipsilateral plus contralateral) for hormone receptor–positive DCIS tumors.[9,10,14,18,19] Although the risk of recurrence is decreased by adding radiation and tamoxifen after surgical excision, no improvement in the rates of distant metastases and OS have been shown in any randomized clinical trial.

The risk of local recurrence after surgical excision without radiation has been reported in a number of randomized and nonrandomized, prospective clinical trials.[8-16,28] The increasing risk of local recurrence over time as seen in the current analysis of ECOG-ACRIN E5194 is consistent with other prospective studies, both randomized and nonrandomized. For patients treated with surgical excision without radiation in randomized clinical trials, the 10-year rate of local recurrence has been reported as approximately 24% to 30%.[9,11,14,15] In the randomized RTOG 9804 study, adding radiation treatment after lumpectomy reduced the 7-year rate of local recurrence from 6.7% to 0.9% (*P* < .001).[16] In a nonrandomized, prospective study, Wong et al[28] reported that the 10-year rate of local recurrence was 15.6% after surgical excision without radiation. The various prospective clinical trials differ with respect to a number of protocol-defined parameters (eg, tumor grade, definition of negative surgical margins, use of tamoxifen), which may, at least in part, account for the reported differences seen in local recurrence rates between studies.

Even though the risk of recurrence is reduced by adding radiation and tamoxifen after surgical excision, ongoing efforts continue in an attempt to identify patients with favorable disease at presentation who have a sufficiently low risk of local recurrence after surgical excision that omitting adjuvant therapy is reasonable. The majority of women with DCIS present with an asymptomatic finding of microcalcifications on routine screening mammography. As most women with newly diagnosed DCIS are eligible for breast conservation surgery, an important aspect of clinical decision making is often whether or not to add radiation treatment, which includes an assessment of the risks of developing a local recurrence and an invasive local recurrence after surgical excision alone without radiation. The lack of survival benefit from adding adjuvant treatments and the small, but real, potential risk of adverse effects are reasons commonly given to omit adjuvant treatments (radiation and tamoxifen) after surgical excision. Therefore, the risk-benefit ratio may favor omitting adjuvant treatment if a cohort of patients could be prospectively identified at presentation with a sufficiently low risk of recurrence after surgical excision alone.

Pathologic grade commonly influences clinical management decisions for the treatment of DCIS. Since the design of this study, guidelines for determining the grade of DCIS have changed, resulting in fewer DCIS tumors classified as low grade (Table 1). In this study, CAP grading was not associated with the risks of developing a local recurrence and an invasive local recurrence, and thus, is not clinically useful in identifying a low-risk cohort of patients (Tables 2 and 3; Appendix Fig A1).

Early efforts to identify a cohort of patients with low-risk disease focused on using clinical and pathologic characteristics. However, prospective clinical trials, randomized and nonrandomized, have not

reproducibly and reliably identified patients with low-risk DCIS, especially with long-term follow-up of at least 10 years. More recent efforts have focused on using molecular markers to determine the risk of recurrence after surgical excision.[21,29-33] The value of molecular markers compared with traditional clinical and pathologic features of DCIS remains an area of great interest.

This study has several notable strengths. First, the present clinical trial prospectively identified and enrolled patients with DCIS who were selected for treatment using surgical excision without radiation on the basis of low-risk clinical and pathologic features at presentation. Second, patients enrolled onto this study have characteristics similar to those of patients in population-based studies, and therefore, this study is relevant to contemporary practice. Third, this study reports long-term follow-up of greater than 10 years, which is especially important after treatment for potentially lower-risk DCIS because of the known risk of late and ongoing local recurrence (Fig 1; Tables 2 and 3). Finally, there was a sufficient number of patients to perform analyses for some clinically meaningful patient subgroups (Tables 2 and 3).

This study has a number of potential limitations. First, the trial design was a nonrandomized cohort study. Thus, the impact of adding radiation or tamoxifen after surgical excision could not be assessed. Second, tamoxifen was administered to approximately 30% of patients in a nonrandomized fashion. Despite this limitation, tamoxifen use was associated with a decreased risk of local recurrence (HR, 0.66; $P = .09$), which is consistent with results from randomized clinical trials. Third, the number of patients in cohort 2 was relatively small (n = 104), limiting the statistical power in this group of patients. Finally, the numbers of patients in some clinically relevant subsets were small (Tables 2 and 3).

In summary, this study has demonstrated that the risks of developing an IBE and an invasive IBE increased over time through 12 years of follow-up, without plateau, for patients with DCIS of the breast who were selected for favorable clinical and pathologic characteristics and treated with surgical excision without radiation. Individual patients and their physicians will need to decide if these 12-year risks are acceptable, and to judge whether or not to add adjuvant treatment after surgical excision. Not all patients and their physicians will agree on what is considered too high a risk of developing an IBE or an invasive IBE to recommend observation after surgical excision, or what risk is considered too low to justify adding radiation treatment. However, this study provides 12-year data to begin those discussions, and to help inform the treatment decision-making process.

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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Appendix

Pathology Evaluation

For the present analysis, there were data available from the central pathology review using the current College of American Pathologists ductal carcinoma in situ guidelines.[23,24] The central pathology review was performed concurrently by two expert breast pathologists (S.S.B. and F.L.B.) for 500 patients (75% of the overall group) for whom pathology specimens were available. Ductal carcinoma in situ pattern, grade, and comedo necrosis were scored. Of the 500 evaluated patients, 343 had undergone central pathology review as part of a prior study.[21,24] Subsequently, central pathology review was performed for 157 new patients, as well as blinded re-evaluation of 145 previously evaluated patients. For the cases evaluated twice, grade for this study was scored as the highest grade on either of the evaluations, and comedo necrosis was scored as present if present on either evaluation.

Patients with (n = 500) and without (n = 165) central pathology review were similar for distribution of cohort, age, menopausal status, minimum negative margin width, and method of detection. Tumor size in patients without central pathology review was slightly smaller than that in patients with central pathology review (tumor size ≤ 5 mm for 46% v 36%, respectively).

		5 Years		10 Years		12 Years		
Table A1. Contralateral Breast Cancer Event Rates								
Variable	No.	%	95% CI	%	95% CI	%	95% CI	P
Contralateral breast cancer								
Overall group	665	3.7	2.2 to 5.1	6.1	4.1 to 8.0	7.5	5.3 to 9.7	
Cohort 1	561	3.6	2.0 to 5.2	5.3	3.4 to 7.3	6.7	4.4 to 9.0	.16
Cohort 2	104	4.0	0.2 to 7.8	10.4	3.9 to 16.9	12.0	4.9 to 19.1	
Invasive contralateral breast cancer								
Overall group	665	2.6	1.3 to 3.8	4.6	2.9 to 6.3	5.8	3.8 to 7.7	
Cohort 1	561	2.3	1.0 to 3.6	3.8	2.1 to 5.5	4.9	2.9 to 6.9	.06
Cohort 2	104	4.0	0.2 to 7.8	9.0	3.0 to 15.0	10.6	3.9 to 17.3	
DCIS-only contralateral breast cancer								
Overall group	665	1.1	0.3 to 2.0	1.5	0.5 to 2.5	1.8	0.7 to 2.9	
Cohort 1	561	1.3	0.4 to 2.3	1.6	0.5 to 2.6	1.8	0.6 to 3.0	.66
Cohort 2	104	0	0 to 0	1.5	0 to 4.5	1.5	0.0 to 4.5	

Abbreviation: DCIS, ductal carcinoma in situ.

		5 Years		10 Years		12 Years		
Table A2. IBE Rates for Clinically Relevant Subsets of Patients								
Variable	No.	%	95% CI	%	95% CI	%	95% CI	P
Age, years								
≤ 49	106	6.8	1.9 to 11.7	9.9	4.1 to 15.7	12.5	5.8 to 19.2	.66
50-69	312	5.1	2.6 to 7.6	12.1	8.3 to 16.0	13.9	9.8 to 18.1	
≥ 70	143	7.5	3.0 to 12.0	15.4	8.7 to 22.1	17.2	9.8 to 24.5	
Minimum negative margin width, mm								
< 5	203	7.3	3.6 to 11.0	13.2	8.2 to 18.1	15.5	10.1 to 21.0	.87
5-9	239	5.4	2.4 to 8.3	12.1	7.6 to 16.5	14.0	9.1 to 18.9	
≥ 10	119	5.3	1.2 to 9.4	12.1	5.9 to 18.3	13.4	6.8 to 19.9	
Tumor size, mm*								
≤ 5	226	5.0	2.1 to 7.9	8.0	4.3 to 11.6	8.6	4.8 to 12.5	< .001
6-10	231	4.3	1.5 to 7.0	14.1	9.1 to 19.1	16.9	11.4 to 22.4	
> 10	104	12.3	5.8 to 18.8	19.7	11.5 to 28.0	23.3	14.0 to 32.5	
CAP grade†								
Low	61	3.5	0 to 8.2	11.0	2.7 to 19.3	11.0	2.7 to 19.3	.61
Intermediate	249	6.4	3.3 to 9.6	12.9	8.4 to 17.4	14.9	9.9 to 19.8	
High	110	6.6	1.9 to 11.4	15.9	8.7 to 23.1	15.9	8.7 to 23.1	

NOTE. Analysis restricted to patients enrolled in cohort 1 (n = 561).
Abbreviations: CAP, College of American Pathologists; IBE, ipsilateral breast event.
*Tumor size was based on central pathology review, when this information was available.
†Restricted to the subset of cases for which a central pathology review was performed using current CAP guidelines.

Table A3. Invasive IBE Rates for Clinically Relevant Subsets of Patients

Variable	No.	5 Years %	5 Years 95% CI	10 Years %	10 Years 95% CI	12 Years %	12 Years 95% CI	P
Age, years								.57
≤ 49	106	2.9	0 to 6.2	5.1	0.7 to 9.5	6.4	1.4 to 11.4	
50-69	312	3.4	1.3 to 5.4	6.8	3.8 to 9.7	8.1	4.8 to 11.4	
≥ 70	143	0.8	0 to 2.4	7.1	2.0 to 12.3	7.1	2.0 to 12.3	
Minimum negative margin width, mm								.46
< 5	203	2.2	0.1 to 4.3	6.3	2.7 to 10.0	6.3	2.7 to 10.0	
5-9	239	3.1	0.8 to 5.4	7.4	3.7 to 11.0	9.4	5.2 to 13.6	
≥ 10	119	2.7	0 to 5.8	4.7	0.7 to 8.8	6.0	1.3 to 10.7	
Tumor size, mm*								.17
≤ 5	226	2.3	0.3 to 4.3	4.8	1.9 to 7.8	4.8	1.9 to 7.8	
6-10	231	1.9	0.1 to 3.7	7.9	4.0 to 11.7	10.0	5.5 to 14.5	
> 10	104	5.4	0.8 to 10.0	6.8	1.5 to 12.0	8.5	2.3 to 14.8	
CAP grade†								.69
Low	61	1.8	0 to 5.3	5.5	0 to 11.6	5.5	0 to 11.6	
Intermediate	249	2.2	0.3 to 4.1	5.3	2.2 to 8.3	6.6	3.1 to 10.2	
High	110	2.9	0 to 6.2	9.3	3.5 to 15.2	9.3	3.5 to 15.2	

NOTE. Analysis restricted to patients enrolled in cohort 1 (n = 561).
Abbreviations: CAP, College of American Pathologists; IBE, ipsilateral breast event.
*Tumor size was based on central pathology review, when this information was available.
†Restricted to the subset of cases for which a central pathology review was performed using current CAP guidelines.

Table A4. IBE Rates and Subset of Invasive IBE Rates Comparing Current CAP Grading to Older Grading Classifications

Variable	No.	5 Years %	5 Years 95% CI	10 Years %	10 Years 95% CI	12 Years %	12 Years 95% CI	P
IBE rates								
Grade*								
Low	63	5.1	0 to 10.8	12.5	3.8 to 21.3	12.5	3.8 to 21.3	.16
Intermediate	268	6.3	3.3 to 9.4	13.2	8.9 to 17.6	15.1	10.4 to 19.9	
High	169	11.1	6.2 to 15.9	20.6	14.2 to 27.0	20.6	14.2 to 27.0	
Grade†								
Low	287	5.1	2.5 to 7.7	10.5	6.7 to 14.2	12.1	8.0 to 16.2	.02
Intermediate	239	7.6	4.1 to 11.1	17.7	12.5 to 22.9	19.1	13.6 to 24.5	
High	64	17.9	8.3 to 27.5	23.9	12.9 to 35.0	23.9	12.9 to 35.0	
Grade‡								
Low	281	5.6	2.8 to 8.3	12.3	8.2 to 16.3	14.0	9.5 to 18.4	.01
Intermediate	280	6.5	3.5 to 9.5	12.7	8.5 to 16.9	14.9	10.2 to 19.5	
High	104	15.0	8.0 to 22.0	24.6	15.7 to 33.4	24.6	15.7 to 33.4	
Subset of invasive IBE rates								
Grade*								
Low	63	1.8	0 to 5.3	5.5	0 to 11.6	5.5	0 to 11.6	.19
Intermediate	268	2.0	0.3 to 3.8	5.4	2.4 to 8.4	6.7	3.2 to 10.1	
High	169	4.5	1.2 to 7.7	11.7	6.4 to 17.0	11.7	6.4 to 17.0	
Grade†								
Low	287	1.8	0.2 to 3.4	5.3	2.5 to 8.1	5.8	2.8 to 8.8	.02
Intermediate	239	3.2	0.9 to 5.6	8.9	5.0 to 12.9	9.7	5.5 to 13.9	
High	64	10.2	2.5 to 18.0	16.7	6.6 to 26.8	16.7	6.6 to 26.8	
Grade‡								
Low	281	1.5	0 to 3.0	5.4	2.5 to 8.3	5.9	2.9 to 9.0	.11
Intermediate	280	3.9	1.5 to 6.2	7.4	4.1 to 10.8	9.1	5.4 to 12.9	
High	104	5.3	0.8 to 9.7	13.4	5.9 to 20.9	13.4	5.9 to 20.9	

NOTE. Cases with unknown information were excluded from analysis.
Abbreviations: CAP, College of American Pathologists; IBE, ipsilateral breast event.
*Second central pathology review using current CAP guidelines.
†First central pathology review.[22]
‡Institutional pathology assessment at the time of study entry.

Table A5. IBE Rates and Subset of Invasive IBE Rates Comparing Current CAP Grading to Older Grading Classifications

Variable	No.	5 Years %	5 Years 95% CI	10 Years %	10 Years 95% CI	12 Years %	12 Years 95% CI	P
IBE rates								
Grade*								
Low	61	3.5	0 to 8.2	11.0	2.7 to 19.3	11.0	2.7 to 19.3	.61
Intermediate	249	6.4	3.3 to 9.6	12.9	8.4 to 17.4	14.9	9.9 to 19.8	
High	110	6.6	1.9 to 11.4	15.9	8.7 to 23.1	15.9	8.7 to 23.1	
Grade†								
Low	286	5.1	2.5 to 7.7	10.5	6.7 to 14.3	12.2	8.0 to 16.3	.25
Intermediate	191	7.9	3.9 to 11.9	17.3	11.5 to 23.1	19.0	12.9 to 25.0	
High	14	7.1	0 to 20.6	15.6	0 to 35.6	15.6	0 to 35.6	
Grade‡								
Low	281	5.6	2.8 to 8.3	12.3	8.2 to 16.3	14.0	9.5 to 18.4	.72
Intermediate	280	6.5	3.5 to 9.5	12.7	8.5 to 16.9	14.9	10.2 to 19.5	
Subset of invasive IBE rates								
Grade*								
Low	61	1.8	0 to 5.3	5.5	0 to 11.6	5.5	0 to 11.6	.69
Intermediate	249	2.2	0.3 to 4.1	5.3	2.2 to 8.3	6.6	3.1 to 10.2	
High	110	2.9	0 to 6.2	9.3	3.5 to 15.2	9.3	3.5 to 15.2	
Grade†								
Low	286	1.8	0.2 to 3.4	5.3	2.5 to 8.1	5.8	2.8 to 8.8	.21
Intermediate	191	4.0	1.1 to 7.0	9.1	4.7 to 13.5	10.0	5.3 to 14.7	
High	14	7.1	0 to 20.6	15.6	0 to 35.6	15.6	0 to 35.6	
Grade‡								
Low	281	1.5	0 to 3.0	5.4	2.5 to 8.3	5.9	2.9 to 9.0	.22
Intermediate	280	3.9	0.8 to 6.2	7.4	4.1 to 10.8	9.1	5.4 to 12.9	

NOTE. Analysis restricted to patients enrolled in cohort 1 (n = 561). Cases with unknown information were excluded from analysis.
Abbreviations: CAP, College of American Pathologists; IBE, ipsilateral breast event.
*Second central pathology review using current CAP guidelines.
†First central pathology review.[22]
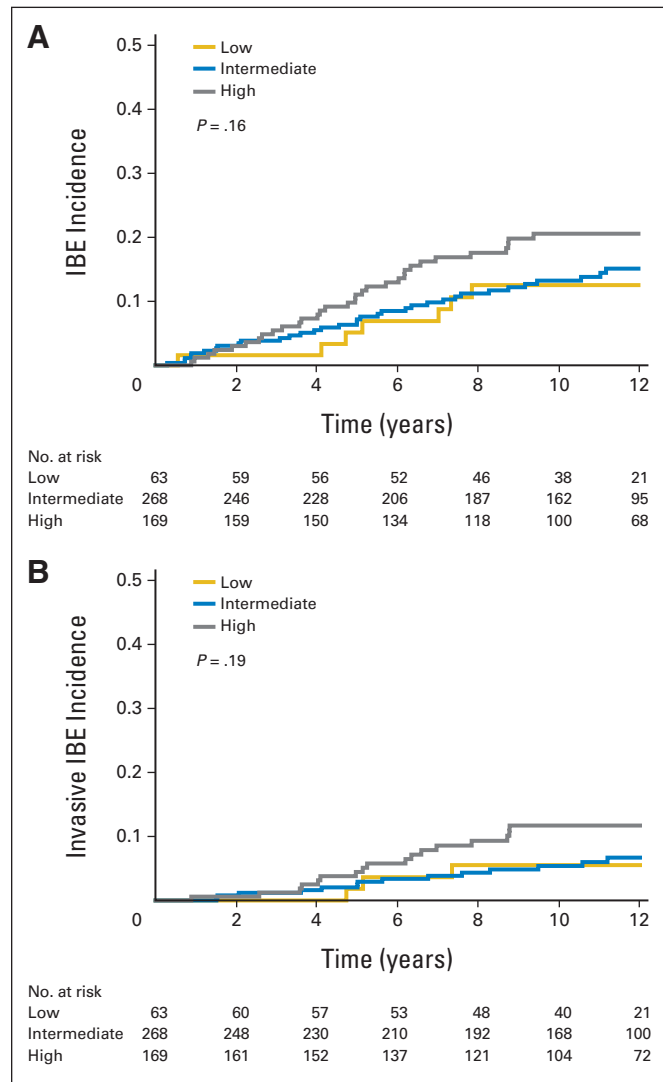‡Institutional pathology assessment at the time of study entry.

Fig A1. Ipsilateral breast events (IBEs) according to grade as scored using current College of American Pathology guidelines. Analyses exclude cases not evaluated. The numbers at risk are given beneath the x-axis. (A) Any IBE. (B) Subset of invasive IBE.