

Ductal Carcinoma In Situ Treated With Breast-Conserving Surgery and Radiotherapy: A Comparison With ECOG Study 5194

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BACKGROUND: Recent data from Eastern Cooperative Oncology Group (ECOG) Study 5194 (E5194) prospectively defined a low-risk subset of ductal carcinoma in situ (DCIS) patients where radiation therapy was omitted after lumpectomy alone. The purpose of the study was to determine the ipsilateral breast tumor recurrence (IBTR) in DCIS patients who met the criteria of E5194 treated with lumpectomy and adjuvant whole breast radiation therapy (RT). **METHODS:** A total of 263 patients with DCIS were treated between 1980 and 2009 who met the enrollment criteria for E5194: 1) low to intermediate grade (LIG) with size >0.3 cm but <2.5 cm and margins >3 mm (n = 196), or 2) high grade (HG), size <1 cm and margins >3 mm (n = 67). All patients were treated with lumpectomy and whole breast RT with a boost to a median total tumor bed dose of 6400 cGy. Standard statistical analyses were performed with SAS (v. 9.2). **RESULTS:** The average follow-up time was 6.9 years. The 5-year and 7-year IBTR for the LIG cohort in this study was 1.5% and 4.4% compared with 6.1% and 10.5% in E5194, respectively. The 5-year and 7-year IBTR for the HG cohort was 2.0% and 2.0% in this study compared with 15.3% and 18% in E5194, respectively. **CONCLUSIONS:** Adjuvant whole breast radiation therapy reduced the rate of local recurrence by more than 70% in patients with DCIS who met the criteria of E5194 (6.1% to 1.5% in the LIG cohort and 15.3% to 2% in the HG cohort). Additional follow-up is necessary given that 70% of IBTRs occurred after 5 years. *Cancer* 2011;117:1156-62. © 2010 American Cancer Society.

KEYWORDS: ductal carcinoma in situ (DCIS), breast-conserving surgery (BCS), radiation therapy (RT), local control, ipsilateral breast tumor recurrence (IBTR).

Ductal carcinoma in situ (DCIS) is a noninvasive entity characterized by a heterogeneous spectrum of histologic features confined to the ductal lumens of the breast. The increased utilization of screening mammography has resulted in a dramatic increase in the incidence of DCIS, which now represents up to 30% of newly diagnosed breast carcinomas.¹ Current management options for DCIS include mastectomy, breast-conserving surgery (BCS), or breast-conserving surgery followed by whole breast radiation therapy (BCS + RT). Multiple randomized controlled trials have shown radiation therapy after BCS reduces the risk of ipsilateral breast tumor recurrence (IBTR) by 50% to 60%.²⁻⁵ Regardless of the type of local treatment, disease-free and overall survival rates exceed 98% by mastectomy, BCS + RT, or BCS alone.⁶

Although the randomized trials have demonstrated an overall reduction in IBTR in all patients with DCIS treated with BCS + RT, the absolute benefit of whole breast radiotherapy may be smaller in subsets of patients based on their age, tumor size, histology, grade, and margin status. Thus, identification of the favorable subset of patients who may be treated by BCS alone continues to be an active area of investigation. Several single institution retrospective studies have shown acceptable local control rates in selected subsets of DCIS patients treated by BCS alone. In a series published by Silverstein et al, patients with small lesions, with favorable histologies, and of low to intermediate grade with widely negative margins (>1 cm) treated by BCS alone reported an IBTR rate as low as 6% at 5 years.⁷ There are, however, conflicting retrospective data demonstrating higher local relapse rates with the omission of radiation therapy in even these favorable patient groups.⁸

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In an effort to address this issue, a trial initiated by the Eastern Cooperative Oncology Group (ECOG) enrolled patients with DCIS into ECOG 5194, a single-arm, multi-institutional, prospective study of observation after breast-conserving surgery, with the end points of ipsilateral and contralateral breast relapse. Patient eligibility included low- or intermediate-grade (LIG) DCIS lesions measuring from 0.3 to 2.5 cm in size with margins ≥ 3 mm, or high-grade (HG) DCIS lesions measuring from 0.3 to 1.0 cm in size with margins ≥ 3 mm. With a median follow-up of 6.1 years, they reported 5- and 7-year IBTR rates of 6.1% and 10.5% in the LIG cohort and 15.3% and 18% in the HG cohort, respectively.⁹ The authors concluded that the LIG cohort had an acceptable rate of IBTR, although they acknowledged further follow-up is warranted and that the HG cohort had an unacceptably high relapse rate of 15.3% at 5 years, suggesting BCS alone may be inadequate treatment in this subgroup of patients.

The ECOG trial, although prospective and well designed, did not randomize patients to BCS + RT versus BCS alone. Based on prior randomized trials in DCIS, one would predict a decrease in local relapse rates with the use of radiotherapy even in the most favorable patients. The purpose of the current study was to evaluate the outcomes in a large cohort of DCIS patients who met the eligibility criteria for ECOG 5194 (E5194), but were treated with BCS and adjuvant whole breast radiotherapy, to compare the ipsilateral and contralateral breast tumor recurrence in these patients treated with radiation with those treated with observation alone in the ECOG study.

MATERIALS AND METHODS

Patient and Tumor Characteristics

After obtaining approval from the Institutional Review Board, patients with DCIS were identified as having been treated with BCS + RT between 1980 and 2009 at the Yale-New Haven Hospital in New Haven, Connecticut, and the Robert Wood Johnson University Hospital and The Cancer Institute of New Jersey in New Brunswick, New Jersey. Data were retrospectively extracted from patient records at each treating institution. The selection of patients for treatment, the method of treatment, including the technical delivery of the radiation treatment, and the method of follow-up were uniform among both institutions. Patient data were then combined into a single data set for analysis.

A total of 538 patients with a diagnosis of clinically occult, mammographically detected DCIS (TisN0M0) of

the breast treated with BCS + RT were identified. Of these patients, a total of 263 (49%) met the eligibility criteria of E5194. To be consistent with the ECOG cohorts, they were stratified into 2 groups as follows: 1) low- to intermediate-grade (LIG) DCIS lesions ($n = 196$) measuring from 0.3 to 2.5 cm in size with margins ≥ 3 mm, or 2) high-grade (HG) DCIS lesions ($n = 67$) measuring from 0.3 to 1.0 cm in size with margins ≥ 3 mm. The patients in these 2 groups made up the patient population included in this analysis.

The surgical treatment included wide local excision (ie, lumpectomy or partial mastectomy) of the primary tumor site. Re-excision was performed for 104 patients (39%) at the discretion of the treating physician. The most common reasons for re-excision included attempting to obtain negative resection margins or to ensure removal of residual microcalcifications seen on postexcision mammogram. Pathologic size was determined from pathology reports; patients whose size was unable to be determined from the pathology report were included if the mammographic abnormality met the size criteria as described above. Low- to intermediate-grade DCIS was defined as nuclear grade 1 or 2 with no foci of necrosis or comedo necrosis. High-grade DCIS was defined as nuclear grade 3 and/or the presence of comedo necrosis. Receptor status of DCIS was not routinely measured until the late 1990s. Adjuvant hormonal therapy was not routinely employed by the treating physician prior to the publication of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24 trial. Tamoxifen treatment was then allowed at the discretion of the treating physician. Hormonal therapy was given to 39% of all patients in our study (compared with 30% from E5194).

All patients received adjuvant whole breast radiation therapy (RT) after BCS. Radiation therapy was delivered using an opposed tangents technique. Regional lymph nodes were not targeted. None of the patients in this study received inverse-planned intensity modulated radiation therapy (IMRT), although physical wedges, dynamic wedges, field-in-field technique, or electronic compensation may have been used to improve dose homogeneity. Patients were treated with conventional fractionation of 1.8 to 2.0 Gy daily to a total median whole breast dose of 50 Gy. A boost to the tumor bed of 10 to 16 Gy was typically delivered with electrons to a total median dose of 64 Gy.

After treatment with radiation therapy and/or hormonal therapy, patients were monitored on a regular basis by the radiation oncologists and referring physicians. Follow-up visits typically occurred every 3 to 6 months for

the first 3 years after treatment and at least annually thereafter. Annual mammography was a routine component of long-term follow-up.

The primary goal of our study was to determine the IBTR rate in DCIS patients with the same eligibility criteria as E5194 who were treated with whole breast radiation therapy after BCS and how the IBTR compared with those patients enrolled on E5194. An IBTR was defined as the occurrence of DCIS or invasive cancer in the treated breast. For each patient, time to failure was collected for all IBTR, new ipsilateral breast cancer, and contralateral breast cancer including but not after first distant recurrence. Time to IBTR was defined as time from last definitive surgery to first occurrence of IBTR. Time to contralateral breast events, development of distant metastases, death from breast cancer, and death from any cause were defined similarly.

Statistical Analyses

All patient characteristics, staging information, treatment parameters, and outcome data, including local, regional, and distant metastases, were entered into a database, and standard statistical methods were used to analyze all data. All time intervals were calculated from the date of diagnosis. Nonparametric estimates of the survival, recurrence-free distributions, or recurrence (failure) distribution were obtained by life table methods. Associations between clinical, pathologic, and treatment-related variables and recurrence or survival event rates were analyzed by fitting parametric models to the failure-time data and examining the significance of the parameter estimates. All tests were declared statistically significant if the calculated *P*-value was <.05. All tests appear as 2-sided *P*-values. Descriptive statistics consisted of numbers and percentages of responses in each category for discrete measures and of median, minimum, and maximum values for continuous measures. Version 9.2 of the SAS statistical software package (SAS, Cary, NC) was used to conduct all statistical analyses.

RESULTS

Of the 538 patients with DCIS identified to have been treated with whole breast radiotherapy, 263 met the E5194 eligibility criteria. Patients were excluded from this analysis when the ECOG eligibility criteria were not met or unclear due to missing information about margin status, size, or nuclear grade. Among the 263 patients, 196 (75%) fit the criteria for the LIG cohort and 67 (25%) for the HG cohort.

Table 1. Patient Demographics and Disease Characteristics and Comparison With ECOG 5194

	Current Study	ECOG 5194
No. of patients	263 (196 LIG, 67 HG)	670 (565 LIG, 105 HG)
Median age, y	55 (30-84)	60 (28-88)
Median lesion size LIG, cm	0.8	0.6
Median lesion size HG, cm	0.8	0.5
Median follow-up, y	6.9	6.3
Median radiation dose, Gy	64	0
% Receiving hormonal therapy	39	30

ECOG indicates Eastern Cooperative Oncology Group; LIG, low to intermediate grade; HG, high grade.

The median age of the entire population was 55 years (range, 30-84 years). In the LIG cohort, the median age was 56 years (range, 30-84 years). The median lesion size in LIG patients was 0.8 cm (range, 0.3-2.5 cm) compared with 0.6 cm in patients enrolled in E5194. In the HG group, the median age was 54 years (range, 34-82 years). The median lesion size in the HG patients was 0.8 cm (range, 0.3-1.0 cm) compared with 0.5 cm in patients enrolled in E5194, respectively. Hormonal therapy was given to 39% of patients overall (41% of the LIG patients and 32% of the HG patients) compared with 30% in E5194. Table 1 characterizes our patient population and its comparison to E5194.

The median follow-up time was 6.9 years for all patients (6.4 years for the LIG cohort and 7.8 years for the HG cohort). There were a total of 10 ipsilateral breast recurrences in the LIG cohort. The 5-year and 7-year IBTR for the LIG cohort in our study was 1.5% and 4.4% (95% CI, 0.5-2.5 and 3.4-5.4, Fig. 1) compared with 6.1% and 10.5% in E5194, respectively (Table 2). There were a total of 6 new contralateral breast cancers leading to a 5-year and 7-year contralateral breast cancer rate of 2.6% and 2.6%, compared with 3.7% and 4.8% in E5194 (Fig. 2).

In the HG cohort, there were a total of 2 ipsilateral breast recurrences. The 5-year and 7-year IBTR for the HG cohort was 2.0% and 2.0% (95% CI, 1.3-2.7 and 1.3-2.7, Fig. 3) in our study compared with 15.3% and 18% in E5194, respectively (Table 2). There were a total of 3 new contralateral breast cancers leading to a 5-year and 7-year contralateral breast cancer rate of 2.7% and 8.1%, respectively, compared with 3.9% and 7.4% in E5194, respectively (Fig. 2).

Of note, 70% of all IBTR occurred after 5 years of follow-up. In the LIG cohort, 75% of all IBTR occurred after 5 years, whereas in the HG cohort, 50% of all IBTR occurred after 5 years.

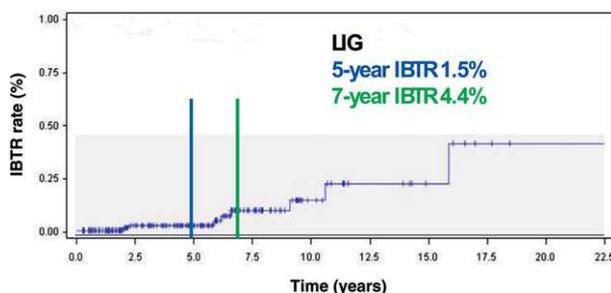


Figure 1. Ipsilateral breast tumor recurrence rate in the low- to intermediate-grade (LIG) group. IBTR, ipsilateral breast tumor recurrence.

Table 2. Comparison of IBTRs in the Current Study Versus ECOG 5194

	LIG: E5194	LIG: Current Study	HG: E5194	HG: Current Study
5-Year IBTR	6.1%	1.5%	15.3%	2%
7-Year IBTR	10.5%	4.4%	18%	2%

IBTR indicates ipsilateral breast tumor recurrence; ECOG, Eastern Cooperative Oncology Group; LIG, low to intermediate grade; HG, high grade.

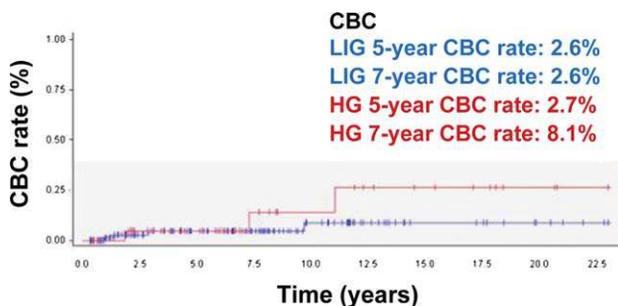


Figure 2. Contralateral breast cancer (CBC) rates in the low- to intermediate-grade (LIG) and high-grade (HG) groups.

Among the patients who received hormonal therapy, the 5-year and 7-year local control was 100% in both the LIG cohort and the HG cohort. In patients who did not receive hormonal therapy, the 5-year and 7-year local control was 97.4% and 93.5%, respectively, in the LIG cohort and 96.7% and 96.7%, respectively, in the HG group.

The 5-year disease-free survival rates for the LIG and HG were 98.5% (95% CI, 97.5-99.5) and 98% (95% CI, 94.3-95.7), respectively. Five patients have died in the LIG group and 3 in the HG group. The 5-year overall survival rates in the LIG and HG were 98.5% (95% CI, 97.9-99.1) and 94% (95% CI, 93.9-94.1).

DISCUSSION

The local management of DCIS ranges from mastectomy to BCS alone or BCS + RT. Recent studies also demonstrate favorable results in selected patients with BCS followed by partial breast irradiation.¹⁰ Currently, for those patients in whom an acceptable cosmetic result can be achieved by wide local excision of the primary tumor with a negative margin, BCS followed by whole breast radiation therapy results in high local control rates and acceptable cosmesis and complications. Omission of radiation therapy in favorable subsets of patients has been the subject of a number of retrospective series as well as prospective, randomized, and single-arm trials. All of the phase III studies on DCIS with or without radiation conducted to date demonstrate a significant reduction in local recurrence with adjuvant, whole breast irradiation compared with breast-conserving surgery alone, although the benefit in selected subsets of patients is relatively small.

In an effort to further evaluate the option of excision alone with omission of radiation therapy in selected patients, ECOG and the North Central Cancer Treatment Group on behalf of the Breast Cancer Intergroup of North America launched a prospective single-arm trial to test the hypothesis that with rigorous pathologic processing and margin assessment, a subset of patients with

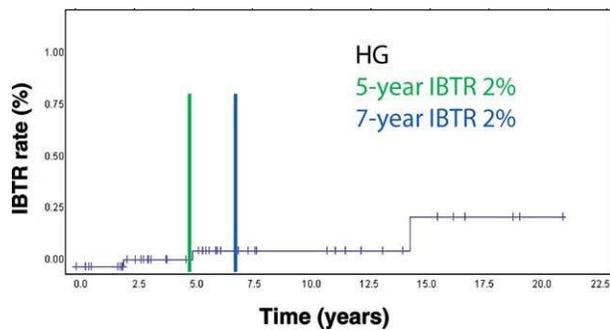


Figure 3. Ipsilateral breast tumor recurrence rate in the high-grade (HG) group. IBTR, ipsilateral breast tumor recurrence.

favorable DCIS histologic features could be treated by excision alone, with omission of whole breast radiotherapy. Despite the fact that the HG patients in E5194 had margins of at least 3 mm and were all ≤ 1.0 cm, with a median size of 5 mm, the 5-year relapse rate was relatively high at 15.9%, indicating the need for adjuvant radiation in this cohort. Although eligibility allowed up to 2.5 cm size limitations in the LIG group, the majority of patients in their cohort had tumors < 1.0 cm with a median size of 6 mm. The authors concluded that observation may be an acceptable option in this cohort but acknowledge that longer follow-up is warranted. As opposed to the 4 major randomized trials in DCIS, the E5194 study, although prospective and well designed, had no radiation therapy arm.

We therefore sought to address this question by evaluating a large cohort of patients with DCIS, who met the eligibility criteria of E5194, but were treated with conventional whole breast irradiation. We selected only those patients in whom a detailed chart and pathology report review revealed tumor size, margin width, histology, and grade criteria as specified by the definitions of the 2 cohorts in E5194. We do acknowledge that our patient population did not necessarily undergo as rigorous a pathologic assessment as was done in E5194. However, if anything, this would bias our population toward a higher relapse rate. As demonstrated in Table 1, our cohorts were quite comparable to the patients in E5194 with respect to tumor size, age, use of adjuvant hormonal therapy, and follow-up. In our study, radiation therapy appeared to reduce the risk of an ipsilateral breast tumor recurrence by more than 70% in both the LIG and HG cohorts. This finding is not unexpected because 4 randomized control trials have shown adjuvant radiation therapy after local excision reduces the risk of both invasive and noninvasive disease equally. The degree of benefit of risk reduction in IBTR in our cohort of patients is larger than that seen in

randomized trials. The difference may be attributed to the fact that patients received uniform radiotherapy treatments and a boost was used routinely in patients; the median tumor bed dose delivered was 64 Gy. The addition of this boost dose after whole breast radiation may account for an increased benefit in reducing the risk of IBTR.

In the 4 randomized, prospective trials of breast-conserving surgery with or without radiation for DCIS, the benefit of radiation therapy to decrease invasive and noninvasive IBTR was applicable to all patients; subset analyses have not been able to identify any patient or tumor characteristic groups in which radiation could be omitted for DCIS to date. Some investigators have retrospectively reported that selected patients with small size DCIS and large margins have low local recurrence rates and can be treated with excision alone. However, a single-arm prospective study by Wong reported a 12% ipsilateral breast tumor rate at 5 years in patients with predominant nuclear grade 1 or 2, ≤ 2.5 cm by mammographic extent, and margins > 1 cm.⁸ In the E5194 study, although the eligibility criteria allowed for microscopic margins ≥ 3 mm, more than 70% of the LIG patients had margins > 5 mm, and 50% were > 10 mm. Similarly in the HG cohort, 83% of patients had margins > 5 mm, and 53% of margins were > 10 mm.

We concur with the conclusions of E5194 in that high-grade, small DCIS lesions with negative margins should be treated with adjuvant whole breast radiation therapy to decrease the 5-year ipsilateral breast tumor recurrence of 15% after BCS alone. In our cohort of HG patients, adjuvant radiation therapy reduced the ipsilateral breast tumor recurrence rate to 2.0%. Considering these data, along with the multiple randomized trials and other prospective and retrospective series, we advocate the use of adjuvant radiation therapy after excision for patients with high-grade DCIS.

Although a 6% IBTR rate at 5 years for the LIG seems reasonable to justify the omission of radiation therapy, these results must be interpreted with caution as the authors of E5194 suggest. In fact, it appears the rate of ipsilateral breast events increases after 5 years in the E5194 study.⁹ A retrospective study by Solin et al showed a 5-year IBTR of 3% in low-risk DCIS patients. The 10-year IBTR of 15% suggests that low-risk DCIS may have a more protracted time to local relapse.¹¹ In both of the randomized National Surgical Adjuvant Breast Project (NSABP) B-17 and European Organization for Research and Treatment of Cancer (EORTC) trials, the rates of IBTR increased by

nearly 40% after 5 years. Of note, we found that the majority of local relapses in our study occurred after 5 years, and furthermore, this finding was more apparent in the LIG cohort (75%) versus the HG cohort (50%)

The randomized EORTC study for DCIS raises the concern for increased contralateral breast cancers with the addition of radiation. Although that study found a relatively higher rate of contralateral breast cancers compared with the 3 other randomized studies, the authors contributed this finding to chance, as the finding was not to be statistically significant in the 10-year update.^{2,12} To address this question, we assessed the risk of contralateral breast cancers in our radiated cohort compared with the ECOG cohort treated with observation, and found that the 5-year contralateral breast cancer rates were comparable. Our findings suggest that the addition of adjuvant whole breast radiation therapy does not confer an increased risk of contralateral breast cancer, although we recognize that these data warrant additional long-term follow-up. Furthermore, our 5-year contralateral breast cancer rate is consistent with reports from the NSABP B-17, Swedish, EORTC, and the United Kingdom, Australia, and New Zealand (UK/ANZ) DCIS trials, which reported rates from 2% to 4% in patients receiving radiation (Table 3).

As was noted by the authors of the ECOG study, we also suggest that our results be interpreted with caution. Although our study had the benefit of slightly longer median follow-up, we realize that the retrospective nature of our investigation is vulnerable to patient selection bias and other inherent flaws, such as lack of a central pathologic review. Furthermore, given that our patient population was treated at 2 tertiary cancer centers, the quality of the diagnostic imaging, breast surgery, and radiotherapy technique may attribute to the disparate findings. In addition, 39% of patients in our study received tamoxifen compared with 30% in ECOG 5194; the difference is likely not large enough to account for the drastic reduction in IBTR seen in our patient population and should have little impact on the interpretation of our results. Although ECOG 5194 was a prospective study, ideally a randomized, prospective study would be the most valuable methodology to answer this important question of observation for selected DCIS patients. The Radiation Therapy Oncology Group 98-04, was a prospective, randomized trial that attempted to answer this question of whole breast radiation versus observation for DCIS using the same patient eligibility criteria as ECOG 5194.

Table 3. Comparison of Contralateral Breast Cancer Rate Versus ECOG 5194 Versus Randomized Controlled Trials

	5-Year Rate of Contralateral Breast Cancer
LIG: E5194	3.7%
LIG: current study	2.6%
HG: E5194	3.9%
HG: current study	2.7%
NSABP B-17	2.5%
EORTC	4%
UK/ANZ	2%
SweDCIS	3.3%

ECOG indicates Eastern Cooperative Oncology Group; LIG, low to intermediate grade; HG, high grade; NSABP, National Surgical Breast and Bowel Project; EORTC, European Organization for Research and Treatment of Cancer; UK/ANZ, DCIS Trialists in the United Kingdom, Australia, and New Zealand; SweDCIS, Swedish Breast Cancer Group.

Unfortunately, the trial failed to meet accrual and closed in 2006, accruing only 600 patients.

In conclusion, our study suggests that adjuvant radiation therapy reduces the risk of an ipsilateral breast tumor recurrence by more than 70% for *both* LIG and HG DCIS compared with the results seen in ECOG 5194. Taking into consideration the significant percentage of patients in our cohort who experienced local failure after 5 years of follow-up, we recommend both LIG and HG DCIS patients be considered for whole breast radiation until longer follow-up of ECOG 5194 is reported. Furthermore, despite the omission of radiation in the ECOG 5194 study, the contralateral breast cancer rate was similar to our current study, suggesting that the addition of whole breast radiation for DCIS does not appear to increase the rate of contralateral breast cancer, but additional follow-up is warranted.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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