Is Lobular Carcinoma In Situ as a Component of Breast Carcinoma a Risk Factor for Local Failure after Breast-Conserving Therapy?

Results of a Matched Pair Analysis

Merav A. Ben-David, M.D.[1]
Celina G. Kleer, M.D.[2]
Chintana Paramagul, M.D.[3]
Kent A. Griffith, M.P.H., M.S.[4]
Lori J. Pierce, M.D.[1]

[1] Department of Radiation Oncology, Cancer and Geriatrics Center, University of Michigan Medical School, Ann Arbor, Michigan.

[2] Department of Pathology, University of Michigan Medical School, Ann Arbor, Michigan.

[3] Department of Radiology, University of Michigan Medical School, Ann Arbor, Michigan.

[4] Biostatistics Core, Comprehensive Cancer Center, University of Michigan Medical School, Ann Arbor, Michigan.

Presented in part at the 46th American Society for Therapeutic Radiology and Oncology Meeting, Atlanta, Georgia, October 3–7, 2004.

Address for reprints: Lori J. Pierce, M.D., Department of Radiation Oncology, 4308 Cancer and Geriatrics Center, University of Michigan Medical School, 1500 E. Medical Center Dr., Ann Arbor, MI 48109-0010; Fax: (734) 647-9654; E-mail: ljpierce@umich.edu

Received March 22, 2005; revision received June 8, 2005; accepted June 21, 2005.

BACKGROUND. The goals of the current study were to compare the clinicopathologic presentations of patients with lobular carcinoma in situ (LCIS) as a component of breast carcinoma who were treated with breast conserving surgery (BCS) and radiation therapy (RT) with those of patients without LCIS as part of their primary tumor and to report rates of local control by overall cohort and specifically in patients with positive margins for LCIS and multifocal LCIS.

METHODS. Sixty-four patients with Stages 0–II breast carcinoma with LCIS (LCIS-containing tumor group, LCTG) that had received BCS+RT treatment at the University of Michigan between 1989 and 2003 were identified. These patients were matched to 121 patients without LCIS (control group) in a 1:2 ratio.

RESULTS. The median follow-up time was 3.9 years (range, 0.3–18.9 yrs). There were no significant differences between the two groups with regard to clinical, pathologic, or treatment-related variables or in mammographic presentation, with the exception of a higher proportion of the LCTG patients who received adjuvant hormonal therapy ($P = 0.01$). The rates of local control at 5 years were 100% in the LCTG group and 99.1% in the control group ($P = 0.86$). The presence of LCIS at the margins and the size and presence of multifocal LCIS did not alter the rate of local control.

CONCLUSIONS. The extent of LCIS and its presence at the margins did not reduce the excellent rates of local control after BCS+RT. The data suggest that LCIS in the tumor specimen, even when multifocal, should not affect selection of patients for BCS and whole-breast RT. ***Cancer* 2006;106:28–34.**

KEYWORDS: lobular carcinoma in situ (LCIS), radiotherapy, breast carcinoma, breast conservation, local control.

In 1941, Foote and Stewart first described lobular carcinoma in situ (LCIS) as a distinct neoplastic lesion, characterized by the proliferation of homogenous malignant cells within the terminal duct–lobular apparatus.[1] LCIS is typically multicentric and bilateral and has no specific clinical manifestation or radiologic features.[2–4] LCIS is usually identified as an incidental pathology finding outside the area of abnormality which prompts a biopsy of the breast. Therefore, the true incidence of LCIS in the general population is unknown.

In a study based on the Surveillance, Epidemiology, and End Results (SEER) database, a fourfold increase in the incidence of LCIS in the last three decades was shown, specifically in postmenopausal women.[5] This finding is consistent with the results of other studies.[6,7]

DOI 10.1002/cncr.2005
Published online 2 December 2005 in Wiley InterScience (www.interscience.wiley.com).

This increase corresponds to a similar increase in the incidence of infiltrating lobular carcinoma (but not infiltrating ductal carcinoma) among women age 50 years and older.[5,8]

LCIS is considered to be a risk factor for bilateral invasive breast carcinoma, either ductal or lobular.[3,4] The relative risk for developing subsequent breast carcinoma after an incidental finding of LCIS in a biopsy reportedly ranges from 5.9–12.0-fold in long-term follow-up studies. Approximately 50% of subsequent breast malignancies occur more than 15 years after LCIS was diagnosed.[2–4] There are conflicting reports regarding the type of cancer diagnosed after LCIS, specifically the percentage of invasive lobular carcinoma (ILC), which ranges from 50–70% of invasive tumors in different series.[2–4,9–12] The percentage of ILC rises when the original diagnosis of LCIS was made according to rigid criteria.[3,4,11] In contrast to the high prevalence of ILC in patients who had LCIS in the past, only 5–10% of breast carcinomas without a history of LCIS are of ILC histology.[13,14]

Recent studies have attempted to prove a genetic correlation between LCIS and ILC when they appear synchronously and to clarify whether LCIS serves as a precursor for the development of ILC or is a marker for advanced genetic changes in breast tissue.[15–17] If LCIS is indeed found to be a precursor for invasive carcinoma, the extent of LCIS and its presence at the surgical margins of the lumpectomy specimens could impact the risk of subsequent in-breast tumor recurrence after breast-conserving surgery (BCS) and radiotherapy (RT).

Therefore, the aims of this study were to compare the clinicopathologic presentations of patients with LCIS as a component of breast carcinoma that were treated with BCS and RT versus matched control patients without LCIS as part of their primary tumor and to report rates of local control in the overall cohort, specifically in patient subsets with multifocal LCIS and positive margins for LCIS.

MATERIALS AND METHODS

Between January 1989 and December 2003, 1196 women with 1224 breast carcinoma primary tumors AJCC Stages 0–II were treated at the Department of Radiation Oncology at the University of Michigan. All patients underwent BCS and RT. After Institutional Review Board approval, 66 patients (5%) diagnosed with ductal carcinoma in situ (DCIS) or invasive breast carcinoma of Stages I–II with LCIS as a component of their primary tumor were identified. They were matched by histology (invasive/noninvasive), stage, age, and date of diagnosis in a 1:2 ratio with control patients treated with BCS and RT for malignancy not associated with LCIS. The controls were randomly selected from our radiation oncology database. This group consisted of 121 patients (7 patients had only 1 match). Two patients with LCIS were excluded becaue no controls could be matched; therefore, there were 64 patients with LCIS and 121 controls in the study. The median age at diagnosis was 59 years in both groups (range, 39–88 yrs) and greater then 70% of the patients were postmenopausal.

All pathology slides (100%) of the LCIS-containing tumors group (LCTG) were centrally re-reviewed by a single pathologist (C.K.) for the presence of LCIS and to assess its distance from the surgical margins, the size of LCIS, and whether the LCIS was unifocal or multifocal. LCIS was defined according to accepted criteria.[13] LCIS was characterized by a population of monotonous and uniform cells filling in and expanding the acini and intralobular ductules. The cells of LCIS were often vacuolated and discohesive. Although the pathology specimens for the controls had initially been reviewed within the University of Michigan Health System, 10% of the control group was randomly selected to have their pathology re-reviewed to evaluate the rate of false-negatives that reported an absence of LCIS. No LCIS was found in this population.

All available mammograms of both groups were reevaluated for breast density, the presence of a mass or calcifications, and the size of the tumor. The breast density was scored using the American College of Radiology Breast Imaging Reporting and Database System (BI-RADS) scoring scheme Grades 0 through 3 in which Grade 0 indicates fatty breast, Grade 1 indicates scattered fibroglandular densities, Grade 2 indicates heterogeneously dense breast, and Grade 3 indicates dense breast.[18] Fifty-six of the LCTG group (88%) and 119 of the control group (95%) had mammograms that were available for analysis.

All patients were treated at the University of Michigan Radiation Oncology Department with whole-breast radiation using two opposed tangential fields calculated with lung density correction. Ninety-seven percent also received a boost to the tumor bed. All patients were treated with megavoltage (MV) radiation, generally 6-MV photo, to the intact breast; the boost was usually administered using electron beam. The details of our treatment techniques have been published elsewhere.[19] From 2001, all treatment plans were generated using computered tomography-based planning. In general, regional lymph nodes were irradiated if more then three axillary lymph nodes were positive, if no axillary evaluation was performed, or if one to three lymph nodes were positive in the absence of a formal lymph node dissection.

The clinical characteristics, including demographics, means of diagnosis, staging, histologic features, surgical procedures, systemic adjuvant chemotherapy and hormone therapy, radiation treatment details, menopausal status, and familial history of breast carcinoma were analyzed and compared. Follow-up information included the date of documented in-breast (local), regional, and/or distant recurrence, contralateral breast carcinoma diagnosis, death, and the date of last known contact. A patient was considered to be free of recurrence if free of disease after the completion of radiotherapy until the last known contact date. The local recurrence-free interval was calculated from the time of the completion of radiotherapy until the occurrence of breast-only tumor failure or local component of first failure. Patients experiencing regional or distant failures first, or who were disease free until their last contact date, were censored. The local recurrence-free interval was estimated using the product-limit technique of Kaplan and Meier for LCIS and control cases separately. Ninety-five percent confidence intervals (95% CIs) were constructed using the Greenwood estimate of variance.[20] The total follow-up time for each patient was calculated from the completion of radiotherapy until the date of their last contact, and the total follow-up time for the entire patient cohort was summarized by the median. As LCIS patients were matched to at least one control patient and conditional logistic regression was used to determine significant differences in the patient and clinical characteristics. *P*-values for Wald-type test statistics were used to determine significant differences between LCIS cases and controls, with *P*-values $\leq$ 5% considered significant.

RESULTS

The clinical characteristics of cases and controls are presented in Table 1. The two groups were comparable (not significantly different) with respect to age at diagnosis, race, menopausal status, percentage of first-degree relatives with breast carcinoma, histology, pathologic stage, number of positive lymph nodes, hormone receptor positivity status, reexcision, axillary surgery performed for invasive disease, and radiation treatment doses, as well as adjuvant hormonal therapy for the DCIS patients and chemotherapy for the invasive cancers. The median total follow-up times for the LCTG group was 3.6 years (range, 0.2–13.1 yrs) and 3.9 years for the control group (range, 0.3–18.9 yrs). Forty percent of the women had follow-up of more than 5 years. Six women in the LCTG group had an earlier contralateral breast carcinoma and two had synchronous contralateral breast carcinomas (total, 12.5%). The control group had seven earlier contralateral breast carcinomas and one later contralateral breast carcinoma (total, 6.6%) ($P = 0.18$.)

There were no significant differences noted with regard to breast density ($P = 0.09$), the presence of a mass and/or calcifications ($P = 0.19$), or the size of the tumor ($P = 0.78$) between the LCTG group and the

TABLE 1
Clinical and Pathologic Characteristics of Cases and Controls

	LCIS group (n = 64)	Controls (n = 121)	*P*-value
Age in yrs			
Median	59	59	Matched by design
Range	39–88	39–85	
< 50 (%)	17	21	
Race (%)			
White	90	87	
African-American	8	3	0.5
Other	2	10	
Menopausal status (%)			
Premenopausal	19	19	
Peri/postmenopausal	76	1	0.38
Unknown status	5	1	
Family history of breast carcinoma (%)[a]	20	20	0.42
Histology (%)			
DCIS	23	25	
IDC	17	38	
ILC	36	23	0.32
ILC + IDC	22	11	
Other invasive	1	2	
Pathologic stage (%)	23	25	Matched by design
Stage 0	62	60	
Stage I	14	15	
Stage II			
ER status (%)[b]			
Positive	72	77	
Negative	10	19	0.29
Unknown	18	2	
PR status (%)[b]			
Positive	48	70	
Negative	34	25	0.10
Unknown	18	4	
Reexcision (%)	67	59	0.27
Axillary surgery (%)[b]			
ALND	59	56	
SLNB	27	25	0.66
Both	6	11	
Neither	8	8	
Lymph nodes			
No. of lymph nodes removed			
Median (range)	14 (1–38)	11 (1–52)	0.87
Positive lymph nodes			
Median (range)	2 (1–10)	2 (1–49)	0.54
Radiation therapy (Gy)			
Whole breast	46	46	0.35
Range	45.4–50	46–50	
Boost (%)	97	97	
Dose (Gy)	14	14	0.42
Range (Gy)	10–22	10–22	
Adjuvant therapy (%)			
DCIS			
Tamoxifen	29	33	0.62
Invasive carcinoma			
Chemotherapy	26	34	0.38
Hormonotherapy	68	45	0.01

LCIS: lobular carcinoma in situ; DCIS: ductal carcinoma in situ; IDC: infiltrating ductal carcinoma; ILC: infiltrating lobular carcinoma; ER: estrogen receptor; PR: progesterone receptor; ALND: axillary lymph node dissection; SLNB: sentinel lymph node biopsy.

[a] First-degree relative with breast carcinoma.

[b] For invasive carcinoma only.

TABLE 2
Mammographic Presentation at Time of Diagnosis

	LCIS group		Control group		
	No.	%	No.	%	*P*-value
Density					
0	3	5	21	17	0.10
1	31	48	51	42	
2	17	27	24	20	
3	5	8	19	16	
Missing	8	12	6	5	
Findings					
Mass	25	39	60	50	0.22
Calcifications	21	33	40	33	
Both	11	17	16	13	
Neither	7	11	4	3	
Missing	0		1	1	
Size of mass					
≤ 1 cm	12	33	21	28	0.56
1.1–2cm	14	39	32	42	
≥ 2.1 cm	3	8	9	12	
Missing	7	20	14	18	

LCIS: lobular carcinoma in situ.

control group in the mammograms performed at diagnosis (Table 2). Therfore, the LCTG group and the control group also were comparable with respect to mammographic presentation. In greater than 60% of the patients the breast density was 0/1 (fatty breast or scattered fibroglandular densities) anticipated by their age distribution.

The groups were comparable with respect to the percentage of cases with invasive and noninvasive disease. For patients with invasive tumors, extensive intraductal component was present in 18% and 10% of the LCTG group and the control group, respectively ($P = 0.09$), and angiolymphatic invasion was observed in 6% and 10%, respectively ($P = 0.41$). In both groups, 92% of the patients with invasive tumors underwent axillary evaluation, either axillary lymph node dissection, sentinel lymph node biopsy, or both.

LCIS was associated with ILC alone in 36% of the cases, and with the combination of ILC with infiltrating ductal carcinoma in 22% of the cases, for a total of 58% (37 patients) of the cohort. The LCIS component was unifocal in 66% and multifocal in 34% of the cases with a median of 5 foci (range, 3–9 foci) per tumor in the multifocal group. The median size of the LCIS component was 0.2 cm (range, 0.05–1.0 cm). The margins were positive in 16.6% or close (≤3 mm) for LCIS in 30% of the LCTG group. For the invasive component, margins were microscopically positive or close in 9.4% of the cases; no DCIS was present at the margins. For the control group, 3% had positive or close margins for DCIS and 10% had positive or close margins for the invasive component ($P = 0.48$).

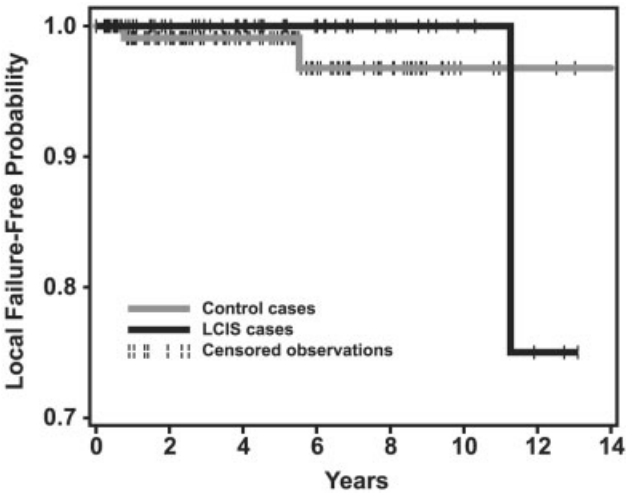

FIGURE 1. Local failure-free probability.

Adjuvant hormonal therapy was given more frequently in the LCTG group (68% vs. 45% in the control group) for invasive tumors ($P = 0.01$). When given, tamoxifen was the drug of choice in both groups (94%).

With a median total follow-up time of 3.9 years, there was no significant difference noted in the crude rates of ipsilateral breast tumor recurrence between the 2 groups (1.6% in the LCTG group [1 local recurrence] vs. 1.7% in the control group [2 local recurrences]) (Fig. 1). There was also no difference noted in the actuarial 5-year local recurrence-free interval between the 2 groups (100% [no failure] in the LCTG group vs. 99.1% [1 failure] in the control group; 95% CI, 97.3–100% [$P = 0.78$]). There were no subsequent failure events for those patients who had breast-only first failure. There were also no cases of regional/distant failure reported in the LCTG group. The control group had four distant failures and one concurrent regional and distant failure. The presence of LCIS at the margins, the size of the LCIS component, and multifocality appeared to have no influence on the rate of local control. No subgroup analyses were attempted due to the low number of events.

DISCUSSION

Although LCIS is known to be a marker for an increased risk of breast carcinoma in women who have never had the disease,[2–4,9–11] it is unclear whether it has any effect on outcome when it is associated with primary breast carcinoma. In the current study, we demonstrated no statistically significant difference in the rate of ipsilateral breast tumor recurrence (IBTR)

TABLE 3
Comparison of Reports with LCIS as a Component of Breast Carcinoma Treated with BCS and RT

Reporting institution	Stage of disease	No. of control patients	No. of patients with LCIS	Median follow-up in mos	Risk of local failure		*P*-value
					+LCIS	−LCIS	
Fox Chase[21]	I–II	1209	65	76	5% 29%	3% After 5 yr 6% After 10 yr	0.003
Yale[22]	0–II	1045	51	127	23%	16%	NS
Harvard[23]	I–II	1062	137	161	13%	12%	NS
University of Michigan (current study)	0–II	121 matched	64	45	1.7%	1.6%	NS

LCIS: lobular carcinoma in situ; BCS: breast-conserving surgery; RT: radiotherapy; +LCIS: with lobular carcinoma in situ; −LCIS: without lobular carcinoma in situ; NS: not significant.

between women who had LCIS as a component of their breast carcinoma and the control group, all of whom were treated with BCS and radiotherapy. To our knowledge, this study is the first attempt to compare outcomes in patients with early-stage LCIS-containing tumors with a matched controlled group. Previously published reports of the influence of LCIS on IBTR in patients treated with BCS and RT have generally compared rates using unmatched controls (Table 3).[21–23] Matching cases and controls by their age at diagnosis, year of diagnosis, and stage of disease eliminates the potential confounding influence of these characteristics when testing for differences in tumor and treatment characteristics between populations. Matching the year of diagnosis can be extremely useful in retrospective series such as ours by assuring the treatment differences between groups are real and not related solely to changes in standards of care over time. Statistically, matching allows for increased precision when estimating the difference in the proportion of a characteristic between cases and controls.[24] The increased precision, in turn, leads to greater power to detect smaller differences in tumor and treatment characteristics between case and control populations.

Among the contemporary breast conservation series, the published rates of IBTR between LCIS-associated tumors and overall controls have generally been comparable, as shown in the current case-matched series, with the exception of the report by Sasson et al. from the Fox Chase Cancer Center.[21] In this series, the 10-year cumulative IBTR rate was 29% in the LCIS group as opposed to 6% in the generally treated population. However, there was no significant difference noted in the IBTR between the two groups when tamoxifen was used as adjuvant therapy (8% in the LCIS group vs. 6% in the control group; $P = 0.46$).

Therefore, with the exception of the Fox Chase series, there appears to be general agreement in the published literature that the rates of IBTR are comparable between LCIS-containing tumors and controls. However, the absolute rates reported by others are greater for both groups compared to the present report. There are several factors that could be responsible for those differences, such as tumor characteristics, treatment, and follow-up time. In the current series, all LCTG slides were centrally reviewed at the time of diagnosis and again for this study by a single pathologist, and 10% of the control pathology cases were sampled for pathology confirmation and the absence of LCIS. The current study excluded patients who were not diagnosed using strict and consistent criteria for LCIS. In addition, the margins were carefully evaluated for LCIS, DCIS, or invasive carcinoma. In 47% of the cases the margins were close or positive for LCIS. For invasive carcinoma or DCIS, the margins were positive in only 9.4% (6 cases) of the LCTG group and in 13% (16 cases) of the control group ($P = 0.48$). Therefore, the only difference between the groups was the presence of LCIS at the margins. In the Fox Chase study, the slides were reviewed only at the time of diagnosis, between 1979 and 1995.[21] Approximately 17% of the LCIS cases had unknown margin status, and the 10-year cumulative rate of IBTR was 53% in this subgroup. In the reported series from Yale,[22] the pathology was also evaluated only at the time of diagnosis. The margins were positive for invasive carcinoma in 14% of the LCIS cases, and no data were provided regarding margin status in the control group or the presence of LCIS at the margins. In the Harvard study,[23] the margins in some cases were not evaluated, and information is available for invasive carcinoma at the margins for only 30% of the patients. In the current series the extent of LCIS in the specimens appeared to have no influence on IBTR. This finding is consistent with the results reported in the Harvard study, but was not routinely evaluated in the Fox Chase study, and only 55% of the cases were evaluated for the extent of LCIS in the Yale study. Therefore, the differences in

the evaluation and reporting of pathologic results, specifically margin status, either for LCIS or invasive/noninvasive carcinoma, may have contributed significantly to the variation in the IBTR observed in the four studies.

Other factors that differed between this report and the reports of others include the stage of disease at presentation and the length of follow-up. Twenty-five percent of the patients in the current series were diagnosed with DCIS as opposed to the Fox Chase and Harvard studies, which included Stages I–II only. The Yale report included 10% of DCIS cases in their study. The median follow-up time in our report was only 3.9 years (range, 0.3–18.9 yrs), and longer follow-up is needed to observe the long-term impact of LCIS in the population treated with excision and whole-breast RT. Follow-up was reported to range between 6–13 years in the other series, and each demonstrated higher IBTR rates.[21–23] We will need to follow our results over time to assess continued high rates of local control.

In the current study, the association between LCIS and ILC in 58% of the cases suggests a correlation between the 2 histologies. A study from the University of California at San Francisco (UCSF) evaluated the clonality of LCIS and synchronous ILC in 24 samples.[15] Those researchers were able to demonstrate striking similarity in genomic changes between pairs of in situ and invasive components that were consistent with a progression pathway from LCIS to ILC. This finding further supports the hypothesis that LCIS is indeed a precursor of ILC, rather than an isolated risk factor for bilateral breast carcinoma. However, other studies do not support this hypothesis. In a study recently reported by Rieger-Christ et al.,[17] the E-cadherin mutations from 23 pairs of invasive carcinoma associated with LCIS were analyzed. They could not identify identical E-cadherin mutations in LCIS and associated invasive lesions in that series. More studies that test for a genetic progression between LCIS and ILC carcinoma are needed.

In our study, 68% of the LCTG group and 45% of the control group with invasive histology received tamoxifen ($P = 0.01$) as adjuvant treatment, and 30% of the DCIS patients in both groups received tamoxifen. The high percentage of adjuvant tamoxifen in the LCTG undoubtedly contributed to the low rate of IBTR observed. The combination of RT and tamoxifen has been shown to decrease the rates of IBTR in noninvasive and invasive carcinoma compared with RT alone. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-21,[25] the combination of tamoxifen and RT resulted in a 63% lower hazard rate of IBTR compared with RT and placebo. Other studies also have demonstrated statistically significant reductions in IBTR rates for patients with early-stage breast carcinoma when tamoxifen was given in combination with RT.[26,27] Tamoxifen has also been shown to reduce the risk of IBTR in patients with DCIS.[28] The favorable impact of tamoxifen on tumor control also was shown in the Fox Chase series, with similar rates of local recurrence reported in the LCIS and the control group cases who received tamoxifen along with RT (i.e., 6% vs. 8%, respectively).[21] Furthermore, tamoxifen has been shown to prevent new tumors in patients with a known history of LCIS. In the NSABP P-1 trial,[29] tamoxifen therapy resulted in a 56% reduction in the risk of invasive carcinoma in the LCIS patients included in the study. In the current series, a high proportion of the LCIS patients received tamoxifen, suggesting a combined benefit in the reduction of true recurrences and the prevention of new tumors.

Although the current results demonstrate no significant difference in IBTR between patients with LCIS as a component of their early-stage breast carcinoma and their matched control group, we acknowledge the limitations of the current study. Studies providing long-term follow-up data of the natural history of LCIS treated with biopsy or local excision alone have demonstrated a 1% per year cumulative long-term risk of breast carcinoma, which persists even 10–20 years after diagnosis.[2–4,9–12,30,31] The median total follow-up time in our report is only 3.9 years, so further follow-up of the entire LCIS cohort will be important to ensure long-term tumor control. However, it should be noted that 37.5% of cases and 44.6% of controls were followed for 5 years and 10% of the patients in each group had at least 9 years of follow-up. In addition, the matching methodology used afforded greater precision when comparing the two groups and further strengthens our conclusions that an LCIS component does not influence the rate of IBTR. Nonetheless, the current LCIS cohort will continue to be followed over time. However, the present 5-year results do not demonstrate an effect of the extent of LCIS in the tumor or at the margins on the rate of IBTR after BSC and RT. Therefore the current study data would suggest that these factors should not be considered contraindications to a breast-conserving approach.

REFERENCES

1. Foote FW, Stewart FE. Lobular carcinoma in situ: a rare form of mammary cancer. *Am J Pathol.* 1941;17:491–505.
2. Wheeler JE, Enterline HT, Roseman JM, et al. Lobular carcinoma in situ of the breast: long-term follow-up. *Cancer.* 1974;34:554–563.
3. Haagensen CD, Lane N, Lattes R, et al. Lobular neoplasia (so-called lobular carcinoma in situ) of the breast. *Cancer.* 1978;42:737–769.

4. Rosen PP, Kosloff C, Lieberman PH, et al. Lobular carcinoma in situ of the breast. Detailed analysis of 99 patients with average follow-up of 24 years. *Am J Surg Pathol.* 1978;2:225–251.
5. Li CI, Anderson BO, Daling JR, Moe RE. Changing incidence of lobular carcinoma in situ of the breast. *Breast Cancer Res Treat.* 2002;75:259–268.
6. Levi F, Te V-C, Randimbison L, La Vecchia C. Trends of in situ carcinoma of the breast in Vaud, Switzerland. *Eur J Cancer.* 1997;33:903–906.
7. Simon MS, Lemanne D, Schwartz AG, Martino S, Swanson GM. Recent trends in the incidence of in situ and invasive breast cancer in the Detroit metropolitan area (1975–1988). *Cancer.* 1993;71:769–774.
8. Li CI, Anderson BO, Porter P, Holt SK, Daling JR, Moe RE. Changing incidence rate of invasive lobular breast carcinoma among older women. *Cancer.* 2000;88:2561–2569.
9. Salvadori B, Bartoli C, Zurrida S, et al. Risk of invasive cancer in women with lobular carcinoma in situ of the breast. *Eur J Cancer.* 1991;27:35–37.
10. Andersen JA. Lobular carcinoma in situ of the breast: an approach to rational treatment. *Cancer.* 1977;39:2597–2602.
11. Page DL, Kidd TE Jr., Dupont WD, Simpson JF, Rogers LW. Lobular neoplasia of the breast: higher risk for subsequent invasive cancer predicted by more extensive disease. *Hum Pathol.* 1991;22:1232–1239.
12. Bodian CA, Perzin KH, Lattes R. Lobular neoplasia: long-term risk of breast cancer and relation to other factors. *Cancer.* 1996;78:1024–1034.
13. Schnitt SJ, Guidi AJ. Pathology of invasive breast cancer. In: Harris JR, Lippman ME, Morrow M, Osborne CK, editors. Diseases of the breast, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2000:541–584.
14. Berg JW, Hutter RV. Breast cancer. *Cancer.* 1995;75:257.
15. Shelley Hwang E, Nyante SJ, Yi Chen Y, et al. Clonality of lobular carcinoma in situ and synchronous invasive lobular carcinoma. *Cancer.* 2004;100:2562–2572.
16. Maluf H, Koerner F. Lobular carcinoma in situ and infiltrating ductal carcinoma: frequent presence of DCIS as a precursor lesion. *Int J Surg Pathol.* 2001;9:127–131.
17. Rieger-Christ KM, Pezza JA, Dugan JM, Braasch JW, Hughes KS, Summerhayes IC. Disparate E-cadherin mutations in LCIS and associated invasive breast carcinomas. *Mol Pathol.* 2001;54:91–97.
18. American College of Radiology. BI-RADS. Breast imaging reporting and data system atlas. Reston, VA: American College of Radiology, 2003.
19. Pierce LJ, Strawderman MH, Douglas KR, Lichter AS. Conservative surgery and radiotherapy for early-stage breast cancer using a lung density correction: the University of Michigan experience. *Int J Radiat Oncol Biol Phys.* 1997;1;39:921–928.
20. Klein JP, Moeschberger ML. Survival analysis: techniques for censored and truncated data. New York: Springer, 1997.
21. Sasson AR, Fowble B, Hanlon AL, et al. Lobular carcinoma in situ increases the risk of local recurrence in selected patients with stages I and II breast carcinoma treated with conservative surgery and radiation. *Cancer.* 2001;91:1862–1869.
22. Moran M, Haffty BG. Lobular carcinoma in situ as a component of breast cancer: the long-term outcome in patients treated with breast conservation therapy. *Int J Radiat Oncol Biol Phys.* 1998;40:353–358.
23. Abner AL, Connolly JL, Recht A, et al. The relationship between the presence and extent of lobular carcinoma in situ and the risk of local recurrence for patients with infiltrating carcinoma of the breast treated with conservative surgery and radiation therapy. *Cancer.* 2000;88:1072–1077.
24. Agresti A. Categorical data analysis. New York: John Wiley & Sons, 1990.
25. Fisher B, Bryant J, Dignam JJ, et al. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. *J Clin Oncol.* 2002;15;20:4141–4149.
26. Hughes KS, Schnaper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. *N Engl J Med.* 2004;2;351:971–977.
27. Fyles AW, McCready DR, Manchul LA, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. *N Engl J Med.* 2004;2;351:963–970.
28. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. *Lancet.* 1999;12;353:1993–2000.
29. Fisher B, Costantino JP, Lawrence D, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst.* 1998; 90:1371–1388.
30. McDivitt RW, Hutter RV, Foote FW Jr., Stewart FW. In situ lobular carcinoma. A prospective follow-up study indicating cumulative patient risks. *JAMA.* 1967;10;201:82–86.
31. Fisher ER, Land SR, Fisher B, Mamounas E, Gilarski L, Wolmark N. Pathologic findings from the National Surgical Adjuvant Breast and Bowel Project: twelve-year observations concerning lobular carcinoma in situ. *Cancer.* 2004;100:238–244.