In Situ Duct Carcinoma of the Breast: Clinical and Histopathologic Factors and Association with Recurrent Carcinoma

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Abstract: There has been a recent increase in the diagnosis of in situ duct carcinoma of the breast (DCIS) as a result of mammographic screening. DCIS is heterogeneous in appearance and likely in prognosis. There is no generally accepted model to predict progression to invasive carcinoma. We investigated the prognostic effect of clinical presentation and pathologic factors for women diagnosed with primary DCIS. A cohort of 124 patients was accrued between 1979 and 1994 and was followed to 1997; 78 had DCIS detected mammographically, and 88 underwent lumpectomy alone. In this article, we provide details about characteristics affecting the choice of primary therapeutic modality, and we examine the effects of factors on progression for the two patient subgroups. Presentation with bloody nipple discharge was associated with a significant increase in DCIS recurrence (p = 0.07). The pattern of duct distribution was important: DCIS in which the involved ducts were more widely separated had a significantly greater recurrence of DCIS than when the involved ducts were more concentrated (p = 0.08 for mammographically detected DCIS, p = 0.07 for patients who underwent lumpectomy alone). For mammographically detected DCIS, younger patients had more DCIS recurrence (p = 0.07). We found considerable heterogeneity in nuclear grade; 50% of patients exhibited more than one grade. Nuclear grade, necrosis, and architecture were not significantly associated with either recurrence of DCIS or development of invasive carcinoma. Longer follow-up will allow further evaluation of the prognostic relevance of the factors assessed.

Key Words: breast neoplasms, ductal carcinoma in situ, neoplasm recurrence, prognosis

In situ duct carcinoma (DCIS) of the breast is being diagnosed more frequently now than previously because of the increasingly widespread use of mammographic screening. In some centers, DCIS accounts for 25% of the breast cancers diagnosed. DCIS is heterogeneous in its histology and clinical presentation, and the risk of developing invasive carcinoma may also differ.

Although there have been many studies of DCIS and subsequent carcinoma (1–22), both the evaluation and
comparison of these studies are hampered by differences in how the DCIS was diagnosed and how the pathology specimen was evaluated, what was considered recurrence (DCIS versus invasive carcinoma), and differences in length of follow-up. For many studies, it is too early for long-term assessment of the risk of developing invasive carcinoma. Recent changes in treatment modalities from mastectomy to lumpectomy, with or without radiotherapy, further complicate evaluation of the long-term risk of breast cancer. However, there is increasing evidence that clinical and pathologic factors are important in both the risk of development of carcinoma and the efficacy of different treatments (6–8, 11–23). In view of the larger number of DCIS cases currently being diagnosed, further studies contributing to the understanding of the prognostic relevance of a wide range of clinical and histopathologic factors and the effects of treatment are needed. A recent consensus conference encouraged detailed reporting of clinical presentation and management and subsequent diagnosis of either in situ or invasive breast cancer (24).

In our multidisciplinary breast center, mammography was introduced early into clinical practice, as was conservative management of breast carcinoma for both invasive as well as in situ carcinoma. Detailed follow-up of these patients has been maintained or is accessible. We previously reported the effects of a set of clinical and pathologic factors on the recurrence of DCIS and development of invasive breast carcinoma in the group of patients who underwent lumpectomy alone (22). We now provide more information about the selection of primary therapeutic management (lumpectomy alone versus lumpectomy with adjuvant radiotherapy or mastectomy) and report the results of a more extensive pathologic work-up for patients who underwent lumpectomy alone. Additionally, we consider the subgroup of patients whose DCIS was detected mammographically.

**METHODS**

The Henrietta Banting Breast Center is a multidisciplinary assessment center for breast diseases. Analysis of patient records from the practices of the group of teaching surgeons identified 260 women who were diagnosed as having in situ carcinoma of the breast between 1979 and 1994. Study cases included had (a) DCIS confirmed by pathology review, (b) histology slides of the initial DCIS and most subsequent carcinomas available for review, (c) no previous breast or other malignancy, and (d) a detailed follow-up (which was up to 1997). One hundred eighteen patients were excluded for the following reasons: 18 on review did not have DCIS; 100 had previous carcinoma, and 18 had no (or limited) follow-up or primary histologic slides were not available for review. Data for the remaining 124 patients with DCIS form the basis of this study. The focus of the investigations is the 88 patients who underwent lumpectomy alone and the cohort who presented mammographically.

**Clinical Factors Assessed**

**Age** The age at diagnosis was in years.

**Manner of Initial Presentation** Seventy eight were detected mammographically (asymptomatic), and 32 presented clinically: 22 with a mass and 10 with bloody nipple discharge. The mode of presentation was unknown in 14 patients.

**Histologic Factors Assessed**

**Nuclear Grade** DCIS was graded as 1, 2, and 3 (by the Van Nuys classification scheme, 13). When more than one grade was present, all grades, the worst (highest) grade, and the predominant (most extensive) grades were recorded.

**Architectural Type** The DCIS was classified into architectural patterns: solid, cribriform, micropapillary, other (e.g., papillary, apocrine, clinging). All of the types present, the predominant (most extensive) type present, and the type with least architectural differentiation (solid versus all other) were recorded. We report the results obtained by considering predominant architecture and least architectural differentiation.

**Calcifications** Calcifications included present (amorphous or crystalline) or not present.

**Size** The specimens were processed uniformly in a manner consistent with standards at the time of the biopsies. For mammographically detected lesions, tissue was sampled rather than assessed in toto, with sampling directed to the area marked by dye instilled preoperatively and/or area marked by a needle placed intraoperatively by a radiologist. Sampling of other specimens was directed by the gross appearance of the specimen. Several assessments were made to reflect
size: (a) estimate from the gross description, (b) maximum dimension per slide, and (c) number of slides with DCIS involvement.

The percent parenchyma involved [<10%, 10 to 50% (Fig. 1), >50% (Fig. 2)] was assessed to reflect the proportion of the total parenchyma (stroma and all ducts and lobules) in the areas on the slides containing DCIS that was occupied by the involved ducts. This reflected whether the involved ducts were concentrated within the parenchyma (higher percentage) or more diffusely scattered (lower percentage). Duct distribution tended to be uniform, and a single categorization could be assigned for each patient.

We report the results obtained by considering the maximum size of the DCIS on any slide and the percentage of parenchymal involvement.

**Necrosis** Necrosis was central confluent (comedo) versus not.

**Resection Margins** Resection margins had been painted with silver nitrate. The shortest distance between an involved duct and resection margin was measured microscopically with an ocular micrometer (in millimeters). The presence of an uninvolved duct between DCIS and painted margin (reported as cannot assess, not present, present) was also assessed.

**Treatment**

The 124 patients with DCIS were treated as follows: local resection only, 88; local resection plus adjuvant radiotherapy, 18; and mastectomy only, 18. Seven of the patients had treatment directed by ongoing clinical trials (NSABP-17 or NSABP-24). Other patients were treated off trial by a group of teaching surgeons who have a uniform approach to patient management (22); they used the NSABP surgical protocol for DCIS.

We tested for imbalances in investigational factor subgroups by treatment modality, with Pearson’s chi-square. Table 1 indicates that therapy was not influenced by clinical factors.

We examined the effects of considerable grading heterogeneity (Fig. 3) on both choice of therapy, and later, on prognosis. From Table 2, 50% (62 of 124) of the DCIS patients had 2 or more nuclear grades; 52 of 62 patients with more than one grade had a mixture of grades 2 and 3 DCIS, and 3 patients exhibited all 3 DCIS grades. As observed in Table 3, pathologic factors did appear to be associated with therapeutic modality. Patients were significantly more likely to have received lumpectomy followed by adjuvant radiotherapy or a mastectomy if the DCIS was larger than 1 cm (p = 0.01), was grade 3 (p = 0.03 by worst grade, p = 0.01 by predominant grade), or had confluent necrosis (p = 0.01).

**Events**

Any diagnosis of breast carcinoma occurring more than 90 days from the time of the initial surgery, in either breast, was designated as an event. The events of interest were diagnoses of DCIS and invasive carcinoma of the breast. There was insufficient power to subdivide the events by location, that is, by whether ipsilateral DCIS was likely a local recurrence or a new primary tumor. Thus, “recurrences” are classified as ipsilateral or contralateral. The only other breast carcinoma observed after primary therapy was in the ipsilateral axillary lymph node of the one patient who received a...
simple mastectomy. As yet, there have been no breast cancer deaths.

**Analyses**

The effects of the histologic and clinical factors were assessed with respect to the development of events. The treatment effects of surgical modality and administration of adjuvant radiotherapy were so dominant that they could not be estimated in standard multivariate analyses with the other prognostic factors. The situation was handled by utilizing data for the subgroup of 88 lumpectomy-alone patients who experienced most of the events, and in the analyses with the subgroup of mammographically detected DCIS, with stratification by treatment (lumpectomy alone versus lumpectomy with adjuvant radiotherapy or mastectomy). The univariate assessments were with Kaplan-Meier plots and the Wilcoxon (Peto-Prentice) test statistic (for patients who underwent lumpectomy alone and for mammographically detected DCIS). The multivariate assessments were with Cox stepwise regressions. The Results section includes the univariate plots for factors that were significant in the multivariate investigation.

**RESULTS**

The median follow-up was 5.0 years following a lumpectomy and 6.7 years following a mastectomy. There was a total of 19 recurrences of DCIS, all ipsilateral (median interval to recurrence was 2.6 years, range was 5.3 months to 5.7 years), 17 of 88 (19%) following lumpectomy alone, 2 of 18 (11%) following lumpectomy and adjuvant radiotherapy, and 0 of 18 (0%) following mastectomy. Twelve patients developed invasive carcinoma, 7 ipsilateral and 5 contralateral (median interval to event 1.8 years, range 9.5 months to 6.6 years). The ipsilateral invasive events occurred with the following frequency: 6 of 88 (7%) following lumpectomy alone, 0 of 18 (0%) following lumpectomy and adjuvant radiotherapy, and 1 of 18 (6%) following mastectomy. The contralateral invasive events all occurred in the lumpectomy alone group [5 of 88 (6%)]. Ipsilateral and contralateral invasive events were considered together as there was inadequate power for separate analyses. Only one of the patients who developed invasive breast cancer had DCIS recurrence detected prior to this: The DCIS was ipsilateral at 5.6 years, and the invasive carcinoma was contralateral, 1 year later. Treatment with lumpectomy was associated with significantly more DCIS recurrence than was mastectomy (19 versus 0 recurrences, \( p = 0.05 \)); there was a nonsignificant reduction in recurrence for lumpectomy patients who received radiotherapy. More patients developed invasive carcinoma in the lumpectomy than in the mastectomy group (11 vs. 1; \( p = 0.37 \)). Eleven of the 78 (14%) patients with mammographically detected DCIS experienced recurrent DCIS, whereas 6 (8%) developed invasive breast cancer.

**Table 1. Number of Patients in Factor Subgroups by Treatment: Clinical Factors**

| Factor                          | Number of cases | Lumpectomy with no radiation | Lumpectomy with radiation/ mastectomy | p value $^1$ |
|---------------------------------|-----------------|------------------------------|--------------------------------------|--------------|
| Age                             |                 |                              |                                      |              |
| ≤39                             | 8               | 6                            | 2                                   |              |
| 40–49                           | 38              | 25                           | 13                                  |              |
| 50–64                           | 45              | 30                           | 15                                  | 0.42         |
| ≥65                             | 33              | 27                           | 6                                   |              |
| Initial presentation            |                 |                              |                                      |              |
| Mammographic detection          | 78              | 58                           | 20                                  | 0.91         |
| Clinically palpable             | 22              | 16                           | 6                                   |              |
| Nipple discharge                | 10              | 8                            | 2                                   |              |

$^1$Based on \( \chi^2 \) test.

**Figure 3.** Heterogeneity of nuclear grade within the same block.

**Table 2. Heterogeneity of Nuclear Grade for Patients**

| Grades          | Number of cases |
|-----------------|-----------------|
| Grade 1 only    | 1               |
| Grade 1 and Grade 2 | 10             |
| Grade 2 only    | 31              |
| Grade 1 and Grade 3 | 0             |
| Grade 2 and Grade 3 | 49             |
| Grades 1–3      | 3               |
| Grade 3 only    | 30              |
Table 3. Number of Patients in Factor Subgroups by Treatment: Pathologic Factors with Significant Differences

| Factor                        | Number of cases | Lumpectomy with no radiation | Lumpectomy with radiation/mastectomy | p value \(^1\) |
|-------------------------------|-----------------|------------------------------|-------------------------------------|----------------|
| Maximum DCIS size             |                 |                              |                                     |                |
| ≤1 cm                         | 54              | 47                           | 7                                   |                |
| >1 to ≤ 2 cm                  | 59              | 34                           | 25                                  |                |
| >2 to ≤ 5 cm                  | 7               | 4                            | 3                                   | 0.01           |
| >5 cm                         | 4               | 3                            | 1                                   |                |
| Predominant nuclear grade     |                 |                              |                                     |                |
| Grade 1                       | 6               | 6                            | 0                                   |                |
| Grade 2                       | 58              | 48                           | 12                                  | 0.01           |
| Grade 3                       | 58              | 34                           | 24                                  |                |
| Worst nuclear grade           |                 |                              |                                     |                |
| Grade 1                       | 1               | 1                            | 0                                   |                |
| Grade 2                       | 41              | 35                           | 6                                   | 0.03           |
| Grade 3                       | 82              | 52                           | 30                                  |                |
| Necrosis                      | None            | 33                           | 29                                  | 4              |
| Confuent (comedo-like)        | 91              | 59                           | 32                                  | 0.01           |

\(^1\) Based on \(\chi^2\) test.

Factors Associated with DCIS Recurrence

Details of analysis are as follows: Univariate analysis for lumpectomy alone patients (22) (Table 4) and for mammographically detected DCIS (Fig. 4), age at presentation; (Fig. 5), parenchymal involvement; (Fig. 6), calcification Multivariate: for both types of patients (Table 5).

Clinical Factors Assessed

For patients who underwent lumpectomy alone, a clinical presentation, especially one with bloody nipple discharge, was associated with a greater recurrence of DCIS (\(p = 0.05\) in univariate analysis, Table 4; \(p = 0.07\) in multivariate, Table 5). There were no significant univariate or multivariate results for the 58 patients with mammographically detected DCIS who underwent lumpectomy alone.

For the full cohort of 78 mammographically detected DCIS, older patients with mammographically detected lesions were less likely to have recurrent DCIS than younger patients (\(p = 0.25\) by univariate analysis; \(p = 0.07\) in multivariate analysis, Table 5). There was no recurrence of DCIS in the 17 patients with mammographically detected DCIS who were ≥65 years of age.

Histopathologic Factors

When ducts involved by DCIS were more widely separated in breast tissue, as reflected by a lower percentage of parenchymal involvement, there was significantly increased DCIS recurrence for lumpectomy-alone patients (\(p = 0.01\) by univariate analysis, Table 4; \(p = 0.07\), in multivariate analysis, Table 5) and for the mammographically detected subgroup of 78 patients (\(p = 0.08\) in multivariate investigations, Table 5).

For the patients whose DCIS was detected mammographically, the effect of microscopic calcification was so dominant that this factor could not be included in the multivariate analysis: 0% (0 of 9) DCIS recurrence when there was no microscopic calcification versus 16% (11 of 69) DCIS recurrence when there was calcification. There were too few patients without calcifications to permit stratification by this factor.

No other histologic factors either individually or in combination showed any association with DCIS recurrence.

Factors Associated with Development of Invasive Carcinoma

Details of analysis are as follows: Univariate analysis for lumpectomy alone patients (22) (Table 4) and for mammographically detected DCIS, results provided later in this article.

There were no clinical or histologic factors with strong univariate or multivariate associations with the development of invasive carcinoma. In multivariate analysis of the data for patients with mammographic presentation, the resection margin was associated with the development of invasive carcinoma, a large resection margin being associated with more invasive events (\(p = 0.08\)).

DISCUSSION

Pure DCIS does not have the potential to metastasize, leading to death; therefore, the main importance of DCIS is in the risk of development of invasive carcinoma. The concept of progression from in situ carcinoma to invasive carcinoma is generally accepted; however, this progression does not always occur. DCIS is currently managed differently than in situ lobular carcinoma (LCIS), which is accepted as a risk factor for the development of invasive carcinoma in either breast. LCIS is not treated surgically; however, there are morphologic types of in situ carcinoma that are indeterminate between duct and lobular type (25), and it has been suggested that low-grade DCIS, like LCIS, may be a risk factor rather than a precursor to invasive disease (22,26,27). Thus, when evaluating the development of carcinoma following a diagnosis of DCIS, we
Table 4. Recurrence of DCIS and Development of Invasive Breast Cancer by Factor Subgroup: All Presentations of DCIS In Patients Who Underwent Lumpectomy Alone

| Factor                          | Number of cases | Recurrence of DCIS | p value | Invasive breast cancer | p value² |
|---------------------------------|-----------------|--------------------|---------|------------------------|---------|
| **Age**                         |                 |                    |         |                        |         |
| ≤ 39                            | 6               | 0 (0%)             |         | 3 (50%)                |         |
| 40–49                           | 25              | 4 (16%)            |         | 3 (12%)                |         |
| 50–64                           | 30              | 9 (30%)            | 0.30    | 4 (13%)                | 0.15    |
| ≥ 65                            | 27              | 4 (15%)            |         | 1 (4%)                 |         |
| **Initial presentation**        |                 |                    |         |                        |         |
| Mammographic detection          | 58              | 9 (16%)            |         | 6 (10%)                |         |
| Clinically palpable mass        | 16              | 3 (19%)            | 0.05    | 3 (19%)                | 0.98    |
| Nipple discharge                | 8               | 5 (63%)            | 1 (13%) |                        |         |
| **Maximum DCIS size**           |                 |                    |         |                        |         |
| ≤ 1 cm                          | 47              | 7 (15%)            |         | 3 (6%)                 | 0.25    |
| > 1 to ≤ 2 cm                   | 34              | 10 (29%)           | 0.12    | 7 (21%)                | 0.30    |
| > 2 cm                          | 7               | 0 (0%)             |         | 1 (14%)                |         |
| **Overall percentage of parenchyma involved** |               |                    |         |                        |         |
| < 10%                           | 5               | 3 (60%)            |         | 0 (0%)                 |         |
| 10–50%                          | 55              | 11 (20%)           | 0.01    | 5 (9%)                 | 0.30    |
| > 50%                           | 28              | 3 (11%)            |         | 6 (21%)                |         |
| **Predominant architecture**    |                 |                    |         |                        |         |
| Cribriform/microcystoid/other    | 59              | 12 (20%)           |         | 8 (14%)                | 0.77    |
| Solid                           | 29              | 5 (17%)            | 0.74    | 3 (10%)                |         |
| **Worst architecture**          |                 |                    |         |                        |         |
| Cribriform/microcystoid/other    | 43              | 9 (21%)            |         | 5 (12%)                | 0.70    |
| Solid                           | 45              | 8 (18%)            | 0.56    | 6 (13%)                |         |
| **Predominant nuclear grade**   |                 |                    |         |                        |         |
| Grade 1/2                       | 54              | 8 (15%)            |         | 6 (11%)                | 0.42    |
| Grade 3                         | 34              | 9 (26%)            | 0.10    | 5 (15%)                |         |
| **Worst nuclear grade**         |                 |                    |         |                        |         |
| Grade 1                         | 1               | 0 (0%)             |         | 0 (0%)                 |         |
| Grade 2                         | 35              | 4 (11%)            | 0.18    | 6 (17%)                | 0.73    |
| Grade 3                         | 52              | 13 (25%)           |         | 5 (10%)                |         |
| **Necrosis**                    |                 |                    |         |                        |         |
| None                            | 29              | 6 (21%)            |         | 4 (14%)                | 0.88    |
| Confluent (comedo-like)         | 59              | 11 (19%)           | 0.83    | 7 (12%)                |         |
| **Calcification**               |                 |                    |         |                        |         |
| None                            | 18              | 2 (11%)            |         | 3 (17%)                | 0.38    |
| Crystalline/amorphous           | 70              | 15 (21%)           | 0.47    | 8 (11%)                |         |
| **Measured margin**             |                 |                    |         |                        |         |
| Zero margin                     | 9               | 3 (33%)            |         | 1 (11%)                |         |
| < 1 mm                          | 40              | 10 (25%)           |         | 4 (10%)                |         |
| 1–5 mm                          | 28              | 2 (7%)             | 0.28    | 3 (11%)                | 0.80    |
| > 5 mm                          | 10              | 2 (20%)            |         | 2 (20%)                |         |
| **Presence of uninvolved intervening duct** |             |                    |         |                        |         |
| Not assessable                  | 14              | 4 (29%)            |         | 2 (14%)                |         |
| No                              | 48              | 10 (21%)           | 0.47    | 4 (8%)                 | 0.42    |
| Yes                             | 26              | 3 (12%)            |         | 5 (19%)                |         |

¹The results for factors, other than Worst Architecture and Worst Nuclear Grade, are reprinted with the kind permission of the Annals of Surgical Oncology (22).
²Based on the Wilcoxon (Peto-Prentice) test statistic.

considered both carcinoma developing in the contralateral as well as the ipsilateral breast as events. Furthermore, we thought that recurrence of DCIS and development of invasive carcinoma are so profoundly different in importance to the patient that these two events should be assessed separately. This contrasts with the approach of evaluating ipsilateral breast events only (6,13,14) and the recurrence of DCIS and development of invasive carcinoma together (6,11,13,14,21).

There are basically two types of studies that evaluate the risk of carcinoma developing following diagnosis of DCIS: those in which biopsies were initially diagnosed as benign but that were on subsequent review (1–5) rediagnosed as DCIS and those in which patients were diagnosed with and treated for DCIS (6–20). In the former studies (1–5), further carcinoma is reported in 20–70% of the patients, with 14–60% developing invasive carcinoma. In the latter group (6–20), further carcinoma is reported in 1–22% of patients, with 2–9% developing invasive carcinoma. Following local excision alone, carcinoma was reported in 7–22% of patients, with invasive carcinoma in 2–16% (6–12). After local
excision with adjuvant radiotherapy, carcinoma was reported in 1–25% of patients. Invasive carcinoma was reported in 2–23% of patients (6,7,13,14,16–20). Following mastectomy, only invasive carcinoma was reported in 0–4% of patients (7,9,10,15).

Our event rates are comparable to those reported by others. Recurrence of DCIS or development of invasive carcinoma may reflect inadequate treatment (i.e., residual DCIS) or DCIS as a risk factor for the remainder of the breast tissue. Although one might postulate that invasive carcinoma develops from DCIS, none of the five contralateral invasive carcinomas that developed had DCIS detected previously in that breast; all of the contralateral invasive carcinomas were in patients for whom lumpectomy alone was the primary therapy.

Treatment

Carcinoma may develop many years after initial diagnosis of DCIS; thus, long follow-up is necessary. Our study patients have an intermediate length of follow-up (median 5.0 years for patients with lumpectomy and 6.7 years for mastectomy). To date, there has been little recurrence of DCIS or development of invasive disease in patients who underwent adjuvant radiotherapy or mastectomy despite our finding that more aggressive therapeutic modalities tended to be chosen for patients with more extensive DCIS, with grade 3 DCIS or confluent necrosis.

Clinical Factors

Recent evidence suggests that patients who present with clinical symptoms are at greater risk for development of carcinoma than those who are asymptomatic and are detected mammographically (12,20). We found that clinical presentation, especially with bloody nipple discharge, was associated with an increased risk of recurrent DCIS (multivariately, p = 0.07 in patients who underwent lumpectomy alone and p = 0.05 in the full DCIS cohort). We did not find a significant association between presentation and the development of invasive carcinoma for those who underwent mastectomy alone. However, in the full cohort, there was weak univariate evidence that patients under 40 were more likely to develop invasive breast carcinoma (p = 0.08); this was restricted to patients who presented clinically, 3 of 5
(60%) of who developed invasive carcinoma. Nipple discharge might reflect DCIS more centrally in the breast, affecting the completeness of excision; galactography was not performed for the patients in this study. In the group of patients with mammographically detected lesions, we found a significant association with age: Older patients were less likely to have DCIS recurrence than younger patients (p = 0.07), and our patients ≥65 years of age had no DCIS recurrence.

### Histologic Factors

Nuclear grade, architecture, necrosis, size, and resection margins, either independently or in combination, are the histologic factors most frequently assessed for DCIS (28), but these factors have not been found to be consistently important in the literature. Lagios et al. found that in mammographically detected DCIS treated with local excision only, nuclear grade identified subsets of DCIS more likely to recur locally (11). Fisher et al., found that nuclear grade, comedo necrosis, margin status, and histologic type were associated with an increased risk of recurrence in univariate analysis, but only comedo necrosis and margin were significant by multivariate analysis (6). Solin et al. found the combination of nuclear grade 3 with comedo architecture to be significantly associated with recurrence by univariate and multivariate analysis (16). Sneige et al. found necrosis and the combination of periductal fibrosis and method of tumor detection to be the only factors significantly associated with recurrence (19). Silverstein et al. combined nuclear grade and necrosis to define groups of DCIS with different recurrent risks and proposed combining this grouping with tumor size and margin width to define a prognostic index, the Van Nuys Prognostic Index (13,14); recently, this group has found that margin width is the most important factor (29).

We found no evidence of an association between architecture of DCIS, or necrosis, and prognosis. There was no evidence here in the two investigational subgroups of an effect of nuclear grade on recurrence of DCIS; however, in the full cohort, there was weak evidence (p = 0.15) that a higher predominant grade was associated with a greater development of invasive cancer. We observed considerable heterogeneity in both the architectural patterns and the nuclear grades of DCIS, present in the same biopsy. We attempted to capture this by evaluating both the “predominant” as well as the “worst” feature present. Heterogeneity in architecture has been reported (28,30). Usually, the architecture assigned is the dominant pattern, but sometimes the worst (comedo) is used (19). Heterogeneity in nuclear grade has usually been handled by grading according to the worst grade present (6,12,19,29). Interobserver variation in assigning grade, architecture, and necrosis has been reported as common (30). Others have found reproducibility in assigning grade, and architecture can be achieved through common use of criteria (31).

With 50% (62 of 124) of our DCIS patients exhibiting more than one nuclear grade, the degree of observed heterogeneity was such that grading categories could not be uniquely separated. Thus, a lack of significant result may be attributed to the effects of heterogeneity on classifying grade, either as predominant or worst.

DCIS is generally unifocal but may be extensive (32,33). Growth pattern has been related to nuclear grade with poorly differentiated DCIS tending to have a continuous growth pattern, whereas well-differentiated DCIS tended to have a discontinuous growth pattern (32). We did not do a stereoscopic study of growth pattern, but our assessment of percentage parenchymal pattern does give some reflection of growth. We previously reported (22) that the 88 patients who underwent lumpectomy alone had

| Table 5. Cox Stepwise Model for DCIS Recurrence |
|-----------------------------------------------|
| Factor                                         | $\hat{b}$/S.E.$^1$ | p value | Model improvement$^2$ | p value$^2$ |
| All presentations (patients underwent lumpectomy alone) | 1.84          | 0.07    | 3.25               | 0.07       |
| Involved parenchyma                             | -1.82         | 0.07    | 2.98               | 0.08       |
| Mammographic presentation (after stratification by treatment: lumpectomy alone versus lumpectomy + adjuvant radiotherapy/mastectomy) | 1.83          | 0.07    | 4.38               | 0.04       |
| Age                                           | 1.71          | 0.08    | 3.47               | 0.06       |

$^1$The standardized coefficients, $\hat{b}$/S.E., permit a comparison of the potential effects across factors. A positive/negative coefficient suggests a positive/negative effect for larger values of the factor on DCIS recurrence and time to this (i.e., less DCIS recurrence with more parenchymal involvement; more, with clinical presentation, especially nipple discharge; less, with older age).

$^2$Based on likelihood ratio criterion test, $-2\log R^2\chi^2$. 

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significantly more recurrence of DCIS when there was less parenchymal involvement, that is, a lower concentration of involved ducts. That result was repeated in this study, with patients who had mammographically detected DCIS (p = 0.08), and is also found with patients in the full DCIS cohort (p = 0.05). We postulate that a low percentage of parenchymal involvement is associated with an increased risk of recurrent DCIS as a result of difficulty in determining the full extent of the lesion and, hence, difficulty in ensuring complete excision. Although we postulate that duct distribution may affect adequacy of resection, we did not observe an association between duct distribution and resection margin; this may reflect the requirement for different margins, depending on the pattern of ductal involvement. We also did not see any evidence of an association between percentage parenchymal involvement and nuclear grade.

Like the NSABP B-17 trial (26,34), we observed the development of invasive breast cancer outside of the ipsilateral breast. There was inadequate power to consider the effects of factors on ipsilateral and contralateral invasive events separately in this study; however, consideration of patients who underwent lumpectomy alone or stratification in the mammographically detected DCIS by therapeutic modalities with similar event rates (lumpectomy alone versus the two modalities with similar event rates, lumpectomy followed by adjuvant radiotherapy and mastectomy) also stratified by contralateral invasive events, as they all occurred in patients who underwent lumpectomy alone. It is unclear whether differences in development of contralateral invasive breast cancer will be maintained with longer follow-up or whether they reflect our particular group of patients. The recent results from the B-17 trial (34) indicated a 3% development of contralateral breast carcinoma in patients who underwent lumpectomy alone and a 5% rate for those who received lumpectomy and adjuvant radiotherapy at 8 years of follow-up. None of the factors associated with recurrence of DCIS appeared important in the development of invasive carcinoma. In our series of patients, the only factor with a significant effect on invasive carcinoma was margin size, and the result was paradoxical in that there was a greater development with larger margins. This unanticipated finding might result from margin size being a surrogate for some other factor, from the small number of patients with margins >5 mm, or from analysis after an intermediate length of follow-up. At 8 years in the B-17 trial (34), there was weak evidence of an effect for DCIS margins on the occurrence of second ipsilateral breast tumors. Meanwhile, margin width has continued to be a dominant predictor of ipsilateral DCIS recurrence and the development of ipsilateral invasive breast cancer in the patient series of Silverstein et al. (29,35,36).

In conclusion, it appears that a number of factors affect prognosis of a patient with DCIS. The study of factors in a clinical context requires careful control of patient selection. We restricted patient accrual to be DCIS patients without previous carcinoma, looked for potential confounding effects of factors by clinical allocation to treatment, included pathological examinations of heterogeneity by nuclear grade and architecture, and examined the effects of factors for distinct presentations of DCIS (mammographic versus clinical). Our study size with 124 DCIS patients is relatively large; the median follow-up exceeding 5 years is intermediate in length, but the number of events limited subgroup analyses and stratifications by clinical and histopathologic factors.

With our group of patients, the effects of treatment modalities (both surgical procedure and adjuvant therapy) were dominant, as was the effect of microscopic calcification for patients whose DCIS was detected mammographically. A lower percentage of parenchyma involved with ducts was associated with increased DCIS recurrence; this is likely due to greater difficulty in adequately determining and excising all of the DCIS. It may be worthwhile to consider the amount of parenchymal involvement in other investigations. Differentiation of DCIS, as reflected in nuclear grade and architecture, did not affect significantly recurrence of DCIS or the development of invasive carcinoma; an effect may have been masked by treatment or extensive heterogeneity of nuclear grade. Age influenced the amount of DCIS recurrence for patients whose disease was detected mammographically. Older patients were less likely to have recurrent DCIS, and the 17 patients who were ≥65 years experienced no recurrence. Patients under 40 were more likely to develop invasive disease, especially if they presented with bloody nipple discharge.

Both unnecessary overtreatment as well as undertreatment of patients should be avoided. For DCIS patients, the aim is to delineate patients who are good candidates for lumpectomy alone from those who should receive adjuvant radiotherapy or mastectomy. Recurrence of DCIS may not be a good surrogate for eventual development of invasive disease, so the two end points were considered separately. Longer follow-up
with the occurrence of more events will allow more detailed evaluation of the prognostic relevance of the factors assessed, especially for particular subgroups. We plan a further update and investigation of this group of patients to effect this.

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