Relationship Between the Size and Margin Status of Ductal Carcinoma In Situ of the Breast and Residual Disease

Liang Cheng, Nadia K, Al-Kaisi, Nahida H. Gordon, Alison Y. Liu, Fadi Gebrail, Robert R. Shenk*

Background: For women with ductal carcinoma in situ (DCIS) of the breast who have been treated with breast-conserving surgery, the usefulness of size and surgical margin status (i.e., presence or absence of disease at the point of excision) as prognostic factors for predicting residual disease has not been well established. This study was conducted to determine more clearly the relationship between size and margin status of mammary DCIS to residual disease.

Methods: The pathology records of 232 consecutive patients with mammary DCIS who had been initially treated with lumpectomy at the University Hospitals of Cleveland were retrospectively reviewed. The size of the DCIS and the surgical margins of lumpectomy were analyzed. Residual disease was defined as the persistence of DCIS in the re-excision and/or mastectomy specimens.

Results: Residual disease was found in 15 of 101 patients with DCIS of less than 1.0 cm in longest dimension, in 27 of 96 patients with DCIS of 1.0–2.4 cm in size, and in 24 of 35 patients with DCIS of greater than or equal to 2.5 cm in size (P<.001). Residual disease was found in 30 of 77 patients with DCIS and positive margins, in 11 of 59 patients with DCIS and close margins (<1 mm), and in 10 of 73 patients with DCIS and negative margins (>1 mm) (P = .0001). In multivariate analysis, the occurrence of residual disease was associated with large tumor size (i.e., ≥2.5 cm) (odds ratio [OR] = 7.75; 95% confidence interval [CI] = 3.13–20.00; two-sided P = .0001) and with positive margin status (OR = 2.22; 95% CI = 1.02–4.55; two-sided P = .04).

Conclusions: The size and margin status of DCIS each were found to be independent predictors of residual disease. [J Natl Cancer Inst 1997;89:1356–60]
results with interobserver variability of less than 10%. The largest dimension of DCIS was used in the final analysis. Residual disease was defined as the persistence of DCIS in the re-excision and/or mastectomy specimens.

**Statistical analysis.** The relationship between residual disease (0 = absent; 1 = present) and several clinicopathologic characteristics was examined. The chi-squared test was utilized to describe the association of residual disease with tumor characteristics. The odds ratio (OR) and its 95% confidence interval (CI) for the relationship of residual disease to the clinical presentation (0 = palpable mass; 1 = mammographic detection), race (0 = white; 1 = black), age, size (0 to <2.5 cm; 1 to \(\geq2.5\) cm), and margin status (0 = negative or close margins; 1 = positive margins) were also utilized. Significance levels for ORs were evaluated by use of the Wald-\(P\) chi-squared statistic. An OR with a 95% CI that does not include 1 denotes a statistically significant relationship. Multivariate analysis of the relationship of residual disease and other clinicopathologic features was performed by use of logistic regression.

**Results**

Residual disease was present in a total of 66 (28%) of 232 cases. Residual DCIS was observed at the previous excision site in the majority of patients for whom these data were available. The mean length of the largest dimension of DCIS was 1.4 cm (range, 0.3–5.4 cm). Residual disease was found in 15 (15%) of 101 DCIS lesions that were less than 1.0 cm in longest dimension, 27 (28%) of 96 lesions that were 1.0–2.4 cm in size, and 24 (69%) of 35 lesions that were greater than or equal to 2.5 cm in size (\(P<.001\)) (Table 1). The margins were positive in 77 (37%) patients, close in 59 (28%) patients, and negative in 73 (35%) patients. The margin status in the remaining 23 patients (all diagnosed prior to 1985) was indeterminate or unknown. Residual disease was found in 15 (65%) of 23 of these patients. Among patients with known margin status, residual disease was found in 30 (39%) of 77 patients who had DCIS with positive margins, 11 (19%) of 59 patients who had DCIS with close margins, and 10 (14%) of 73 patients who had DCIS with negative margins (Table 1). The increase in the patient’s risk of residual disease when the margins were positive for DCIS was statistically significant (overall \(P = .001\)). The presence of close margins in biopsy specimens was associated with a slightly higher but not a statistically significant increase in risk of residual disease (19% versus 14% for negative margins, \(P=.3\)). Residual disease increased in frequency with increasing tumor size (Fig. 2, A). In addition, tumor size correlated significantly with margin status (Fig. 2, B). Seventy-seven percent of patients with DCIS of greater than or equal to 2.5 cm in size had positive margins at initial biopsy versus 30% of patients with DCIS of less than 2.5 cm (\(P<.001\)).

In the multivariate analysis, the finding of residual disease was significantly associated with large size of DCIS (\(P = .0001\)) and positive margins (\(P = .04\)). Patients with DCIS of greater than or equal to 2.5 cm in size had an OR of 7.7 (95% CI = 3.13–20.00) for residual disease compared with patients with DCIS of less than 2.5 cm. If we control for the size of DCIS, patients with positive margins in lumpectomy specimens had an OR for risk of residual disease of 2.2 (95% CI = 1.02–4.55) compared with those with negative or close margins. Fig. 3 illustrates that 29 (46%) of 63 patients with DCIS of greater than or equal to 1.0 cm with positive margins had residual disease compared with eight (23%) of 35 patients with DCIS of greater than or equal to 1.0 cm with close margins and five (26%) of 19 patients with DCIS of greater than or equal to 1.0 cm with negative margins. Among patients with small DCIS (<1.0 cm), residual disease was found in two (14%) of 14 patients with positive margins, in two (8%) of 24 patients with close margins, and in three (5%) of 54 patients with negative margins. Age, race (black versus white), and clinical presentations (palpable mass versus mass detected mammographically) were not signifi-

**Table 1.** Association of histologic size and margin status of mammary ductal carcinoma in situ with residual disease

<table>
<thead>
<tr>
<th>Tumor size, cm</th>
<th>No. of patients</th>
<th>Residual disease</th>
<th>(P^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.0</td>
<td>101</td>
<td>15 (15%)</td>
<td>86 (85%)</td>
</tr>
<tr>
<td>1.0–2.4</td>
<td>96</td>
<td>27 (28%)</td>
<td>69 (72%)</td>
</tr>
<tr>
<td>(\geq2.5)</td>
<td>35</td>
<td>24 (69%)</td>
<td>11 (31%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Margin status</th>
<th>No. of patients</th>
<th>Residual disease</th>
<th>(P^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>73</td>
<td>10 (14%)</td>
<td>63 (86%)</td>
</tr>
<tr>
<td>Close</td>
<td>59</td>
<td>11 (19%)</td>
<td>48 (81%)</td>
</tr>
<tr>
<td>Positive</td>
<td>77</td>
<td>30 (39%)</td>
<td>47 (61%)</td>
</tr>
</tbody>
</table>

\(^a^\) Two-sided \(P\) value was obtained by chi-squared test.

\(^\dagger\) A positive margin was defined as tumor extending to the inked margins; a close margin is tumor \(\leq1\) mm from the inked margins; a negative margin is tumor >1 mm from the inked margins.
cantly associated with residual disease in the multivariate analysis.

Local recurrence of disease was seen in 10 (7%) of 142 patients during a mean follow-up period of 49 months. All of these 142 patients were initially treated conservatively with lumpectomy with or without re-excision. The mean interval from lumpectomy to recurrence was 77 months (range, 29–165 months; median, 67 months). Four of these patients had positive margins in the lumpectomy specimen, and three had close margins. The tumors ranged in size from 0.4 to 4.0 cm (mean, 2.0 cm). Half of these recurrences were invasive carcinomas. None of the patients who had mastectomy following lumpectomy developed local recurrence. Six patients died during the period of the study (four from lung cancer, one from congestive heart failure, and one from contralateral breast cancer).

Discussion

DCIS of the breast is a heterogeneous group of lesions with a wide spectrum of clinical and pathologic manifestations (2,17–21). The optimal treatment for DCIS is still controversial. The ultimate outcome of breast preservation in the treatment of DCIS is largely unknown. Multiple factors have to be considered when one is deciding upon the optimal treatment for a particular patient with mammary DCIS. It is evident that a subgroup of patients is at higher risk of local failure after breast-conserving surgery. Factors contributing to local failure are important considerations in selecting the appropriate therapeutic approach for mammary DCIS. Additional therapy such as postoperative radiation treatment or mastectomy may benefit patients who are at high risk for local failure.

Three-dimensional imaging of DCIS provides an accurate evaluation of the extent of DCIS in the mammary ducts (22). This technique, however, is difficult to apply to routinely processed surgical specimens. Since most DCIS lesions cannot be identified grossly with certainty, assessment of the extent of DCIS in routinely processed breast biopsy specimens is feasible utilizing the diagrammatic mapping of biopsy specimens. Our findings indicate that measurement of the DCIS size from the histologic slides in conjunction with margin status evaluation provides an accurate assessment of risk of residual disease. Lesions smaller than 1.0 cm in the longest dimension, accounting for 44% (101 of 232) of the patients with mammary DCIS in this study, had no residual DCIS. Patients with DCIS lesions that were greater than or equal to 2.5 cm in longest dimension had 28% risk of residual disease. The ability to predict residual disease is greatly improved by assessing the margin status in these patients. Thirty (39%) of 77 patients with positive margins had local failure versus 11 (19%) of 59 patients with close margins and 10 (14%) of 73 patients with negative margins. After we controlled for the tumor size, patients with positive margins had approximately twice the risk of residual disease than patients with negative or close margins. The risk of residual disease was higher in patients with positive margins than in patients with close margins (39% versus 19%), whereas there was only a marginal increase in risk of residual disease in patients with close mar-
gins compared with those with negative margins. The risk of residual disease in patients with close margins was only slightly higher than that in patients with negative margins (19% versus 14%, \(P > 0.3\)). In addition, there was a significant (\(P < 0.001\)) association between the extent of DCIS and positive margin status. At initial biopsy, 77% of large tumors (\(\geq 2.5\) cm) had positive surgical margins. Because of the small number of patients who received radiation therapy following lumpectomy, the role of adjuvant radiation therapy as a treatment modality cannot be assessed in this study.

Our findings support the important role of margin status assessment in local disease control in patients treated conservatively. Negative margins, however, will not guarantee complete excision of the DCIS, and local recurrence can still occur. A high percentage of patients had local recurrence of disease because of residual disease even when the margins of lumpectomy were clear (14,23–25). Additional risk factors, such as tumor size, should be considered in the assessment of risk of residual disease in patients treated with breast-conserving surgery. Our data indicate that both margin status and size of DCIS are important considerations in stratification of patients for different therapeutic options. The combination of DCIS size and surgical margin status identified a subgroup of patients with increased risk of local failure. More aggressive treatment may be appropriate in such patients. At present, there is general agreement on what constitutes a clear margin for invasive breast carcinomas (11). It is not clear, however, what constitutes a clear surgical margin for DCIS. Our study arbitrarily uses 1 mm as a clear margin for DCIS. Faverly et al. (22) have demonstrated skip lesions (i.e., areas of DCIS with intervening normal breast epithelial tissue) in low-grade DCIS. In addition, depending on the plane of sectioning, the distance between any two branches of the same duct involved by DCIS can exceed the distance designated as a clear margin. Therefore, residual DCIS may remain in the patient’s breast after surgery even when the “clear margin” exceeds 10 mm. The DCIS observed in the re-excision most likely represents DCIS that was incompletely removed by the initial excision rather than multicentric/multifocal DCIS or recurrent disease.

This hypothesis is supported by our findings and the findings of Silverstein et al. (23) who reported residual DCIS in the immediate vicinity of the previous biopsy/excision site in the majority of cases. Clearly, as Silverstein et al. (25) elegantly demonstrated, histopathologic features such as nuclear grade and presence of comedo-type necrosis are important prognostic factors that can influence the rate of recurrence of DCIS (25). Some evidence exists that these histopathologic features are not independent prognostic factors but rather that they define subsets of DCIS having different histopathologic, clinical, molecular, and biologic features (9,25). Further studies are necessary to clearly characterize these subsets of DCIS.

In summary, the size and the margin status of mammary DCIS are each independent, statistically significant factors predicting local failure. Small DCIS tumors (<1.0 cm) with negative margins carry a low risk of local failure and can be treated conservatively with lumpectomy. Large DCIS tumors (\(\geq 2.5\) cm) pose a particular risk of residual disease regardless of margin status, and additional adjuvant therapy may be necessary.

References

Cancer Incidence in a Population-Based Cohort of Patients Hospitalized With Diabetes Mellitus in Denmark

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Background: Diabetes has been associated with an increased risk of several cancers, notably cancers of the pancreas, liver, endometrium, and kidney. Since most previous studies have involved a limited sample size or focused on specific cancer sites, we conducted a comprehensive assessment of the risk of cancer in a nationwide cohort of diabetics in Denmark. Methods: Discharge records of 109,581 individuals hospitalized with a diagnosis of diabetes from 1977 through 1989 were linked with national cancer registry records through 1993. Standardized incidence ratios (SIRs) were calculated for specific cancer sites. Results: The SIRs for primary liver cancer were 4.0 (95% confidence interval [CI] = 3.5–4.6) in males and 2.1 (95% CI = 1.6–2.7) in females. These SIRs remained elevated with increasing years of follow-up and after exclusion of patients with reported risk factors (e.g., cirrhosis and hepatitis) or patients whose cancers were diagnosed at autopsy. Kidney cancer risk was also elevated, with SIRs of 1.4 (95% CI = 1.2–1.6) in males and 1.7 (95% CI = 1.4–1.9) in females. For both sexes combined, the SIR for pancreatic cancer was 2.1 (95% CI = 1.9–2.4), with a follow-up time of 1–4 years; this SIR declined to 1.3 (95% CI = 1.1–1.6) after 5–9 years of follow-up. Excess risks were also observed for biliary tract and endometrial cancers. The SIRs for kidney and endometrial cancers declined somewhat after exclusion of diabetics with reported obesity. Conclusions: Patients hospitalized with a diagnosis of diabetes appear to be at higher risk of developing cancers of the liver, biliary tract, pancreas, endometrium, and kidney. The elevated risks of endometrial and kidney cancers, however, may be confounded by obesity. [J Natl Cancer Inst 1997;89:1360–5]

Diabetes mellitus is a metabolic disease of two major subtypes that is characterized by abnormalities in the synthesis and cellular uptake of insulin, a critical hormonal regulator of glucose metabolism. In insulin-dependent diabetes mellitus (IDDM), insulin synthesis ceases as a result of the autoimmune destruction of insulin-producing pancreatic islet cells, which is thought to be triggered by an environmental factor (i.e., viral infection) primarily in individuals who are positive for the histocompatibility antigens HLA-DR3 and/or HLA-DR4 (1). In noninsulin dependent diabetes mellitus (NIDDM), pancreatic islet cells continue to secrete insulin, but target tissues (e.g., muscle and liver) are resistant to its uptake and use because of a decrease in the number of insulin receptors, alterations in postreceptor function, or the presence of blocking antibodies.

Elevated risks have been reported in diabetics for several cancers, notably cancers of the pancreas (2,3), liver (4–8), endometrium (5,8), and kidney (5,9). Most previous studies of cancer risk in diabetics have been based on a limited sample size, or they have focused on population subgroups or specific cancer sites. This study provides a comprehensive assessment of multiple cancer sites in a large population-based cohort of diabetics and was undertaken by linking computerized records from nationwide hospital and cancer registries in Denmark.

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