Predicting Residual Disease and Local Recurrence in Patients With Ductal Carcinoma In Situ

Melvin J. Silverstein*

There is an old real estate joke that goes like this. **Question:** What are the three most important factors to consider when buying a house? **Answer:** "Location, location, location!"

A form of this question might well be asked about patients with ductal carcinoma in situ (DCIS) of the breast. For example, what are the three most important factors for predicting local recurrence in patients with conservatively treated DCIS? Read on and I will give my answer.

The examination of serial tissue sections by Faverly et al. (1) and Holland et al. (2,3) revealed that DCIS is usually unicentric but commonly multifocal. In other words, it is generally confined to a single segment of the breast. It is often larger than expected, extending beyond mammographic microcalcifications, and skip areas (i.e., areas of DCIS with intervening normal breast epithelial tissue) are common. In spite of its extent, however, DCIS is a local disease, lacking the following two important components of the fully expressed malignant phenotype: invasion and metastasis. Therefore, complete excision will likely cure most patients. If complete excision cures the disease, how then does one accomplish this within the confines of obtaining an acceptable cosmetic result? Although there is no perfect tool, current data suggest that margin width is the best judge of complete excision.

In 1994, Faverly et al. (1) showed that 90% of DCIS lesions, regardless of their histologic type, were completely excised if all margins were 10 mm or more in dimension. Silverstein et al. reported in 1996 (4) and in 1997 (5) an 8% local recurrence rate for all conservatively treated DCIS lesions with margins of 10 mm or more. In 1997, Lagios and Silverstein (6) showed a 5% local recurrence rate at 84 months for conservatively treated patients with 10 mm or more margins, and the Nottingham Group (7) reported a 6% local recurrence rate among 48 patients with 10 mm or greater margins treated with excision only after a median follow-up of 58 months. These data clearly show the increasing importance given to wider margin width in the recent literature.

In this issue of the Journal, Cheng et al. (8) discuss the relationship between tumor size, margin status, and the probability of residual DCIS. I was particularly happy to read that most patients in their study had complete tissue processing with ink- ing of all surfaces, serial sectioning of all tissue at 3-mm intervals, and three-dimensional reconstruction by the pathologist. It is only with this type of thorough, meticulous evaluation that size and margin status can be accurately assessed.

The relationship between tumor size, margin status, and the probability of residual DCIS is extremely important, since residual disease leads to most local recurrences. With this study, Cheng et al. indirectly corroborate our previous conclusions that size and margin status are independent predictors of local recurrence (4,5). Since most local recurrences are at or near the original lesion and are often a product of inadequate surgical removal of the primary lesion, resulting in residual disease, the conclusion drawn in the report by Cheng et al. makes perfect sense and further supports existing data.

I do, however, have a problem with some of the methodology used in their study. Cheng et al. (8) properly defined residual disease as "the persistence of DCIS in the re-excision and/or mastectomy specimens." Therefore, for the determination of the presence of residual disease, each patient had to undergo an initial excision of the lesion followed by re-excision or mastectomy. Of the total of 232 patients, only 148 met these criteria and were evaluable for the presence of residual disease (90 patients subsequently treated with mastectomy and 58 subsequently treated with re-excision); 84 additional breast conservation patients had neither re-excision nor mastectomy (16 received radiation therapy following the original lumpectomy and 68 were treated with lumpectomy only), and, hence, they should not be included in the calculation of residual disease because their residual disease status is unknown.

When Cheng et al. state that only 28% of patients (66 of 232) had residual DCIS, they are underestimating the number of patients in whom DCIS was left behind. By including the 84 patients who had neither re-excision nor mastectomy as patients without residual DCIS, they dilute their results. The true estimate of residual disease should be derived from 66 patients with proven residual disease divided by 148, the number of patients who underwent re-excision or mastectomy and who were therefore evaluable for the presence of residual disease. By use of this calculation, the percentage of patients with residual DCIS is 45%, a number which matches more closely the one reported previously (9).

This methodology, using 232 patients as the number of evaluable patients, has been employed throughout the study, resulting

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*Correspondence to: Melvin J. Silverstein, M.D., The Van Nuys Breast Center, 14624 Sherman Way #600, Van Nuys, CA 91405. E-mail: Melsilver9@aol.com

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in an underestimation of the amount of residual disease in the analyses by tumor size and margin status [see Table 1 in (8)]. In each of these subgroups, I believe that the true percentage of residual disease for the various sizes and margin statuses is likely to be higher than that stated. In our own previously published data (9), we found residual disease in 76% of patients with initially involved margins (margins were scored as involved if DCIS was found less than 1 mm from the inked margins). Surprisingly, we found that 43% of patients with clear margins (all DCIS lesions 1 mm or more from the inked margin) had residual disease upon re-excision or mastectomy. A logistic regression analysis of our data revealed that, as margin width increased, the probability of local recurrence decreased and, at 10 mm or more, it was only about 5%–6% (10). It quickly became obvious to us that 1-mm margins, although clear by most definitions, were woefully inadequate when it came to complete removal of DCIS.

As mentioned previously, a few recent studies (5–7), in which 10-mm margins were achieved in every direction, have yielded extremely low local recurrence rates with or without additional radiation therapy. In December 1997, at the 20th Annual San Antonio Breast Cancer Symposium, my colleague Michael D. Lagios will present the updated results of our combined data analyzed by margin width and nuclear grade (11). Those data reveal that margin width is critical. The local recurrence rate increases as margin width decreases and nuclear grade increases. If, however, the margin width is 10 mm or more in every direction, the local recurrence rate is less than 11% for all categories studied, regardless of nuclear grade or whether or not postoperative radiation therapy was given.

In summary, the most likely cause of local recurrence after breast-conserving therapy for DCIS is inadequate surgery resulting in residual disease, e.g., a fractional persistence of the original lesion. DCIS is often larger than it appears on mammography, and pathologic skip areas are common. The narrower the margin, the more likely it is that there is residual disease. The gold standard for clear margins today is 10 mm; with larger lesions, however, this is more difficult to achieve.

Recently, I was talking to a real estate broker. She asked, ‘‘What are the three most important factors in DCIS recurrence?’ I didn’t have to think. ‘‘Margins, margins, margins!’’

References