

Perspectives on Margins in DCIS: Pathology

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Key Words

Carcinoma in situ, ductal carcinoma in situ, lobular carcinoma in situ, pathology, margins

Abstract

All breast carcinomas must originate within the ductal/lobular system as carcinoma in situ, but only a subset of these lesions progress to invasive carcinoma. Although pathologic evaluation of the extent of ductal carcinoma in situ (DCIS), the distance to margins, and the degree of margin involvement provides an estimation of the likelihood of residual disease, the amount of disease in the remaining breast cannot be predicted with certainty. Factors other than residual disease may be more important in determining whether patients with DCIS survive or succumb to breast cancer, including biologically new ipsilateral cancers, contralateral cancers, and the degree of resistance of the normal stroma to invasion. (*JNCCN* 2010;8:1219–1222)

All epithelial cells in the breast are enclosed within a basement membrane surrounding the ducts and lobules. Because the first malignant epithelial cells arise within this compartment, by definition all primary breast cancer must begin confined to the ducts and lobules or as carcinoma in situ (CIS). However, for women undergoing mammographic screening, most cancers (70%–80%) are detected only after the basement membrane has been breached and an invasive carcinoma is present. Thus, the preceding CIS in these cases was undetectable by current imaging modalities. In most cases,

CIS is present surrounding the invasive carcinoma but was not detected with mammography because the characteristics that produce a radiologic finding are not present (i.e., calcifications or a stromal response creating an area of density). In a small subset of invasive carcinomas, the associated CIS is not apparent on imaging because it is very scant or only present within the area of the invasive carcinoma. This is particularly true for carcinomas lacking hormone receptors and HER2/neu expression (triple-negative cancers, including basal-like cancers).^{1,2} These cancers may have a short in situ phase with early breach of the basement membrane, and a small in situ component may be overgrown by the invasive carcinoma.

The 20% to 30% of cases of breast cancer detected as CIS (predominantly ductal carcinoma in situ [DCIS], with fewer women with lobular carcinoma in situ [LCIS]) are likely to have biologic differences when compared with CIS associated with invasive carcinoma, because not all untreated cases progress to invasive carcinoma, even with long-term follow-up.^{3,4} However, because some patients with DCIS develop invasive carcinomas in the area of the prior DCIS, and because a few of these women will develop distant metastases, surgical eradication of DCIS is recommended.

Mastectomy removes the entire involved ductal system in most patients and is very effective in preventing subsequent invasive carcinomas; only 1% to 2% of women treated in this manner will die of breast cancer. The rare failures are from residual disease not being removed (occasionally ducts can be present in subcutaneous fat of the chest wall or extend into the axilla) or from an undetected invasive carcinoma at surgery.

However, many women would prefer breast conservation therapy if the risk of future cancer is low enough. Ideally, surgical treatment for DCIS would remove the entire affected ductal system. However, there are many

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difficulties in achieving this goal. Imaging is not always reliable, because although it may show a portion of the DCIS, the true extent of the disease in the breast is often much greater. In addition, DCIS is rarely palpable or visible at surgery. The distribution of ductal systems in the breast does not follow any regular pattern. Few ductal systems are confined to a single quadrant, and in some cases ducts can branch and ramify in 2 widely separate areas of the breast. Thus without radiologic, visual, or palpable guidance, surgeons must make an educated guess as to where and how much tissue to remove. After removal, the surgeon should orient the specimen and mark the location of margins. This is important to help guide additional surgery and identify areas in which the breast tissue has been entirely removed (i.e., chest wall, subcutaneous tissue).

The pathologic evaluation of these specimens is also challenging for the same reasons. The presence or absence of DCIS can only be determined with certainty once the tissue is observed under the microscope. Breast specimens change shape after removal, and the surface is irregular, often with deep clefts in the adipose tissue.^{5,6} Although the surfaces can be marked with ink, the ink may leak into these clefts, making identification of the true margin difficult. Cautery and crush artifact can make it impossible to distinguish DCIS from atypical ductal hyperplasia, or even hyperplasia without atypia. Complete sampling of specimens can require many blocks and may not be practical in all cases. Because DCIS can involve ducts smaller than 1 mm, multiple levels on each block would be necessary to find every involved duct. Pathologists should, nevertheless, report an estimation of the extent of DCIS, the distance from margins, and the extent of margin involvement when possible.⁷ However, even if the exact distribution of all DCIS in a specimen could be mapped out and the distance to each margin measured accurately, correctly predicting whether residual DCIS remains in the breast would still be impossible for at least the following 3 reasons: limited extent of ductal systems, gaps, and atypical ductal hyperplasia.

Limited Extent of Ductal Systems

The ducts and lobules generally do not extend into subcutaneous tissue of the skin and rarely, if ever, beyond the fascia of the pectoralis muscle. A close

or even positive margin for DCIS at the boundary between breast and skin or muscle may not be predictive of residual disease if the ductal system does not extend into these adjacent tissues. In addition, usually a rim of cautery is present in the biopsy cavity of the patient, which could eliminate a small area of residual cancer.

Gaps

In low-grade DCIS, gaps of up to 1 cm have been described.⁸ These are areas of intervening normal-appearing cells between areas of DCIS detected by careful microscopic examination of specimens. If a margin were to cross a gap, then it could appear negative.

Atypical Ductal Hyperplasia

Adjacent areas of atypical ductal hyperplasia, or even normal-appearing breast tissue, can share genetic changes with DCIS.⁹ Thus, removal of the entire area of cells with these changes may not be possible based on the histologic features of lesions at the margin.

The pathologic examination of the specimen provides a probability of residual disease based on the extent of the DCIS, the closeness to margins, and the extent of DCIS at or close to the margins. Many different ways of evaluating margins have been proposed, all of which provide greater or lesser probabilities of finding additional disease.⁷ Positive margins (ink on DCIS) are associated with a higher probability of residual disease than margins that are negative by some distance. However, studies attempting to completely remove DCIS with surgery and wide margins without radiation have not been successful at eliminating the risk of recurrent carcinoma.^{10,11} In a recent study, the average size of low/intermediate-grade DCIS was only 0.6 cm (more commonly DCIS is 2 to 3 cm in extent) and about half of the patients had margins greater than 10 mm.¹⁰ However, at 7 years the ipsilateral recurrence rate was 10.5%. In addition, no difference was seen in the rate of local recurrence whether the margins were greater or smaller than 10 mm. Therefore, even in this very carefully selected and rigorously evaluated patient population, the width of the margin, as long as the margins were not positive, did not seem to be important.

It is useful to consider what a recurrent cancer in the same breast might represent. A subsequent cancer is not always the same malignant clone as the first cancer, and this is a crucial distinction when determining the best preventative local treatment. For invasive carcinomas, studies have shown that a third of ipsilateral recurrences are actually new cancers¹² and that some ipsilateral recurrences of invasive carcinoma after DCIS are new cancers.¹³ In these studies, morphologic comparisons could not reliably make this distinction; additional larger studies of recurrent cancer after DCIS would be helpful. In the study previously discussed, the 7-year rate of contralateral breast cancer was 4.8%, or almost half that of ipsilateral breast cancer.¹⁰ If the rate of unrelated cancers in the opposite breast is the same as those in the same breast, then approximately half of the ipsilateral recurrences could be biologically new cancers.

The greater effectiveness of radiation, tamoxifen, and mastectomy over breast-conserving surgery alone may arise from the fact that these modalities treat the entire breast, and not just the one involved ductal system. Efforts to lower the recurrence rate through even more detailed attention to margins or larger margins may be a futile quest.

Ultimately, the most important end point is mortality. Women with treated DCIS who die of breast cancer are uncommon—fewer than 2% in most studies. SEER data show that women with DCIS actually have a better overall survival than those without breast cancer.¹⁴ Although this may be attributed partly to better medical care, it is difficult to improve the outcome in a group with such a favorable prognosis. Surprisingly few details have been published about the small number of events that the efforts toward detection and treatment of DCIS are attempting to prevent.

A greater understanding of why DCIS can lead to death, as opposed to local recurrences that lead to more treatment but not necessarily improved outcomes, should be possible through learning more about these women. For example, do women die of ipsilateral or contralateral cancer? In large trials, 20% to 30% of subsequent invasive carcinomas are contralateral.^{15–19} Certain subtypes of DCIS that are more likely to progress to a type of invasive carcinoma that would cause death may also be able to be identified.²⁰ Triple-negative DCIS and HER2/neu-

positive DCIS, constituting fewer than 15% of all cases of DCIS, would be candidates. However, the difference between women with DCIS who do not die of breast cancer and those who do may have more to do with the patient than the cancer. It is remarkable that in some women DCIS can be very extensive and present in all 4 quadrants of the breast without invasion, whereas in other women it progresses to invasion when still very limited. The answer may lie in the patient's stroma rather than in the cancer. Perhaps stromal factors help maintain the basement membrane intact for longer periods and prevent DCIS from becoming invasive carcinoma.²¹

It is an important goal to reduce the likelihood of local recurrences by attempting to eradicate DCIS with surgery and to continue to evaluate the completeness of the surgery through margin evaluation. However, margin status and the molecular analysis of DCIS may only address one aspect of a patient's risk for subsequent disease. In many cases, new cancers and a patient's own stroma may ultimately determine the fate of women with DCIS.

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