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Local Outcomes in Ductal Carcinoma In Situ Based on Patient and Tumor Characteristics

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The term ductal carcinoma in situ (DCIS) encompasses a heterogeneous group of lesions that differ in their clinical behavior. Clinical factors such as symptomatic presentation and young age are associated with an increased risk of local recurrence in patients with DCIS managed with breast-conserving therapy. Treatment factors such as wider surgical margins, the use of radiation therapy, and the use of tamoxifen reduce the local recurrence risk. Pathological characteristics such as larger lesion size, high nuclear grade, comedo necrosis, and involved margins are associated with an increased risk of local recurrence in many studies. However, there are complex interactions between these pathological risk factors and other parameters such as treatment and length of follow-up. In fact, the magnitude of the effect of these pathological features on local recurrence risk is modified by these other factors. Analysis of genetic and molecular alterations as well as study of the microenvironment associated with DCIS are important avenues of research that may provide new insights into DCIS recurrence and progression risk, and this in turn may lead to new strategies for treatment and prevention.

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Ductal carcinoma in situ (DCIS) is a lesion of the breast in which the neoplastic epithelial cells are confined to the mammary ductal–lobular system without light microscopic evidence of invasion into the surrounding stroma. As such, DCIS is best considered a breast cancer precursor rather than breast cancer per se, and the major goal in the management of these patients is to prevent the development of an invasive breast cancer.

It is now well recognized that DCIS is not one disease. Rather, this term encompasses a heterogeneous group of lesions that vary in their clinical presentation, distribution in the breast, pathological features, biomarker expression, genetic and molecular alterations, and biological potential (1–3). Given this heterogeneity, there is considerable controversy regarding how best to manage patients with DCIS. Mastectomy cures almost all patients but represents overtreatment for many women, particularly those with small lesions detected by mammography. The results of four randomized clinical trials comparing breast-conserving surgery and radiation therapy with breast-conserving surgery alone have demonstrated that radiation therapy reduces the risk of recurrence in the ipsilateral breast (local recurrence) by approximately 50% (4–7). However, it is likely that not all patients with DCIS require radiation following breast-conserving surgery.

Understanding factors associated with local recurrence following a diagnosis of DCIS is important for several reasons: 1) to identify patients at high risk of recurrence or progression to invasive breast cancer who are unsuitable candidates for breast-conserving treatment and who are better served by mastectomy; 2) to identify patients at low risk of such events who could be spared radiation therapy and be adequately treated by breast-conserving surgery alone; and 3) to identify patients in whom the risk of recurrence or progression to invasive breast cancer is so low that they can simply be observed following a diagnostic biopsy (analogous to the "watchful waiting" approach for the management of some men with prostate cancer).

Unfortunately, at the present time, our ability to distinguish those DCIS lesions likely to recur or progress to invasive breast cancer from those that are not is limited, despite more than two decades of research addressing this important clinical issue. The purpose of this article was to review our current understanding of risk factors for local recurrence in patients with DCIS treated with breast-conserving therapy, with an emphasis on pathological risk factors; clinical and treatment factors are discussed in detail in other articles in this monograph. Moreover, several limitations of the available data on pathological risk factors for local recurrence will be emphasized.

Overview

Local recurrences in patients with DCIS treated with breast-conserving therapy may consist of either DCIS or invasive breast cancer and, in most studies, these events have been observed in approximately equal proportions (8). The results of the various studies that have examined risk factors for local recurrence are often difficult to compare because of differences in such factors as study design; patient selection and eligibility for inclusion; extent of breast-conserving surgery; details of radiation therapy (where applicable); extent of tissue sampling; rigor of specimen margin evaluation; definitions of positive, negative, and close margins; number of local recurrences; length of follow-up; and statistical methods. Despite these limitations, a number of clinical factors, treatment factors, and tumor characteristics have been reported to be associated with recurrence of DCIS and/or progression to invasive breast cancer following breast-conserving therapy.

Clinical Factors

The major clinical factors associated with an increased risk of local recurrence following breast-conserving treatment for DCIS are symptomatic presentation and young patient age at diagnosis, although the definition of "young" has not been uniform across studies (3,6,9–12).

Treatment Factors

As noted earlier, the use of radiation therapy following breast-conserving surgery is associated with about 50% reduction in the risk of local recurrence (4–7). In one prospective randomized trial, the addition of tamoxifen further reduced the local recurrence risk among patients treated with excision and radiation therapy (13). A similar beneficial effect of tamoxifen was not seen in another randomized trial; however, the design of that trial makes it somewhat difficult to assess the impact of tamoxifen on local recurrence (5). The impact of treatment factors on outcome of patients with DCIS is reviewed in detail in other articles in this monograph.

Pathological Factors

Both retrospective and prospective studies have identified various pathological factors associated with an increased risk of local recurrence following breast-conserving therapy for DCIS. The features that have been the most consistently reported to be associated with a higher risk of local recurrence are high nuclear grade, comedo necrosis, larger tumor size, and involved margins of excision (1–3,8). However, the magnitude of the effect of these factors on local recurrence risk and their relative importance as risk factors has varied among these studies (3).

There are several points regarding these pathological factors that are frequently overlooked. First, their impact on local recurrence needs to be viewed in the context of other factors such as the use of radiation therapy, the extent of surgical excision, and the length of follow-up. Second, combinations of pathological factors are likely to be more important in defining the level of the risk of local recurrence than individual factors. Third, the importance of these factors in predicting noninvasive vs invasive local recurrences has not yet been well defined. Each of these issues will be discussed individually.

Interaction of Pathological Risk Factors for Local Recurrence With Other Factors

The impact of pathological factors on the risk of local recurrence in patients with DCIS varies according to several treatment factors as well as length of follow-up. This point is emphasized by the following examples. First, the results of the pathological analysis from the National Surgical Adjuvant Breast Project (NSABP) B17 trial have been widely cited as indicating that the presence of moderate or marked comedo necrosis in DCIS is associated with a high risk of local recurrence. However, in that trial moderate or marked comedo necrosis was significantly associated with an increased risk of local recurrence only among patients treated with excision alone. In that group of patients, local recurrence rates at 8 years were 40% for those with moderate or marked comedo necrosis compared with 23% for those with absent or slight comedo necrosis. In contrast, among patients treated with the combination of excision and radiation therapy, local recurrence rates were similar for those with absent or slight comedo necrosis and for those with moderate or marked comedo necrosis (13% and 14%, respectively) (4). Thus, the impact of comedo necrosis on risk of local recurrence appears to vary with the use of radiation therapy.

In a second example, data published by Silverstein et al. (14) have indicated that DCIS size, grade, and margin status are all significantly related to the risk of local recurrence. However, the Silverstein group has also reported that for patients with DCIS who undergo surgical excision with margin widths of 10 mm or more, the risk of local recurrence is unaffected by nuclear grade, the presence of comedo necrosis, lesion size, and the addition of radiation therapy. In contrast, these factors remain significant predictors of local recurrence in patients with small margin widths (15).

Finally, the impact of DCIS grade on local recurrence risk appears to be related to the length of follow-up, as emphasized by the results of the study of Solin et al. (16). In that study, patients whose DCIS showed the combination of comedo architecture and grade 3 nuclei had a significantly higher 5-year local recurrence rate after breast-conserving surgery and radiation therapy than patients whose DCIS did not show this combination of features (11% vs 2%, respectively; $P = .009$). However, at 10 years, this difference was no longer statistically significant (18% vs 15%, respectively; $P = .15$). Early results from the prospective nonrandomized Eastern Cooperative Oncology Group E5194 trial, which indicate that the ipsilateral breast tumor recurrence rate at 5 years is higher for high-grade DCIS (15.3%) than for low or intermediate grade DCIS (6.1%) treated with excision with at least a 3 mm margin should be viewed with this observation in mind (17).

Taken together, the results of these studies indicate that there are complex interactions between pathological factors and other factors in determining the risk of local recurrence and that pathological risk factors should not be viewed in isolation.

Combining Risk Factors for Local Recurrence

Among patients with invasive breast cancer, a variety of factors are routinely used to assess prognosis and to select the appropriate treatment. These include patient age, menopausal status, lymph node status, tumor size, histological grade, lymphovascular invasion and estrogen receptor, progesterone receptor, and HER2 status. Considering these factors in combination is of greater clinical value than viewing each alone, and the combined approach forms the basis of a number of schema used to group patients into various risk categories such as the St Gallen criteria (18,19), the National Institutes of Health consensus criteria (20), the Nottingham Prognostic Index (21), and Adjuvant!Online (www.adjuvantonline.com). More recently, gene expression signatures have been used in combination with these traditional factors to assess risk (22).

Based on the experience with invasive breast cancer, it is reasonable to conclude that considering risk factors for local recurrence in patients with DCIS in combination would be of more value than viewing each factor individually. In this regard, Silverstein et al. (14) in 1996 proposed that lesion size, grade, and margin status be considered in combination to assess prognosis and to select therapy for patients with DCIS (the Van Nuys

Prognostic Index [VNPI]). A more recent variation of this index also included age among the factors (University of Southern California [USC]-VNPI) (23). Although all of the factors included in the VNPI and USC-VNPI are important considerations in the selection of treatment options for patients with DCIS, their relative importance and the interactions among them are not well understood (24). Better methods are needed to quantify local recurrence risk and to communicate risk to patients with DCIS to assist in therapeutic decision making. Recently, a web-based nomogram was developed to help assess the risk of local recurrence in patients with invasive breast cancer (IBTR!) (25,26). A similar multiparametric tool to assess risk of local recurrence for patients with DCIS would be of great value.

Risk Factors for Noninvasive vs Invasive Local Recurrences

There is a general perception that the pathological risk factors for noninvasive and invasive local recurrences following breast-conserving therapy for DCIS are the same. However, few studies have directly addressed this issue primarily because the relatively small number of local recurrences in any given study population precludes analysis of factors that might differentially predict noninvasive and invasive local recurrences. Even the randomized clinical trials of breast-conserving therapy for DCIS do not have enough events to stratify patients by both type of treatment and type of local recurrence.

There are clues from the published literature that suggest that risk factors for recurrent DCIS and invasive local recurrence may not be identical. For example, in the European Organization for Research and Treatment of Cancer 10853 trial, nuclear grade was significantly associated with DCIS recurrence ($P = .006$) but not with invasive local recurrence ($P = .35$) (6). In a study by Kerlikowske et al. (27), factors significantly associated with recurrent DCIS included high and intermediate nuclear grade, larger lesion size, positive or uncertain margins, and poor cell polarity. In contrast, the only pathological factor associated with invasive local recurrence was high nuclear grade. Finally, Collins et al. (28) recently reported that among patients with DCIS treated with breast-conserving therapy, the presence of lobular carcinoma in situ in association with DCIS was associated with over a twofold risk of DCIS recurrence (relative risk = 2.3, 95% CI = 1.2 to 2.9) but was not significantly associated with invasive local recurrence (relative risk = 1.3, 95% CI = 0.7 to 2.6) . Taken together, these data suggest that risk factors for recurrent DCIS and invasive local recurrence may not be identical and that combining these events into a single group for the purposes of analysis may obscure important differences between them. This also suggests that the biological basis for noninvasive and invasive local recurrences may well differ.

Newer Risk Factors for Local Recurrence

The identification of biological markers that predict the outcome of patients with DCIS is an area of active investigation (1,2,29,30). However, the level of expression of many biomarkers that have been studied in DCIS is highly correlated with grade (eg, estrogen receptor with low-grade lesions; HER2, p53, and high Ki67 proliferation rate with high-grade lesions), and there is a pressing need to identify biomarkers that predict local recurrence and progression to invasive breast cancer independent of standard prognostic markers such as grade and margin status. The results of a recent case–control study suggested that among women with DCIS treated by excision alone, lesions that are detected as palpable masses and that are also triple positive for p16, Cyclooxygenase-2, and Ki67 have a significantly higher rate of progression to invasive breast cancer than those that are detected by mammography and are negative for these three biomarkers (8-year risks of subsequent invasive cancer 19.6% and 4.1%, respectively) (31). However, the results of this retrospective study should be considered hypothesis generating and need to be confirmed in additional patient cohorts before being considered ready for clinical use. Currently, the only biomarker used in clinical practice to help manage patients with DCIS is estrogen receptor status. In an analysis of data from the NSABP B24 trial, designed to evaluate the role of tamoxifen in the treatment of patients with DCIS treated with breast-conserving surgery and radiation therapy, the use of tamoxifen was associated with a significantly reduced risk of local recurrence only in patients whose DCIS was estrogen receptor positive (32). Therefore, testing DCIS for estrogen receptor is now routine practice.

Analysis of tumor heterogeneity, genetic alterations, gene expression signatures, and proteomic profiles as well as study of the microenvironment associated with DCIS are other important avenues of research that may provide new insights into DCIS recurrence and progression that may ultimately lead to novel treatment and prevention strategies (33–38).

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