Treatment of Ductal Carcinoma In Situ After Excision: Would a Prophylactic Paradigm Be More Appropriate?

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With increasing use of mammographic screening, the incidence of ductal carcinoma in situ (DCIS) has risen dramatically over the past 30 years (Figure 1). In the United States, the incidence of DCIS increased from 5.83 per 100,000 women in 1975 to 37.25 per 100,000 in 2009 (1). By 2013, approximately 64,640 new DCIS diagnoses will be made, representing approximately 22% of all new breast cancers (2). The extent of DCIS within the breast is the major determinant of surgical treatment options available to a patient. In contrast, postsurgical treatment decisions for DCIS depend on the extent to which DCIS should be considered a cancer itself rather than a precursor of invasive breast cancer, as well as a marker of future invasive cancer risk.

DCIS: A Cancer or a Precursor of Cancer?

The key feature distinguishing DCIS from invasive carcinoma is its location. By definition, DCIS is confined to the mammary ductal-lobular system, surrounded by a layer of basement membrane and myoepithelial cells. It is, therefore, incapable of spread to regional lymph nodes or metastasis to distant sites. The major goal in the management of DCIS is to reduce the risk of progression to invasive carcinoma. The available data suggest that without treatment, this risk is substantial. In one series of breast biopsies originally thought to be benign but in which DCIS was identified on retrospective review, invasive carcinoma developed in almost 40% of women, the majority diagnosed within 10 years (3). All cancers were located in the index breast and usually in the vicinity of the biopsy site. However, this series represented DCIS diagnoses presenting with a mass, and may not be representative of DCIS detected by screening mammography.

Indirect support for the hypothesis that DCIS is a precursor lesion for invasive cancer is also found from studies of breast cancers that have both an invasive and in situ component. One such study found that all cases with loss of heterozygosity of chromosome 11q13 in the DCIS component had the same loss in the invasive component (4). Another study found that the expression of tumor markers was almost identical in the DCIS and invasive components (5). Gene expression profiling has demonstrated that low-grade DCIS and low-grade invasive cancer have similar signatures, distinct from those of high-grade DCIS and high-grade invasive cancer (5–7). These studies suggest that the most dramatic changes in gene expression occur during the transition from normal epithelium to DCIS with many of the genetic alterations found in invasive cancer already present in DCIS.

Given that DCIS and invasive breast cancer are similar with respect to microscopic appearance of the cells, gene expression patterns, and genetic alterations, should patients with DCIS be told that they have breast cancer? Physicians vary widely in the terminology they use to present the diagnosis. Two-thirds report that they “always” or “almost always” refer to DCIS as cancer, whereas 21% “never” or “almost never” do (8). If cancer is defined as an abnormal growth of cells that proliferates uncontrollably, then DCIS fits the definition. However, “cancer” is not used to describe benign tumors, only malignant ones—those that have a tendency to spread to other sites of the body—which DCIS does not. Perhaps the label of “carcinoma” or “cancer” explains why the majority of DCIS patients greatly overestimate their risk of recurrence, with more than one-quarter incorrectly believing that there is at least a moderate likelihood of DCIS spreading to other places in their body (9). Indeed, the 2009 National Institutes of Health State-of-the-Science Conference recommended that “the medical community…consider eliminating the term ‘carcinoma’…as DCIS is by definition not invasive—a classic hallmark of cancer” (10). Instead,
it may be most appropriate to consider DCIS as a precursor of cancer: DCIS has the potential to progress to a potentially lethal breast cancer, but on its own carries no risk of spread or death.

**Adjuvant Treatment Options for DCIS**

Historically, DCIS was routinely treated with mastectomy; however, the use of breast-conserving therapy for DCIS has increased over time ([Figure 2](#)). No randomized trial has compared breast-conserving surgery with mastectomy for DCIS. Nevertheless, the excellent long-term prognosis following breast-conserving approaches for DCIS argues that any increased risk for development of breast cancer resulting from breast preservation is highly unlikely to affect survival (11).

“Adjuvant therapy” in oncology refers to treatment given after surgery with the intent of eradicating microscopic residual disease, thereby decreasing the risk of cancer recurrence and improving survival. For example, adjuvant treatments with radiation and systemic therapy following surgery for invasive breast cancer have been shown to improve overall survival (12,13). Applying this same adjuvant treatment paradigm, many DCIS patients are referred to medical and radiation oncologists after breast-conserving surgery to discuss further therapy aimed at reducing the risk of local recurrence, defined as subsequent DCIS or invasive carcinoma in the index breast.

Treatments after breast-conserving surgery for DCIS may include whole breast radiation therapy, systemic hormonal therapy, or both. Randomized trials have shown that radiation therapy after breast-conserving surgery for DCIS reduces the risk of second diagnosis (either new diagnosis or local recurrence) in the ipsilateral or index breast by about one-half (14–17). With or without radiation, half of local recurrences after an initial DCIS diagnosis are DCIS and the other half are invasive breast cancers (14–17). Tamoxifen, a selective estrogen-receptor modulator, administered after surgical therapy and radiation therapy, decreases the risk of new breast cancers and may modulate the risk of recurrence after DCIS (11).

However, there are important differences in outcomes following these treatments for invasive breast carcinoma vs DCIS. In contrast to invasive carcinoma, a meta-analysis of randomized trials of radiation therapy for DCIS failed to demonstrate a survival difference (18). This is not surprising, as any expected benefit in survival for DCIS patients would necessarily be very small given that only half of the breast events after a DCIS diagnosis represent invasive disease. Tamoxifen decreases the risk of new breast cancers in both the ipsilateral and contralateral breast, and may also directly affect the risk of recurrence after DCIS. However, studies analyzing the impact of tamoxifen therapy after breast-conserving surgery for DCIS have demonstrated mixed results (19–21). Although tamoxifen appears to reduce the risk of developing a new primary breast cancer (22), its impact on the risk and timing of recurrence is less clear. Tamoxifen may only affect risk of recurrence among those patients with DCIS that expresses the estrogen receptor and may actually only delay recurrence even among these patients (11,23). An update of the UK, Australia and New Zealand (UK/ANZ) DCIS trial found that tamoxifen reduced the incidence of all new breast events, but had no effect on the risk of developing invasive disease in the index breast (21).

These studies underscore the need to distinguish between invasive and noninvasive treatment outcomes for DCIS. Although the term “recurrence” after DCIS is generally used to describe both recurrence of DCIS and the diagnosis of invasive cancer in the index breast, the implications of an invasive diagnosis with its concomitant risk of nodal and distant disease are different from a recurrence of DCIS alone. Despite this difference, reports from many studies of DCIS often fail to separate invasive cancer and noninvasive recurrences, combining the two events in their definition of
ipsilateral breast tumor recurrence. In addition, clinical trials and population-based studies have failed to consistently stratify women with DCIS by risk of subsequent invasive cancer (24,25). Perhaps a more appropriate term for invasive cancer that develops after DCIS is invasive “occurrence,” as “recurrence” implies that DCIS is a cancer. And if DCIS is more appropriately considered a precursor of cancer instead of a cancer itself, then an adjuvant treatment paradigm with the goal of eradicating microscopic cancer cells in the breast or distant sites to improve survival does not apply.

Ambiguity about the applicability of the adjuvant treatment paradigm to DCIS may contribute to the great regional variability in the use of adjuvant therapy. For example, in the United States, there is currently a large ongoing randomized trial (NSABP B-43) evaluating trastuzumab in DCIS, an agent known to improve survival in the adjuvant setting for invasive breast cancer, but with occasional serious toxicity. In contrast, radiation therapy is rarely used for DCIS in areas of Australia, suggesting that oncologists there are much less inclined to follow an adjuvant paradigm for this cancer precursor (26). Population-based analyses reveal that among patients who receive breast-conserving surgery for DCIS, about half do not receive radiation therapy, with substantial regional variation in its use (Figures 3 and 4) (27–29). A study of leading cancer

Figure 2. Trends in the use of mastectomy (green diamonds) vs breast-conserving surgery (pink squares) for ductal carcinoma in situ (DCIS). Source: National Cancer Institute Surveillance Epidemiology and End Results (SEER) limited use files database.

Figure 3. Trends in the use of radiation therapy (turquoise squares) following breast-conserving surgery for ductal carcinoma in situ (DCIS). Source: National Cancer Institute Surveillance Epidemiology and End Results (SEER) limited use files database.
centers in the United States also found statistically significant heterogeneity in the use of tamoxifen for DCIS (30).

**Prophylactic Paradigm for DCIS Treatment**

Although less common than DCIS, lobular carcinoma in situ (LCIS) is the other major type of in situ carcinoma recognized in the breast. Like DCIS, LCIS lesions contain genetic alterations consistent with breast carcinomas but carry no risk of nodal or distant spread. But unlike DCIS, LCIS has long been considered a marker of future invasive breast cancer risk in both the breast in which LCIS is diagnosed and the contralateral breast rather than a cancer. Therefore, the goal of treatment is not local excision of the LCIS lesion itself; instead, treatment is viewed as prophylactic and focuses on reducing the risk of invasive carcinoma in both breasts. Treatment options for LCIS include bilateral mastectomy, chemotherapy prevention, or observation.

Prophylactic or preventive treatment aims to decrease the risk of development of invasive cancer, whereas adjuvant treatment serves to eradicate residual disease to reduce recurrence. Data on the natural history of DCIS after excision and LCIS suggest that there is little basis for following an adjuvant paradigm in one case and a prophylactic one in the other. Similar to LCIS, DCIS serves as a marker of increased risk of new breast cancers (14,15,19,31). This risk is similar to that carried by patients with a previous diagnosis of invasive breast carcinoma (14,15,31). The NSABP B-24 study randomized women with DCIS treated with breast-conserving surgery and radiation to tamoxifen vs placebo (19). Its placebo arm revealed a risk of almost 1% per year of a new breast cancer diagnosis in the contralateral breast, the majority of which were invasive breast cancers. Moreover, although the risk of invasive cancer after DCIS that is not excised is much higher than for LCIS, after breast-conserving surgery the risk conferred by DCIS is similar. A retrospective population-based analysis of patients not treated with mastectomy showed little difference between DCIS and LCIS relative to the incidence of invasive breast cancer in the index breast and in the contralateral breast when adjusted for the use of radiation therapy (32). Although it had been previously thought that LCIS conferred an equivalent invasive cancer risk in both breasts, a more recent analysis showed the risk to be three times greater in the ipsilateral breast (31). After breast-conserving surgery for DCIS, the invasive carcinoma risk in the ipsilateral breast is also about three times the risk in the contralateral breast (11).

The value of adopting a prophylactic treatment paradigm after breast-conserving surgery for DCIS (as in LCIS) is that it focuses attention on the need to carefully weigh the risks and benefits of interventions designed to reduce future invasive cancer risk. This is critical because the choice of initial therapy for DCIS may limit

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**Figure 4.** Regional variation in the percentage of women who received radiation therapy following breast-conserving surgery for ductal carcinoma in situ (DCIS) by registry between 2000 and 2008. Source: National Cancer Institute Surveillance Epidemiology and End Results (SEER) limited use files database.
options at the time of a new diagnosis. Importantly, the use of radiation usually commits a patient to mastectomy should a local recurrence or new cancer develop in the same breast, as full-dose radiation can only be given once to a single breast due to limits of normal tissue tolerance. Radiation therapy may also complicate surgical decisions at time of recurrence, particularly regarding reconstruction options, and may increase the risks of complications following surgery (unpublished data).

Risk and Benefit Stratification to Optimize Upfront DCIS Treatment Decisions

A prophylactic paradigm also leads to greater appreciation of the importance of refining risk estimates for individual patients. Work has begun to identify which constellation of biomarkers and patterns of gene expression, in addition to clinical and histopathological factors, may help identify those DCIS lesions that carry elevated risk of subsequent invasive breast cancer occurrence vs noninvasive or DCIS recurrence (35,36). Studying only epithelial cells for prediction of invasive carcinoma development may miss the potential role of the host microenvironment in regulating the progression of DCIS to invasive breast cancer (37,38). The myoepithelial cells that surround mammary ducts and lobules have natural tumor suppressor functions (37,38). Recent molecular studies have indicated that the myoepithelial cells around spaces involved by DCIS differ substantially from normal myoepithelial cells (38–41). These findings raise the possibility that progression of DCIS to invasive cancer may be due in part to abnormalities in the surrounding myoepithelial cells that result in a loss of their normal tumor suppressor functions (38,42).

While efforts proceed to quantify the risk of invasive cancer occurrence after DCIS, studies to better characterize the type of invasive cancer that occurs after DCIS will provide a better foundation for treatment decision making. Follow-up data from randomized studies of radiation therapy or breast-conserving surgery alone for DCIS reveal very low risk of breast cancer mortality, suggesting that most invasive cancer after DCIS is early stage and/or nonaggressive and can be successfully treated (14–17,21). Several large studies have demonstrated both favorable stage distribution and very low (5%) risk of breast cancer–specific mortality from ipsilateral breast cancer following a diagnosis of DCIS (43).

New data suggest that characteristics of the initial DCIS lesion may be helpful in tailoring risk reduction strategies. Two studies of recurrences after DCIS found concordance between the index DCIS lesion and a subsequent breast diagnosis for estrogen-receptor status and nuclear grade (44,45). If these studies are confirmed, estrogen-receptor status and grade of the index DCIS may modulate initial treatment decisions by helping to define which type of invasive cancer diagnosis is likely should it occur.

In addition to improved estimates of the risk and type of cancer diagnosis after DCIS, refining estimates of treatment benefit will also improve decision making within a prophylactic paradigm. Although randomized trials have shown that radiation reduces the risk of new ipsilateral breast diagnosis (14–17), a recent meta-analysis revealed that the efficacy of radiation therapy may vary across patient subgroups (18). In this report, the proportional reduction in ipsilateral breast events, defined as either a DCIS or invasive occurrence, was greater in women older than age 50 than in younger women (12).

Future Directions and Implications

Radiation therapy and tamoxifen modulate the risk of developing invasive cancer after breast-conserving surgery, in the ipsilateral breast for radiation, and in the contralateral breast for tamoxifen. Therefore, postsurgical therapy for DCIS may be more appropriately viewed as preventive or prophylactic treatment. This paradigm is already used in treatment of LCIS, where risk of future invasive cancer is deemed not to be high enough to necessitate surgery. In contrast, the risk of invasive cancer with a DCIS diagnosis is greater, leading to the recommendation for surgical excision.

However, after surgical excision of DCIS, treatment decisions should be driven primarily by the risk of subsequent invasive breast cancer, and should take into account the impact of the treatment on options at time of occurrence, should it happen in accordance with a prophylactic paradigm. Further research will likely yield more individualized estimates of the risk of invasive cancer imposed by a DCIS diagnosis for more informed decision making. Patients with features that place them at low risk of invasive recurrence may be more likely to forego additional therapy after surgical excision of DCIS. As noted in the National Institutes of Health Conference Statement, “combinations of new and existing clinical, pathological, and molecular factors should be investigated and validated to better risk-stratify patients who have DCIS” (10). Moreover, “better decision-making tools are needed to aid patients and their care providers in choosing among therapeutic options” so that treatment decisions reflect both the risk of invasive carcinoma and an individual patient’s preferences for the tradeoffs associated with treatment (10).

For the patient with DCIS, the use of an adjuvant treatment paradigm may be an important contributor to the anxiety and misperceptions about prognosis. By removing the term “carcinoma” from DCIS and redefining postsurgical treatment for DCIS as prophylaxis, this impact for DCIS patients may more appropriately match their low likelihood of mortality from breast cancer. Within a prophylactic paradigm, more patients may opt for breast preservation with a DCIS diagnosis, and again should they have a recurrence of DCIS after initial diagnosis. Indeed, even an invasive breast cancer after breast-conserving surgery alone for DCIS may be more likely to be treated with breast conservation if feasible, as a patient may not view the invasive cancer as a second cancer diagnosis or “recurrence.” Most would agree that the quality of life for patients with breast cancer has improved with the feasibility of breast-conserving surgery. The paradigm shift to prophylaxis for DCIS would not only help alleviate the current issues surrounding overdiagnosis in oncology, but its downstream effects would continue to improve the quality of life for the almost one million women living after a diagnosis of DCIS.

References


**Notes**
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