Renaming Ductal Carcinoma in Situ: Would Removing “Carcinoma” Reduce Overtreatment?

Sara H. Javid, MD; L. Christine Fang, MD; Larissa Korde, MD, MPH; and Benjamin O. Anderson, MD

In both the medical literature and lay press, a flurry of controversy has arisen surrounding the treatment and, more specifically, the potential overtreatment of ductal carcinoma in situ (DCIS). Since the advent of population-based screening mammography in the mid-1980s, the incidence of DCIS has increased more than 8-fold, with DCIS now accounting for nearly 22% of new breast cancer diagnoses. Since 1990, death rates from breast cancer in the United States have decreased by approximately 34%, a favorable outcome that has been attributed to the combination of increased screening mammography and improved adjuvant therapy. However, despite the steady increase in DCIS detection and treatment in the 1990s, the subsequent incidence of invasive breast cancers did not proportionately decrease. Invasive breast cancer incidence among women older than 50 years declined sharply between 2002 and 2003 but has since stabilized, a finding that could reflect a reduced pool of prevalent breast cancer cases as a result of widespread screening, but also could relate to the decreased use of hormone replacement therapy or trends in mammography screening rates that peaked in 2000.

Approximately 1 in every 1300 screening mammography examinations leads to a diagnosis of DCIS, of which up to 30% will be treated with mastectomy. Several recent publications suggest the possibility that, although implementation of routine screening mammography has led to an overall increase in breast cancer detection and has been associated with a decrease in overall breast cancer mortality, it has not produced the magnitude of reduction in advanced-stage cancers one would expect based on detection of breast cancer at its nascent stage, namely DCIS.

DCIS can be defined, to patients and providers alike, as noninvasive, preinvasive, a precursor to, stage 0, or, quite simply, what most patients hear at the end of such a preface: breast cancer. This dilemma in terminology has led to heated discourse at national breast specialty meetings and to front-page cover stories in The New York Times, and is an important issue to the growing constituency of breast cancer survivors who drive breast cancer awareness in this country. DCIS is a non–life-threatening, atypical intraductal proliferation that, if left untreated, can progress to invasive breast cancer. However, DCIS progression is not obligatory and not inevitable.

Sanders et al showed that a significant fraction of DCIS cases will not progress to clinically apparent invasive disease. They examined the incidence of invasive breast cancer among a large cohort of patients originally diagnosed in the 1950s and 1960s as having benign breast pathology but who, on retrospective review were found to have low-grade DCIS. Of those with DCIS, only 40% subsequently developed an invasive breast cancer in the same quadrant of the same breast, most of which occurred within 10 years. Other studies, including population-based modeling experiments, have examined the natural history of low-grade DCIS and suggest that as few as 20% of cases might progress to invasive cancer over a protracted period spanning from 5 to 40 years.

In the absence of progression to invasive cancer, overall survival after a diagnosis of DCIS is upwards of 98%. The goal of treatment is solely to prevent either local recurrence or progression to invasive breast cancer. Based on data from 4 randomized clinical trials, local treatment options for patients with DCIS currently include either breast-conserving surgery followed by radiation therapy, or mastectomy. Tamoxifen is also considered as possible adjuvant therapy for patients with estrogen receptor–positive DCIS, both for reduction of local recurrence risk after breast-

The ideas and viewpoints expressed in this commentary are those of the author and do not necessarily represent any policy, position, or program of NCCN.
conserving therapy\textsuperscript{12} and for prevention of a contralateral breast cancer after mastectomy.\textsuperscript{15}

Altogether, these DCIS treatment protocols have lowered the odds of in-breast recurrence of any breast cancer to less than 10\%, and of invasive breast cancer to less than 5\%. Despite the satisfying statistics, many surgeons feel a sense of defeat when a patient elects or requires a mastectomy for DCIS. Simply stated, mastectomy seems like an overly drastic procedure for a non–life-threatening condition that may remain dormant until a patient’s death from another cause. In her poignant piece entitled “Our Feel-Good War on Breast Cancer” published in \textit{The New York Times}, Peggy Orenstein, a breast cancer survivor herself, tells the story of a patient so distraught over a DCIS diagnosis that she chose to “amputate” both breasts to restore her sense of control.

The dilemma of potential overtreatment of DCIS is highlighted further by the growing trend in this country toward bilateral mastectomy, notably among those with DCIS.\textsuperscript{16} The decision to proceed with bilateral mastectomy is most often linked to anxiety over future recurrence rather than strong family history or known genetic predisposition.\textsuperscript{17} Similarly, we often feel conflicted about recommending or even offering 5 to 6 weeks of radiation treatment to a patient with subcentimeter low-grade DCIS excised to widely clear surgical margins. There is, as we often witness in our clinics, a disproportionate alarm and fear in the minds of our patients with DCIS. This anxiety likely stems from our own ambiguous definition of DCIS and our inability to predict in whom DCIS will progress to invasive cancer if untreated or recur if treated.

Current clinical and pathologic parameters are imprecise in calculating a patient’s risk of developing an invasive breast cancer subsequent to their diagnosis of DCIS. Rudloff et al\textsuperscript{18} devised a nomogram to predict 5- and 10-year local recurrence (of either DCIS or invasive cancer) among patients with DCIS with or without receipt of adjuvant radiation or endocrine therapy. The nomogram’s variables include patient age, histologic grade of cancer, adequacy of surgical margins, number of surgical excisions, and year of treatment. Although validated using internal data with a robust concordance index (0.7), the nomogram has not been fully validated externally. Applied to a seemingly similar cohort of patients with DCIS treated at MD Anderson Cancer Center between 1990 and 2007 (n=794), the nomogram was found to overestimate the risk of local recurrence for presumed high-risk cases, while its predictive accuracy declined with longer-term follow-up (10 years). Conversely and paradoxically, local recurrences are seen after treatment for so-called low-risk DCIS (low or intermediate grade, small volume).

In a prospective study at Dana-Farber Cancer Institute of patients with small volume (\(\leq2.5\) cm) low- or intermediate-grade DCIS treated with wide excision alone, local recurrence rates were prohibitively high at 2.4\% per year (12\% at 5 years). Of these recurrences, 31\% were invasive, causing the study to be closed prematurely.\textsuperscript{19} Furthermore, the ECOG 5194 trial has shown that, with longer-term follow-up, 10-year risk of local recurrence approaches 15\% in low-intermediate–grade and 20\% in high-grade DCIS, even among carefully selected cases (small lesion size and \(\geq3\) mm margins).\textsuperscript{20}

Given that conventional clinical and pathologic variables fail to reliably predict recurrence risk, attention has turned toward the promise of molecular diagnostic tools to measure recurrence and progression risk. Genomic assays, including Oncotype Dx, have been well validated and are commonly used among patients with invasive breast cancer to help predict risk of distant metastatic recurrence and guide decisions regarding systemic chemotherapy. Solin et al\textsuperscript{20} examined the value of the Oncotype Dx DCIS score (a different assay from that used to predict recurrence risk for patients with estrogen receptor–positive invasive breast cancer) to predict local recurrence risk among patients with DCIS treated with lumpectomy without radiation.\textsuperscript{20} They found that, after adjusting for tamoxifen use, the Oncotype Dx DCIS score predicted overall

L. Christine Fang, MD
L. Christine Fang, MD, is a radiation oncologist at the University of Washington in Seattle, Washington. She specializes in breast cancer and gynecologic malignancies.
and invasive in-breast events (IBE) in their study population. In multivariable analysis, Oncotype DX DCIS score, tumor size, and menopausal status were found to be significant independent IBE predictors. The authors concluded that the DCIS score quantifies overall and invasive IBE risk, and complements traditional clinical and pathologic factors for selecting individualized treatment for women with DCIS.

However, the findings of this study have yet to be validated in other series. This study was weakened by the highly selected ECOG 5194 study cohort used for the analysis, which was composed primarily of patients with low- to intermediate-grade DCIS. In addition, the median lesion size in the ECOG study was small (5 mm), most cases were estrogen receptor–positive, and 83% had surgical margins exceeding 5 mm. Therefore, additional confirmatory studies are needed using a more biologically diverse, higher-risk population of patients with DCIS before concluding that Oncotype DX is a well-validated tool for predicting recurrence risk for a condition as heterogeneous as DCIS.

Amidst the ambiguity surrounding treatment of DCIS and the anxiety the diagnosis imposes on patients, there are many vocal proponents of renaming DCIS a precursor lesion or high-risk marker rather than a cancer. What would be the consequences? What’s in a name? In a survey by Omer et al., 394 healthy women without breast cancer were asked how they would proceed with treatment depending on terms used to describe DCIS. When DCIS was described as a high-risk condition instead of a cancer, more than 65% of women opted for nonsurgical treatments, including endocrine therapy or active surveillance, compared with 53% when DCIS was described as a noninvasive cancer. Thus, removal of the term carcinoma and recoining DCIS as a high-risk marker would likely shift the paradigm of managing DCIS to that used for managing atypical ductal hyperplasia (ADH) or lobular carcinoma in situ, limiting treatment to excisional biopsy alone, with only consideration of risk-reducing prophylaxis with tamoxifen or an aromatase inhibitor. However, such a change overlooks the significant difference in biological behavior associated with DCIS compared with ADH. ADH incurs a far lower risk of breast cancer, approximately one-half that of low-grade DCIS. Prospective randomized evidence confirms the benefit of postlumpectomy radiation therapy for DCIS after complete excision with negative surgical margins. One would have to anticipate that, with nondiscriminatory omission of adjuvant radiation therapy after lumpectomy for DCIS and disregard for attaining negative margins, a significant spike in invasive breast cancers would be seen.

Although the morbidity of locoregional therapies for DCIS should not be underestimated, the morbidity of invasive cancer treatment, including the use of chemotherapy, should not be overlooked, because it cannot be assumed that poor locoregional control of DCIS has no impact on overall breast cancer survival. A meta-analysis of breast conservation trials showed that when local recurrence for early breast cancer exceeds 10% at 5 years, avoidance of 4 local recurrences at 5 years predicts one life saved at 15 years. Assuming that these findings have no relevance to DCIS, locoregional management would be cavalier.

Conclusions
Although we agree that a subset of patients with DCIS is being overtreated with the current therapy paradigms, we also feel strongly that a broad, sweeping change in terminology is premature, because such a change would overlook the biological diversity of DCIS, from which at least 20% to 40% of cases will progress to invasive cancer if not properly managed. One size does not fit all for patients with DCIS. We contend that, although an effort to rename DCIS as noncancer could reduce overtreatment, doing so at this juncture is overly simplistic and could yield dangerous outcomes.

Instead, treatment for DCIS should be individually tailored based on the clinical and pathologic predictive markers currently available, including a frank conversation...
Benjamin O. Anderson, MD

Benjamin O. Anderson, MD, is Professor of Surgery and Global Health Medicine at the University of Washington (UW) in Seattle where his practice is devoted to caring for patients with breast health issues and cancer. Dr. Anderson’s clinical interests include oncoplastic breast surgery, which simultaneously improves oncologic and cosmetic outcomes with complex cancer resections. He holds joint faculty positions at the Fred Hutchinson Cancer Research Center Division of Public Health Sciences and the UW Department of Global Health. He directs the Breast Health Clinic at the Seattle Cancer Care Alliance (SCCA). Dr. Anderson created and chairs the Breast Health Global Initiative, which develops resource-stratified guidelines for breast cancer early detection, diagnosis, and treatment in low- and middle-income countries. Dr. Anderson has served as President of the American Society of Breast Disease. On the US delegation to the 58th World Health Assembly in Geneva, Dr. Anderson contributed to the 2005 World Health Organization Cancer Prevention and Control Resolution. Dr. Anderson as received many awards, including being elected to the Board of Directors of the Union for International Cancer Control.

with each patient regarding the risks and benefits of various multidisciplinary treatment strategies, and a thorough explanation of the difference between invasive and noninvasive disease. We predict that within the next several years, further research will yield new biomarkers and molecular diagnostic tools that will help us identify which cases of DCIS portend a higher risk of progression to or recurrence of invasive cancer and which will remain dormant, or nonmalignant. Only then will we feel confident that we are doing no harm in not treating, and not labeling, DCIS as cancer.

References