Melchior de Hondecoeter, 1670. *A Golden Eagle Attacking a Menagerie of Birds* (detail). From the collection of Dr. and Mrs. Gordon Gilbert of St. Petersburg, FL.

Ductal Carcinoma In Situ of the Breast

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Noninvasive breast cancer has diverse clinical presentations, histologic features, and biologic potential.

Background: *Ductal carcinoma in situ (DCIS) is detected more often since the advent of mammography. A standardized pathologic staging and grading system does not exist, but nuclear grade is assuming greater importance. The history of DCIS is long, and its treatment is a controversial issue in breast cancer today.*
Methods: *Data have been reviewed regarding the role of HER-2 expression as a prognostic variable, as a predictive factor for response to chemotherapy and hormonal therapies, and as a directed therapeutic target for breast cancer.*
Results: *The NSABP protocol B06 revealed a recurrence rate of 43% in patients treated with local excision alone. Half of recurrences are still DCIS, but 50% are invasive. Local control is markedly improved by the addition of radiation. Recurrence is also minimized by careful cytologic review of margins. Sentinel lymph node biopsy has resulted in more accurate nodal staging.*
Conclusions: *As a heterogeneous lesion, DCIS may not lend itself to a uniform treatment approach. Careful analysis of resection margins is required. As our understanding of the diagnosis and treatment of this disease develops, a coordinated team approach is optimal.*

Introduction

Major advances in the detection of carcinoma of the breast have occurred in the past several decades. The increased use of mammography for screening and early detection has resulted in a significant increase in the diagnosis of early breast cancer and specifically ductal carcinoma *in situ* (DCIS). The number of patients found to have this lesion has grown 10-fold (from 2% to 20%) in the last two decades.[1]

DCIS includes a heterogeneous group of lesions with diverse clinical presentations, histologic features, and biologic potential. Histologically, DCIS is defined as proliferating malignant ductal cells limited to existing ductal and lobular units without invasion through the basement membrane. Conventionally, DCIS has been classified into *comedocarcinoma* and *noncomedocarcinoma* subtypes. Comedocarcinoma DCIS is characterized by the presence of necrosis and cells with marked cytologic atypia and frequent mitotic figures. Noncomedocarcinoma DCIS is further divided into cribriform, micropapillary, and solid subtypes and is characterized by proliferation of a uniform population of cells with mild to moderate cytologic atypia. DCIS is often heterogeneous, usually occurring with several subtypes noted within the same lesion.

This morphologic categorization is less reproducible in terms of prognosis and biologic behavior compared with lesions that are defined by nuclear grade and the presence of necrosis, as recognized in the classification system of Holland et al[2] and Lagios et al.[3] This classification system groups DCIS by nuclear grade from low to high. This method is particularly useful when variations in growth patterns are demonstrated with a dominant cell type noted since it is unusual to see cells of inconsistent nuclear grade within a single lesion.

High-grade DCIS is the easiest to identify (Fig 1A-B). The tumor cells have pleomorphic nuclei, irregular nuclear contours, prominent nucleoli, and frequent mitoses. Multiple growth patterns may be apparent, often with central necrosis and calcifications. It is noted that the tumor cell morphology is fundamental for this designation, even in the absence of necrosis. *Low-grade* DCIS (Fig 2A-C) exhibits a uniform population of cells that are generally in a cribriform or micropapillary pattern and lack necrosis or cytologic atypia. *Intermediate-grade* DCIS (Fig 3) consists of types that cannot easily be specified as either high or low nuclear grade. The proliferating cells display mild to moderate cytologic atypia with variable architectural growth patterns such as cribriform, micropapillary, or solid. Central necrosis may be present.
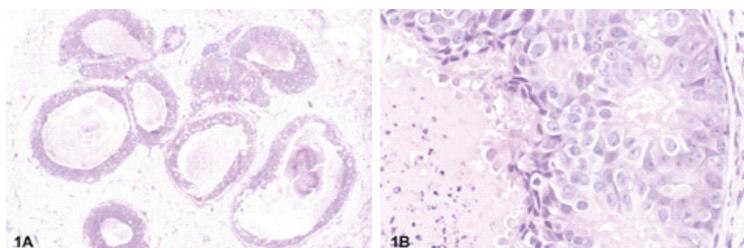

Fig 1A-B. — High-grade DCIS, comedocarcinoma.
(A) Multiple ducts with central necrosis and focal microcalcifications.
(B) Markedly atypical ductal cell proliferation with prominent nucleoli and associated necrosis.
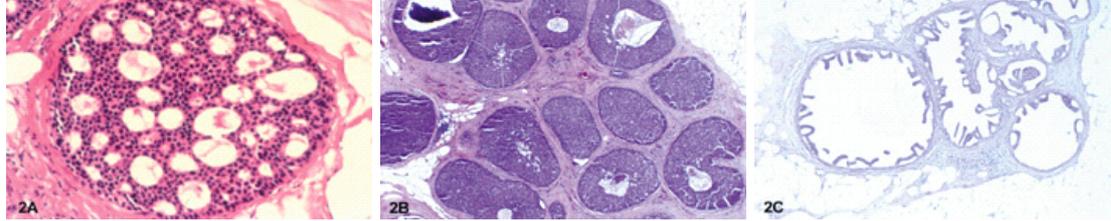
Fig 2A-C. — Low-grade DCIS, noncomedocarcinoma.
(A) Cribriform growth pattern with a uniform cell population forming rounded lumens.
(B) Predominantly solid growth pattern,
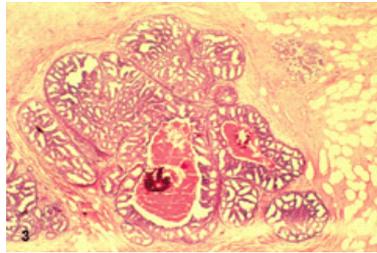(C) Micropapillary pattern

Fig 3. — Intermediate-grade DCIS. Multiple ducts with cribriform and micropapillary forms showing central necrosis, microcalcifications, and mild cytologic atypia.

Some architectural patterns of DCIS, regardless of the nuclear grade, may be more extensive and often multicentric, such as micropapillary and apocrine variants. Consequently, results of a DCIS consensus conference on classification were described in 1997, which include five categories: high grade, intermediate grade, low grade, pure or predominantly micropapillary, and pure apocrine.[4-6]

Natural History and Epidemiology

The natural history of a disease forms the basis for recommended treatment and assessment of prognosis. However, few studies are available on the natural history of DCIS. The best measures of the course of this disease have been found in autopsy studies and in retrospective reviews of biopsies for what was originally thought to be benign disease and later was diagnosed as DCIS.

Seven major autopsy studies of women not known to have had breast cancer have provided insight. Six studies found an incidence of 4% to 18%.[7] The seventh and largest study showed a 0.2% incidence (1 in 519 cases).[8] However, this study included a significant proportion of groups known to have a smaller than usual risk of breast cancer. Of the more than 1,000 cases comprising these seven studies, only one case of invasive cancer was detected. Further analysis with fixed criteria is needed.

In considering cases of DCIS followed after biopsy alone, we know that the natural history of the lesion has been modified. The Vanderbilt experience is the largest with adequate follow-up.[9,10] Twenty-eight patients were identified as having DCIS after histologic re-review of what was originally assessed as benign disease and followed for an average of approximately 30 years. These women had small, noncomedocarcinoma-type, mostly cribriform-variety DCIS tumors. Originally, seven women — and later two — developed invasive cancer in the same breast quadrant that initially showed DCIS for a rate of 32%. The first case of invasive cancer in this series presented some 15 years after the initial biopsy. Another woman developed distant metastases with invasive cancer more than 30 years later. No cases of comedocarcinoma DCIS were included in this series. It is striking that the natural history may require more than 20 years to fully develop and that a patient who has not undergone definitive treatment maintains a substantial risk. It is evident that some intraductal lesions will progress, but identifying the subset at risk for a poor outcome is difficult.

Clinical Features

The clinical presentation of DCIS is varied. Prior to the widespread use of screening mammography, most patients presented with nipple discharge, Paget's disease, or a palpable mass. A more recent review of patients participating in screening mammography found that nearly 60% of DCIS cases were discovered solely by mammography.[11]

Currently, most cases of DCIS consist of small lesions detected by mammography. In fact, while DCIS comprises approximately 5% of symptomatic breast cancers, it represents 15% to 20% of those detected at radiologic screening.[12,13] A change over time in a mammographic finding is associated with malignancy approximately 18% of the time; of these, most are *in situ* lesions. A mass that is greater than 1 cm on a mammogram represents a malignancy in approximately 25% of cases. However, most of these are invasive lesions.[14] The palpable forms of DCIS are associated with multicentricity, occult invasion, and an overall poorer prognosis.[15] The finding on a mammogram that commonly leads to biopsy is a focus of microcalcifications, which is seen in as many as 95% of cases of DCIS. Calcium deposits in DCIS are dystrophic calcifications secondary to necrotic tumor cells. The number of clustered microcalcifications and their presentation, such as branching or linear distribution, are associated with the likelihood of finding malignancy (Figs 4-6). Studies that have attempted to link pathologic and radiologic findings have largely been unsuccessful. Overall findings agree that screening-detected DCIS is less extensive, has smaller calcification cluster size, and has less retroareolar and upper inner quadrant involvement than symptomatic DCIS.[13] The issue of recognizing cancers with extensive intraductal involvement has been improved with mammography. The extent of calcium deposits is readily discernible on today's mammograms and aids in evaluating treatment options.
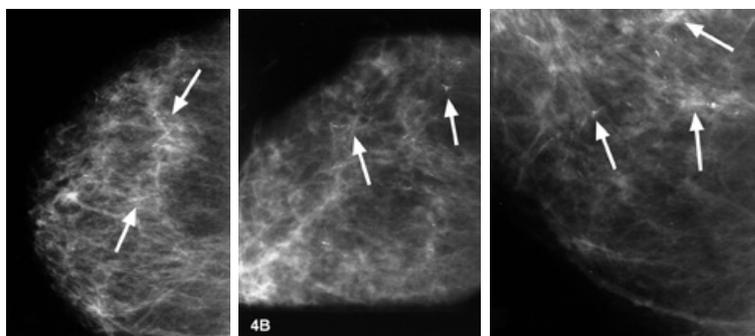
Fig 4A-C. — Mammogram (craniocaudal and magnification views) demonstrating numerous scattered clusters of microcalcifications.
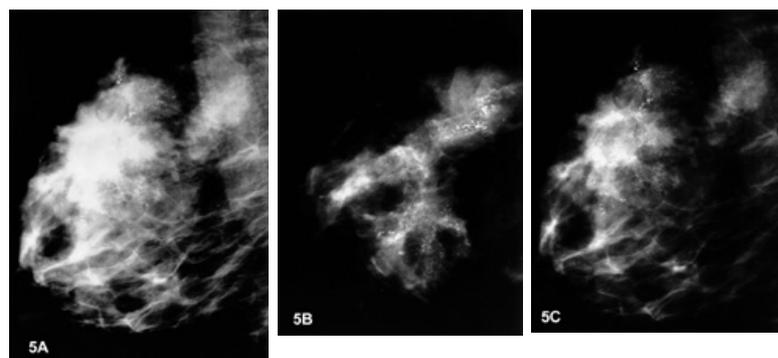

Fig 5A-C. — Mammogram (mediolateral oblique, mediolateral, and craniocaudal views) exhibiting extensive branching microcalcifications.
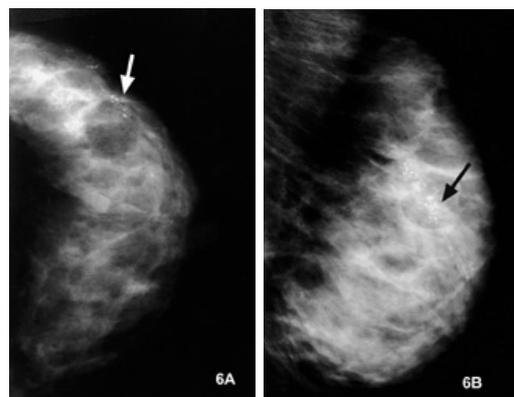

Fig 6A-B. — Mammogram (craniocaudal and mediolateral views) showing a linear pattern of microcalcifications.

Treatment of Ductal Carcinoma *In Situ*

A wide array of treatment plans have been developed to treat DCIS. This is partly the result of the uncertainty of the natural history of the lesion and lack of pathologic standardization. Today, the treatment and management of noninvasive carcinoma are among the most controversial areas of breast cancer.

In the past, the removal of the breast in its entirety was thought to be the only appropriate treatment of breast carcinoma, and that was the traditional treatment of DCIS. Cure rates with this approach were close to 100%. We are now detecting more cancer with mammography, and the result has been a push toward breast conservation therapy. It is becoming more difficult to recommend a highly invasive treatment for a lesion that has a risk of cancer death of only 1% to 2%, although a mechanism to identify women at high risk for developing recurrence of invasive carcinoma would be advantageous.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) has conducted two studies examining treatment outcomes in women with DCIS randomized to treatment with excision alone or excision plus radiation therapy.[16,17] The NSABP protocol B06 found a recurrence rate of 43% in patients treated with local excision alone. These patients were originally misdiagnosed as having invasive cancer and were all clinically detected. Mean follow-up was 83 months for the 76 patients.[16] Lagios et al[3] also studied 79 patients treated locally. They noted 13 recurrences (16%) at a mean follow-up of 124 months. Seven were DCIS and six were invasive, which is consistent with most studies on the management of DCIS. In general, when local failures in the treatment of DCIS occur, the pathology is split evenly between invasive and noninvasive ductal carcinoma.

In exploring the use of radiation therapy to improve local control with excision, the NSABP B17 trial randomized 818 women to excision alone or excision plus 50 Gy of radiation.[17] The irradiated group had an almost 60% decrease in the ipsilateral recurrence. A recurrence rate of 16% was seen in patients receiving excision alone and 7% in patients receiving excision plus radiation. Originally, follow-up was a median of 43 months. Fisher and colleagues[18] extended these findings to a mean of 90 months in a 1998 report. Again, all cohorts benefited from radiation independent of mammographic or clinical attributes. Since half of the recurrences are invasive carcinoma, the result of salvage therapy is a substantial issue. Solin et al[19] reported high rates of salvage in 42 (15%) cases of local failure in a total of 274 cases of DCIS treated with excision plus radiation. The intraductal recurrences (19 patients, 45%) were predominately detected with mammography, and all were disease-free for the median follow-up of 4.7 years. Of those with invasive recurrence, five had distant metastases. In the entire group of patients with local recurrence at a median follow-up of 3.7 years after salvage, 36 (86%) were alive and free of disease, 1 was alive with disease, and 4 (10%) died of disease. Another died of other causes.

Accurate assessment of the extent of DCIS lesions is often complex. The status of the lumpectomy margin in DCIS is a strong prognostic factor for recurrence.[20,21] Several techniques have been used to assess the lumpectomy margins in DCIS, including inked radial permanent section margins, tangential permanent section margins, frozen section, and imprint cytology. An initial review of 894 women with breast conservation and radiation therapy who were treated at our center from 1984 to 1996 included 701 patients with lumpectomy margins evaluated by imprint cytology and the remaining 193 by conventional histology. The overall recurrence rate for all patient groups was 16 (2.27%) of the 701 patients assessed by imprint cytology compared with 26 (13.5%) of the 193 patients assessed by conventional histology (Table 1 — Please see printed version for Table 1.)[22] In this series, T0 lesions (DCIS) had a recurrence rate of 1.3% when evaluated by imprint cytology vs 13.8% when conventional histology was used. Imprint cytology was both sensitive (99%) and specific (98%) for the intraoperative evaluation of surgical margins for DCIS with rapid feedback at the time of surgery.

Our experience with DCIS and imprint cytology was recently updated.[23] Of the 218 cases of DCIS reviewed in this follow-up series, 96 patients (44%) were treated with breast conservation, demonstrating an overall recurrence rate at 57.5 months of 6.15% and a specific recurrence rate of 2% for pure DCIS without extensive intraductal component (EIC) or microinvasion. Silverstein et al[24] reported a 10% recurrence rate at a median follow-up of 62 months in patients treated similarly but without imprint cytology

evaluation of margins.

Generally, axillary lymph node dissection is not considered necessary in the treatment of DCIS.[25] It has been the widespread opinion that the risk of axillary metastases is less than 4%. Since 1994, sentinel lymph node mapping with biopsy has gained expanding validation and usage. Although a notable learning curve exists for surgeons who are training to perform this new procedure,[26] sentinel node mapping is highly predictive of axillary nodal status with minimal morbidity.[27] A significant expansion of the precision of sentinel lymph node diagnostics has occurred with the application of molecular and immunohistochemical markers to detect occult metastases. More intensive examination of these nodes occurs and more accurate staging results[28] in DCIS patients with occult micrometastases to the regional lymphatic basin staged with greater precision. Our studies have shown that the seeming lack of microinvasion in the primary lesion does not prevent the presence of nodal disease. Data from our consecutive prospective series of 1,147 breast cancer patients who underwent lymphatic mapping are noted in Table 2, which presents positive sentinel lymph nodes in relation to tumor size. All patients with a preoperative diagnosis of DCIS, regardless of size or pathologic staging, were evaluated with sentinel lymph node biopsy. Positive sentinel lymph nodes were found in 8.6% of the T0 or presumed pure DCIS patients.[28] We believe that sentinel lymph node evaluation is an excellent method for determining whether microinvasion is present at the primary tumor site. Furthermore, it may be a more sensitive method, as it has been in one case to date, of detecting occult invasive cancer not otherwise identified on examination or mammography in a patient diagnosed with DCIS. Additional investigation is necessary to assess the clinical significance of micrometastatic nodal disease, the role of axillary lymph node dissection in patients with micrometastases, and the true clinical relevance of upstaging with cytokeratin (Fig 7).

Table 2. — Tumor Size vs Positive Lymph Nodes				
Tumor Size	All Patients (1,143)	Number of Patients With Positive Axillary Nodes	Mapped Patients (1,094)	Number of Patients With Positive SLNs
T0 (DCIS)	208	18 (8.6%)	200	18 (9.0%)
T1a	72	13 (18.0%)	69	13 (18.8%)
T1b	239	46 (19.7%)	228	45 (19.7%)
T1c	385	121 (31.4%)	370	118 (31.9%)
T2	211	112 (53.1%)	202	108 (53.5%)
T3	28	24 (85.7%)	25	22 (88.0%)

Tumor size in 1,143 breast cancer patients undergoing lymphatic mapping at Moffitt Cancer Center related to the number of patients with positive SLNs (sentinel lymph nodes).

Note: 49 patients failed mapping; 10 (20.4%) had positive nodes on complete axillary dissection.
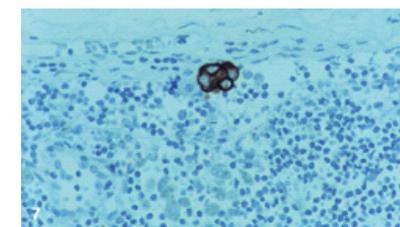

Fig 7. — Micrometastatic ductal carcinoma in a sentinel node from a DCIS patient.

There is no evidence to support the use of cytotoxic chemotherapy in the treatment of DCIS, and it is currently not indicated. However, hormonal manipulation with tamoxifen may benefit this group. The NSABP Breast Cancer Prevention Trial (P-1) found that treatment of high-risk women with tamoxifen for five years produced a 50% reduction in the incidence of noninvasive carcinoma.[29] Currently, the NSABP protocol B24 is investigating the addition of tamoxifen to lumpectomy and radiotherapy in the treatment of DCIS.[30] Preliminary results show the addition of tamoxifen reduces the cumulative five-year incidence of a subsequent invasive tumor from 3.4% to 2.1%. Due to the risk of overlooking an area of invasion, estrogen- and progesterone-receptor status is generally not performed on biopsy tissue without a mass. Hormonal receptor data to guide treatment in patients with DCIS are of unknown significance. Most literature indicates that histopathologic prognostic factors have no clinical use and do not affect patient outcome. Life-long observation is recommended for women with DCIS, beginning with a mammogram obtained within six months of breast-conserving therapy to reestablish a baseline and to verify the removal of any prior suspicious lesion; annual bilateral mammograms are indicated thereafter.

Prognosis

As DCIS is a heterogeneous rather than a uniform group of lesions, a single treatment program is not feasible. A clear, concise approach to this entity was not available until recently. Investigators at the Breast Center at Van Nuys, California, developed the Van Nuys Prognostic Index (VNPI) to assist in the recommendation of a treatment plan.[31] The scoring system parameters include three significant predictors of local recurrence — margin width, tumor size, and pathologic classification. A score of 1 (best) to 3 (worst) is assigned to each parameter to arrive at a final score of 3 to 9. According to this index, patients with DCIS who score 8 or 9 on the VNPI should be considered for mastectomy because of their high local recurrence rates of 60% at 8 years regardless of irradiation. Scores of 5 to 7 require radiation to reduce the local recurrence sufficiently after lumpectomy. For patients with VNPI values of 4 or less, no statistical difference was found whether or not radiation therapy was included. Used as a guideline, this index highlights the diversity of DCIS and the need to review each case independently.

Determining the exact size of DCIS as well as establishing accurate margin widths can be difficult. After review of our local recurrence statistics for DCIS, subset analysis identified a group with a particularly poor outcome. Patients with multifocal DCIS with microinvasion have a five-year actuarial disease-free survival of 78% compared to 98% in patients with simple DCIS.[23] Our data also show that the chance of recurrence of tumor following lumpectomy and radiation therapy correlates with the presence of EIC and microinvasive disease. However, we have not identified any statistically significant difference in recurrence among histologic subtypes of DCIS and surmise that there is a fundamental difference in behavior of microinvasive and multifocal tumors aside from their histologic subtype (Table 3).

Table 3. — Characteristics of Seven Patients With DCIS Who Recurred and Required Conversion to Mastectomy						
Patient Number	Age (Yrs)	Tumor Size (cm)	Mammogram Finding	Histology	Location	Residual
1	60	5	Central calcification	Comedo	Central	No
2	43	2.5	Clustered calcification	Multifocal/microinvasive comedo	UIQ	Yes

3	72	5	Multifocal/multicentric calcification	Multifocal comedo	UIQ	Yes
4	38	4.4	Clustered calcification	Multifocal noncomedo	UOQ	Yes
5	36	5	Clustered calcification	Noncomedo	UOQ	No
6	66	5	Central multifocal/multicentric calcification	Multifocal comedo	Central	No
7	39	3	Clustered calcification	Comedo	UOQ	Yes

UIQ = upper inner quadrant
UOQ = upper outer quadrant

In an attempt to isolate genetic differences in DCIS tumor cells compared to nonmalignant cells, Deng et al[32] used a technique of micro-dissection followed by polymerase chain reaction amplification and comparison of genetic patterns Of significance, the genetic patterns of malignant and adjacent nonmalignant cells were essentially identical. This loss of heterozygosity may imply that the adjacent pathologically benign ductal elements are genetically predestined to become malignant, which further validates the observation in the NSABP P-1 data regarding a high rate of tumor development in patients with atypical hyperplasia. This concept may explain the late recurrence rate seen in patients with histologically negative margins and would explain why wide margins and radiation therapy are crucial in curtailing recurrence.

Conclusions

DCIS is a mixed disease entity with divergent presentations and attributes. A standard mode of pathologic reporting, classification, treatment, or prognosis has been lacking. As a heterogeneous lesion, a uniform approach is not feasible. Aggressive analysis of the margins is indicated. There is no role for chemotherapeutic management of any patient with DCIS except for those with positive nodal disease — and those patients may actually be misdiagnosed with aggressive occult lesions in the breast. Hormonal therapy may have a role, however, based on recent NSABP data. Surgeons and pathologists have been more aggressive in subcategorizing and identifying lesions that may exhibit greater risk of recurrence; this has been accomplished by evaluating numerous markers such as Ki 67, carcinoembryonic antigen, estrogen/progesterone receptor, HER-2/neu, S-phase fraction, and DNA ploidy, many of which produce frightening profiles of malignant potential in patients with DCIS. Despite these findings, the overall biologic behavior of DCIS of the breast is favorable. Adequate diagnosis and treatment continue to require a coordinated team approach among radiologists, surgeons, pathologists, radiation oncolgists, and medical oncologists.

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