REVIEW ARTICLE

MEDICAL PROGRESS

Ductal Carcinoma in Situ of the Breast

Harold J. Burstein, M.D., Ph.D., Kornelia Polyak, M.D., Ph.D., Julia S. Wong, M.D., Susan C. Lester, M.D., Ph.D., and Carolyn M. Kaelin, M.D.

From the Division of Medical Oncology and the Departments of Medicine (H.J.B., K.P.), Radiation Oncology (J.S.W.), and Surgery (C.M.K.), Dana–Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School; and the Department of Pathology, Brigham and Women's Hospital and Harvard Medical School (S.C.L.) — all in Boston. Address reprint requests to Dr. Burstein at the Dana–Farber Cancer Institute, 44 Binney St., Boston, MA 02115, or at hburstein@partners.org.
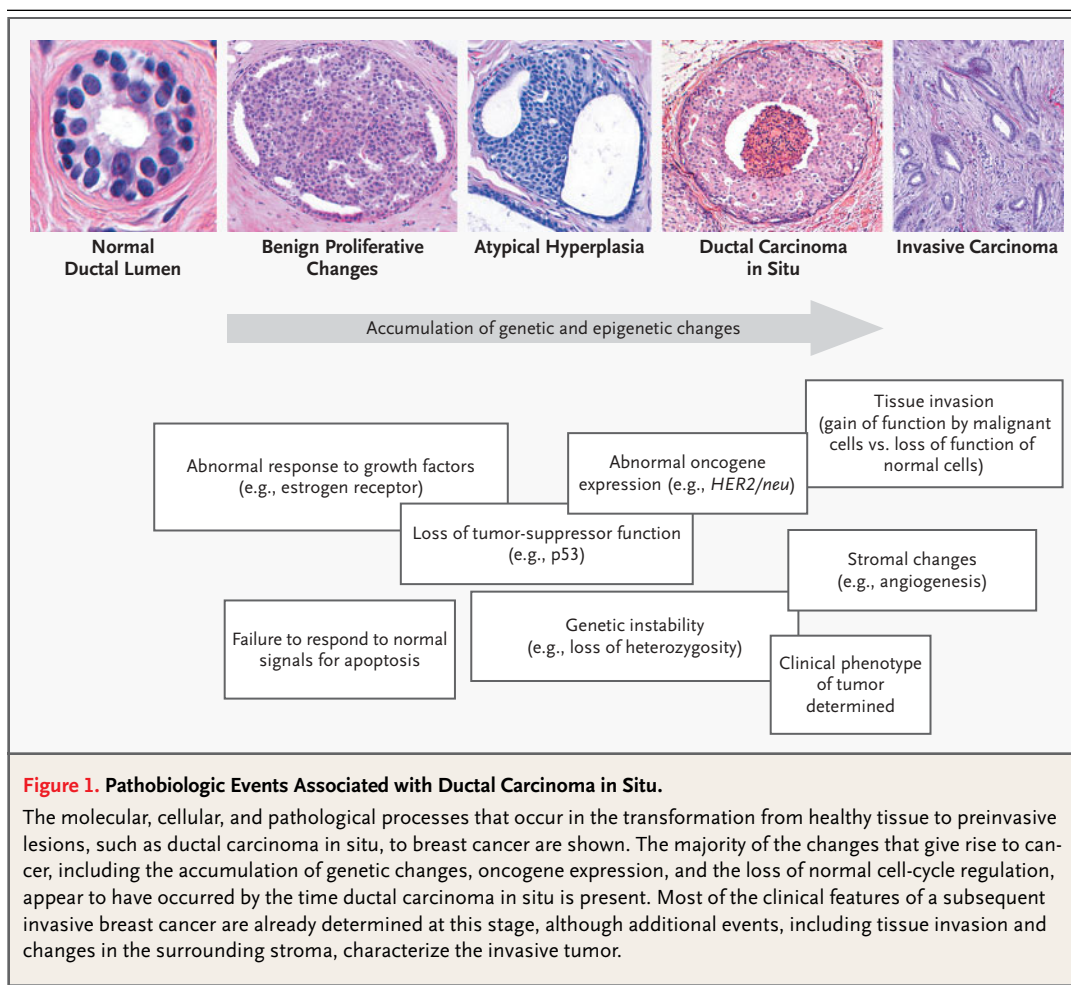
DUCTAL CARCINOMA IN SITU OF THE BREAST (ALSO CALLED INTRADUCtal carcinoma) consists of the clonal proliferation of cells that appear malignant and that accumulate within the lumens of the mammary duct. There is no evidence of invasion beyond the epithelial basement membrane into the adjacent breast stroma. This lesion, which is a precursor to invasive ductal carcinoma, is frequently diagnosed on screening mammography. In the past 20 years, concomitant with the wide use of screening mammography, the incidence of ductal carcinoma in situ has risen dramatically, and data from large cohort studies and randomized trials have emerged to guide treatment. Furthermore, advances in molecular biology are providing important insights into the relationship between ductal carcinoma in situ and invasive breast cancer. This review summarizes progress in the understanding and therapy of ductal carcinoma in situ.

BIOLOGIC CHARACTERISTICS

Ductal carcinoma in situ lies along a spectrum of preinvasive lesions originating within normal breast tissue, with histologic progression from atypical hyperplasia to invasive breast cancer (Fig. 1).[1] Although the initiating steps and precise pathways of breast tumorigenesis remain poorly defined, it appears that nearly all invasive breast cancers arise from in situ carcinomas. The presence of shared chromosomal changes in both ductal carcinoma in situ and synchronous, adjacent invasive cancers demonstrates their clonal, evolutionary relationship.[2,3]

Multiple clinicopathological and biologic features distinguish ductal carcinoma in situ from both normal breast tissue and other benign proliferative breast lesions. Chromosomal imbalances occur, with gain or loss at multiple loci, as hyperplastic lesions progress through ductal carcinoma in situ to invasive breast cancer. For instance, loss of heterozygosity is noted in more than 70 percent of high-grade ductal carcinomas in situ, as compared with 35 to 40 percent of cases of atypical hyperplasia and 0 percent in specimens of normal breast tissue.[4-6] Molecular markers associated with breast tumorigenesis have been identified. The estrogen receptor — normally expressed by luminal breast epithelial cells — is expressed by over 70 percent of ductal carcinoma in situ lesions. The *HER2/neu* proto-oncogene is overexpressed in roughly half of all ductal carcinoma in situ lesions but not in atypical hyperplasia.[7] The *p53* tumor-suppressor gene is mutated in approximately 25 percent of all ductal carcinoma in situ lesions, but is rarely mutated in normal or benign proliferative breast tissue.[8] The frequency with which these molecular markers are expressed in ductal carcinoma in situ generally mirrors their expression in invasive breast cancers.

Genomic[9,10] and proteomic[11] approaches have identified numerous differences in patterns of gene and protein expression between normal or hyperplastic breast tissue and ductal carcinomas in situ. Factors known to be related to cell growth and differen-

Figure 1. Pathobiologic Events Associated with Ductal Carcinoma in Situ.

The molecular, cellular, and pathological processes that occur in the transformation from healthy tissue to preinvasive lesions, such as ductal carcinoma in situ, to breast cancer are shown. The majority of the changes that give rise to cancer, including the accumulation of genetic changes, oncogene expression, and the loss of normal cell-cycle regulation, appear to have occurred by the time ductal carcinoma in situ is present. Most of the clinical features of a subsequent invasive breast cancer are already determined at this stage, although additional events, including tissue invasion and changes in the surrounding stroma, characterize the invasive tumor.

tiation, cytoskeletal function, intracellular transport of cell membranes, and the function of the surrounding microenvironment have been examined. The most dramatic changes in patterns of gene expression during breast tumorigenesis appear during the transition from normal tissue to ductal carcinoma in situ.[10,12,13] In contrast, the gene-expression profile of ductal carcinoma in situ is quite similar to that of invasive breast cancer.[10,12-15] Genes that are uniquely associated with invasive tumors have not been identified, which suggests that many of the hallmark cellular events specific to the transformation process in breast cancer arise during or before the development of ductal carcinoma in situ.

Ductal carcinoma in situ may be associated with changes in the surrounding breast parenchyma. High-grade ductal carcinoma in situ, in particular, has been associated with the breakdown of the myoepithelial cell layer and basement membrane surrounding the ductal lumen,[16] proliferation of fibro-blasts, lymphocyte infiltration, and angiogenesis in the surrounding stromal tissues[17,18] (Fig. 1 and 2). Whether these stromal changes reflect important steps that facilitate primary tumor transformation or secondary alterations in response to ductal epithelium that is being transformed is unknown. Quantitative changes in the expression of genes related to cell motility, adhesion, and extracellular-matrix composition, all of which may be related to the acquisition of invasiveness, occur as ductal carcinoma in situ evolves into invasive carcinoma.[19]

Ductal carcinoma in situ is biologically heterogeneous, with variable pathological, molecular, and clinical features (Fig. 2). For instance, the gene-expression profile of high-grade ductal carcinoma in situ differs from that of low-grade lesions and exhibits a greater overall genetic change from normal breast tissue. There is good, if incomplete, concordance between synchronous ductal carcinoma in situ and invasive tumors with respect to the tumor

grade, estrogen-receptor status, *HER2/neu* status, and *p53* status,[20] although these markers have a heterogeneous distribution of expression. More than 90 percent of low-grade ductal carcinoma in situ lesions are positive for estrogen receptors, and less than 20 percent exhibit overexpression of *HER2/neu* or *p53* mutations. In contrast, overexpression of *HER2/neu* or *p53* mutations arise in two thirds of high-grade ductal carcinoma in situ lesions, whereas only one quarter express estrogen receptors.

Data suggest that ductal carcinoma in situ represents a stage in the development of breast cancer in which most of the molecular changes that characterize invasive breast cancer are already present, though the lesion has not assumed a fully malignant phenotype. A final set of events, which probably include gain of function by malignant cells and loss of function and integrity by surrounding normal tissues, is associated with the transition from a preinvasive ductal carcinoma in situ lesion to invasive cancer. Most, if not all, clinically relevant features of breast cancer, such as hormone-receptor status, the level of oncogene expression, and histologic grade, are probably determined by the time ductal carcinoma in situ has evolved.[21-24] Thus, the variable clinical characteristics of invasive breast cancer may be explained by the heterogeneous nature of the preceding ductal carcinoma in situ lesions.

CLINICAL AND PATHOLOGICAL FEATURES

With the introduction of widespread screening mammography, the incidence of ductal carcinoma in situ has increased by a factor of 10 in the past two decades, from 4800 cases in 1983 to more than 50,000 cases now diagnosed annually in the United States.[25] Ductal carcinoma in situ accounts for nearly 20 percent of all breast cancers detected by screening (1 case of ductal carcinoma in situ detected per 1300 screening mammograms) in North America.[26,27]

Figure 2. Photomicrographs Showing Pathological Features of Ductal Carcinoma in Situ (Hematoxylin and Eosin, ×100).

Panel A shows low-grade cribriform ductal carcinoma in situ with secretory calcifications. Panel B shows high-grade comedo ductal carcinoma in situ with central necrosis and calcifications. Panel C shows high-grade comedo ductal carcinoma in situ with central necrosis and foci of microinvasion (arrow).
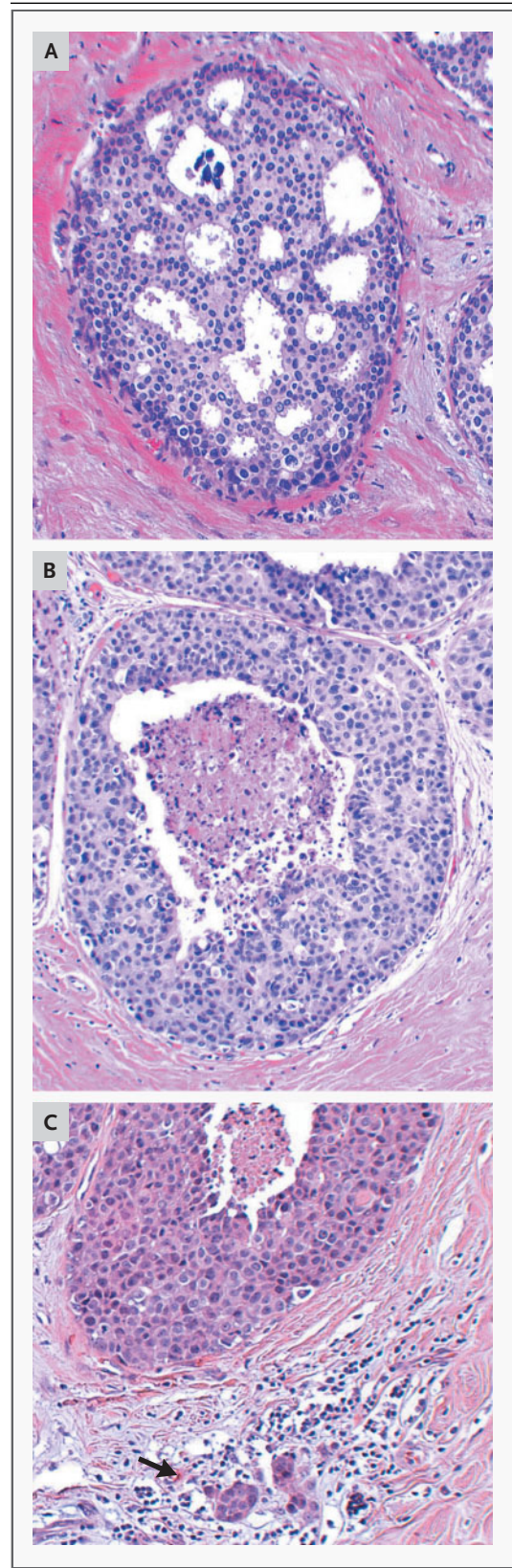
Older age, benign breast disease, a family history of breast cancer, and reproductive factors such as nulliparity or an older age at the time of the first full-term pregnancy are all associated with an increased risk of both invasive breast cancer and ductal carcinoma in situ.[28-30] Population-based models that use family history and demographic data predict that 5 percent of women with ductal carcinoma in situ carry a mutation in the *BRCA1* or *BRCA2* hereditary cancer gene.[31] Postmenopausal hormone-replacement therapy may increase the risk of ductal carcinoma in situ.[32,33] Like invasive breast cancer, ductal carcinoma in situ overwhelmingly affects women; it is rare among men.[34]

Before the use of screening mammography became widespread, ductal carcinoma in situ was diagnosed after the finding of a palpable breast mass or thickening or nipple discharge or after the diagnosis of Paget's disease of the nipple. In contrast, currently, nearly 90 percent of ductal carcinomas in situ are diagnosed while they are clinically occult because of mammographic detection of microcalcifications (in 76 percent of cases), soft-tissue densities (11 percent), or both (13 percent).[35] Calcification patterns on mammography are only moderately correlated with pathological types of ductal carcinoma in situ.[36]

Microcalcifications in the breast are frequently evaluated by stereotactic core needle biopsy; they can be benign or malignant. Patients with atypical ductal hyperplasia that has been identified on core needle biopsy should undergo wider, surgical biopsy because 10 to 50 percent of such lesions may include ductal carcinoma in situ or invasive cancer on subsequent excision.[37,38] Similarly, patients with ductal carcinoma in situ that is diagnosed on core needle biopsy require surgical excision to remove the ductal carcinoma in situ and rule out associated invasive carcinoma, which is found on excision in approximately 10 to 15 percent of cases — a likelihood that increases with the grade of ductal carcinoma in situ.[38,39]

The crucial task on pathological assessment is to distinguish ductal carcinoma in situ from invasive cancer. The pathological classification of ductal carcinoma in situ is based on the nuclear grade of the tumor cells (low, intermediate, or high), the architectural pattern of tumor growth (solid, papillary, micropapillary, or cribriform), and the presence or absence of comedonecrosis (Fig. 2). Classification remains a challenge owing to differing pathological criteria, interobserver variability,[40] and the heterogeneous nature of tumor growth. High-grade lesions and lesions associated with comedonecrosis are associated with the greatest risk of recurrence after breast-conserving surgery (Table 1).[50]

Discontinuous growth within the ductal system of the breast and the irregular nature of associated calcifications make the extent of ductal carcinoma in situ difficult to determine. Ductal carcinoma in situ originates in a single glandular structure but may spread within the breast through the ductal system.[51,52] Two thirds of patients with low-to-intermediate-grade ductal carcinoma in situ have multifocal disease, characterized by discontinuous intraductal growth, with gaps of up to 1 cm between tumor foci. In contrast, high-grade lesions tend to be continuous, with most having no gaps greater than 5 mm.[51,52] Because of the discontinuous spread of ductal carcinoma in situ through the ductal system, the use of standard mammographic views may underestimate the extent of the lesion, especially in the case of low- and intermediate-grade tumors. Thus, magnification views are warranted. True multicentric ductal carcinoma in situ, originating in two discrete ductal systems, is uncommon.

Ductal carcinoma in situ may be associated with an occult microinvasive tumor (one that does not exceed 0.1 cm in diameter) (Fig. 2). Such cases are classified as microinvasive breast cancer[53] and are generally treated according to the guidelines for invasive disease. Occult microinvasive tumors are most common in patients with ductal carcinoma in situ lesions that are greater than 2.5 cm in diameter,[54] those presenting with palpable masses or nipple discharge, and those with high-grade ductal carcinoma in situ or comedonecrosis.[55-57]

The natural history of untreated low-grade ductal carcinoma in situ has been defined in long-term, follow-up studies of women who underwent diagnostic biopsy alone in the era before widespread screening mammography.[58-60] After 10 years of follow-up, 14 to 60 percent of the women had received a diagnosis of invasive cancer in the affected breast. Such risk is widely thought to justify present treatment approaches to ductal carcinoma in situ. The natural history of untreated high-grade ductal carcinoma in situ or ductal carcinoma in situ detected clinically is not well characterized, since in most cases, the tumor has been fully excised surgically.

Table 1. A Comparison of the Risk of Contralateral or Recurrent Ipsilateral Breast Tumor in Randomized Clinical Trials of the Treatment of Ductal Carcinoma in Situ.

Trial*	No. of Patients	Follow-up	Risk of Ipsilateral Tumor Recurrence† (percent)			Hazard Ratio for Intervention‡	P Value	Risk of Contralateral Breast Cancer§ (percent)	Factors Significantly Associated with Recurrence¶	Treatment Results
			Excision Alone	Excision plus Radiotherapy	Excision plus Radiotherapy plus Tamoxifen					
NSABP B-17[1-45]	818	5 Yr (actuarial)	16	7	—	0.43	<0.001	6.6	Moderate or marked comedonecrosis (1.72–1.94)	Radiotherapy reduced risk of local relapse in all subgroups
		8 Yr (actuarial)	27	12	—				Uncertain or involved margins (1.48–2.33)	
		12 Yr (actuarial)	32	16	—					
EORTC 10853[46,47]	1010	4 Yr (median)	16	9	—	0.62	0.005	3	Age ≤40 (2.1) Cribriform or solid or comedo histologic findings (2.6) Clinical presentation (1.8) Close or involved or unspecified margins (2.1)	Radiotherapy reduced risk of local relapse in all subgroups
NSABP B-24[43,48]	1804	5 Yr (actuarial)	—	9	6	0.69	0.02	Tamoxifen, 2 No tamoxifen, 5	Age >50 yr (0.46) Positive margins (1.84)	Tamoxifen reduced risk of local relapse in all subgroups
		7 Yr (actuarial)	—	11	8				Comedonecrosis (1.82) Clinical presentation (1.90)	
UKCCCR[49]§	1701	5 Yr (actuarial)	14	6	No tamoxifen, 15 Tamoxifen, 13	Radiotherapy, 0.38 Tamoxifen, 0.90	Radiotherapy, <0.001 Tamoxifen, 0.42	2		

* NSABP denotes National Surgical Adjuvant Breast and Bowel Project, EORTC European Organization for Research and Treatment of Cancer, and UKCCCR United Kingdom Coordinating Committee on Cancer Research.

† The dose of radiation was 50 Gy given in 25 fractions of 200 cGy, without a boost. Tamoxifen was given orally, 20 mg per day for five years. In UKCCCR, not all patients receiving tamoxifen received radiotherapy.

‡ In NSABP B-17 and EORTC 10853, the hazard ratios are for excision alone as compared with excision plus radiotherapy. In NSABP B-24, the hazard ratio is for excision plus radiotherapy as compared with excision plus radiotherapy and tamoxifen. In UKCCCR, on the basis of a two-by-two factorial design, the hazard ratios are for excision alone as compared with excision plus radiotherapy, and for local therapy or local therapy plus tamoxifen, respectively.

§ The risk was assessed through the longest reported follow-up period.

¶ The numbers in parentheses denote the relative risk as compared with patients or tumors without the given factor.

TREATMENT

The goal in treating ductal carcinoma in situ is prevention of local recurrence — in particular, invasive breast cancer. The options for surgical treatment include simple mastectomy or breast-conserving surgery (often called lumpectomy, though in most cases, there is no lump), with only the affected areas of the breast excised. Mastectomy and breast-conserving surgery as treatments for ductal carcinoma in situ have not been compared in prospective, randomized trials. Data from some surgical trials[61] and large treatment registries[62-64] suggest that the rates of local or regional recurrence are significantly lower after mastectomy than after breast-conserving surgery, but there have been no significant differences in overall survival. Metastatic breast cancer can follow the recurrence of an invasive tumor or the development of cancer in the contralateral breast. However, death related to breast cancer within 10 years after the diagnosis of ductal carcinoma in situ occurs in only 1 to 2 percent of all patients, irrespective of whether mastectomy or breast-conserving surgery was performed.[62]

Historically, ductal carcinoma in situ was treated with mastectomy. Simple mastectomy is highly effective for ductal carcinoma in situ — curing at least 98 percent of lesions — and is a potential treatment option for all patients. Breast cancer recurs in 1 to 2 percent of patients with ductal carcinoma in situ who have undergone mastectomy, owing to the presence of occult invasive disease at the time of diagnosis, recurrence within residual breast tissue, or contralateral breast cancer. Women with ductal carcinoma in situ in one breast are at risk for a second tumor (either invasive or in situ) in the contralateral breast[65]; the rate at which such tumors develop is similar to that among women with primary invasive breast cancer — approximately 0.5 to 1 percent per year (Table 1).
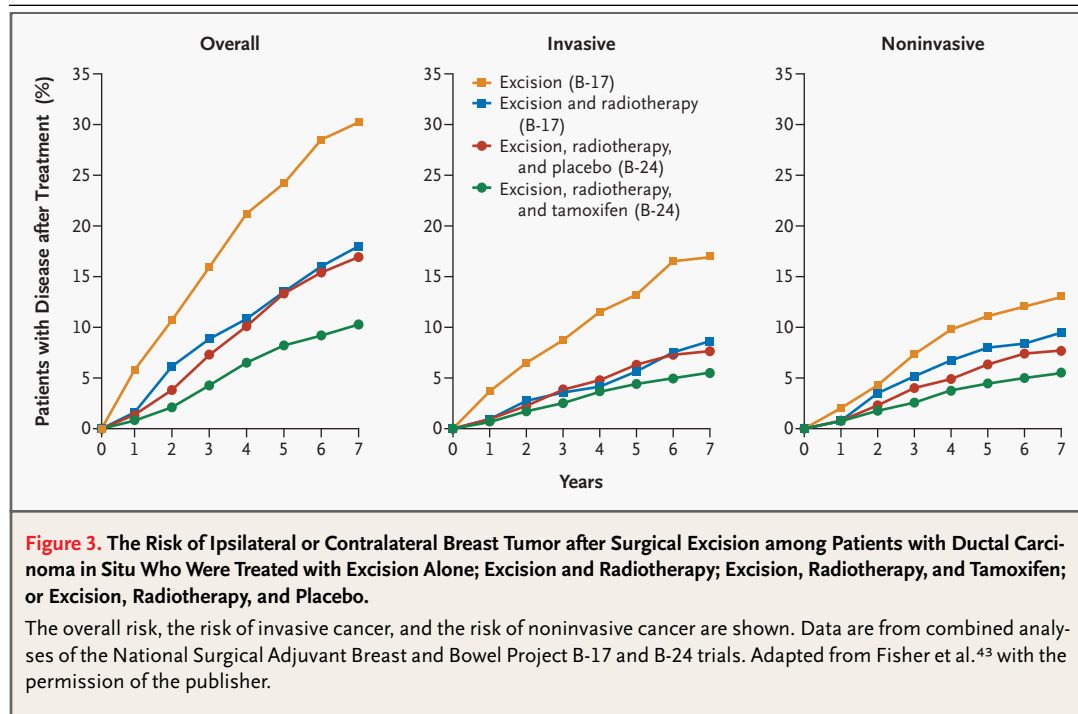
At the present time, most women in the United States are treated with breast-conserving surgical excision.[66,67] This pattern reflects the detection of smaller, clinically occult ductal carcinoma in situ lesions with the use of mammography and the shift in treatment toward breast-conserving surgery for invasive breast cancer, after the demonstration that modified radical mastectomy and breast-conserving surgery are associated with equivalent survival rates.[68] It seems paradoxical to offer more extensive surgery for preinvasive cancer than for invasive cancer. Early studies of the treatment of ductal carcinoma in situ with excision alone[69,70] as compared with excision and radiotherapy[71] showed acceptably low recurrence rates that justified further exploration of breast conservation.

After breast-conserving surgery for ductal carcinoma in situ, women are at risk for recurrence within the breast. Half the recurrences in the ipsilateral breast are invasive tumors, and half are ductal carcinoma in situ. Most recurrences are at or near the original site of the tumor, with pathological features that are similar to those of the index lesion,[69] including shared histologic features such as the grade and expression of estrogen receptor and *HER2*, as well as clonal genetic features.[72,73] Thus, although true second cancers may occur, most recurrences in the ipsilateral breast arise from residual microscopical disease at or near the original site of the tumor.

Principles for managing ductal carcinoma in situ in women who have undergone breast-conserving surgery have been defined on the basis of large, prospective, randomized clinical trials (Table 1). Three randomized trials directly compared excision alone with excision and radiotherapy for fully excised ductal carcinoma in situ among patients with negative margins, defined as the absence of tumor at the inked surgical surface.[41,46,49] Most patients in these studies had small areas of ductal carcinoma in situ (less than 2 cm in diameter), detected with mammography. Radiotherapy consistently reduces the risk of recurrence in the ipsilateral breast by 40 to 60 percent. At five years of follow-up, excision alone is associated with approximately a 16 percent risk of recurrence in the ipsilateral breast; radiotherapy reduces this risk to approximately 8 percent. These relative benefits persist for at least 12 years, though the absolute risk of recurrence continues to increase over time (Table 1 and Fig. 3).[42,43] In two large international-registry studies of the treatment of ductal carcinoma in situ, the rates of local recurrence were 16 and 19 percent at 15 years[74,75] among women who were treated with breast-conserving surgery and radiation — results that are generally consistent with those of randomized trials.

The selective estrogen-receptor modulator tamoxifen has also been studied as adjuvant therapy in women with ductal carcinoma in situ who have undergone excision and radiation treatment.[43,48] In the B-24 trial of the National Surgical Adjuvant Breast and Bowel Project (NSABP), tamoxifen reduced the likelihood of recurrence in the ipsilateral breast at five years from 9 to 6 percent, an absolute risk reduction of 3 percent, and reduced the risk of a

Figure 3. The Risk of Ipsilateral or Contralateral Breast Tumor after Surgical Excision among Patients with Ductal Carcinoma in Situ Who Were Treated with Excision Alone; Excision and Radiotherapy; Excision, Radiotherapy, and Tamoxifen; or Excision, Radiotherapy, and Placebo.

The overall risk, the risk of invasive cancer, and the risk of noninvasive cancer are shown. Data are from combined analyses of the National Surgical Adjuvant Breast and Bowel Project B-17 and B-24 trials. Adapted from Fisher et al.[43] with the permission of the publisher.

tumor in the contralateral breast (Table 1 and Fig. 3). In a related study with a two-by-two factorial design in which patients were randomly assigned to radiation or no radiation and to tamoxifen or no tamoxifen, the women who received both radiotherapy and tamoxifen had the lowest rate of recurrence in the breast; however, the additional benefits of tamoxifen were small and did not reach statistical significance.[49] Tamoxifen may be especially valuable in preventing ipsilateral tumor recurrence among patients also receiving radiotherapy, as has been demonstrated in the treatment of small, invasive breast cancers.[76] There is no role for chemotherapy in the treatment of ductal carcinoma in situ.

In a preliminary retrospective analysis, estrogen-receptor expression was a marker of a benefit of tamoxifen in patients with ductal carcinoma in situ.[77] Tamoxifen reduced the risk of recurrence by 60 percent in patients with estrogen-receptor–positive ductal carcinoma in situ, whereas the risk reduction for estrogen-receptor–negative lesions was not statistically significant. Thus, as with invasive breast cancer, the role of tamoxifen in the treatment of ductal carcinoma in situ may be limited to tumors that are estrogen-receptor positive, but this awaits confirmation. Figure 3 shows the risk of recurrence in the ipsilateral breast or a tumor in the contralateral breast among women treated with excision

alone, excision and radiation, or excision, radiation, and tamoxifen in the NSABP randomized trials.

The predictors of recurrent tumor after breast-conserving surgery for ductal carcinoma in situ have been extensively studied. Close (less than 1 mm) or positive surgical margins and high-grade or comedonecrotic lesions are associated with an increased risk of local recurrence.[74,75,78-83] Subgroup analyses from randomized trials have demonstrated that the absolute benefits of radiotherapy are greater in women at increased risk for tumor recurrence, such as women with involved surgical margins (identified on retrospective pathological review), younger women, and those with tumors that have high-grade or comedonecrotic features.[44,45,47] However, radiotherapy still lowers the incidence of recurrence among all such subgroups, regardless of the base-line risk.

Younger age (usually defined as less than 40 or less than 45 years) is a significant predictor of recurrence after breast-conserving surgery.[75,84] Younger age is also associated with other adverse clinical factors, including a higher tumor grade or necrosis, clinical (as opposed to mammographic) findings on presentation, and more extensive disease. Some data suggest that younger women are treated with less extensive resection of ductal carcinoma in situ at the time of lumpectomy.[85] However, none of

these factors in themselves make younger patients ineligible for breast-conserving therapy.

Ipsilateral tumor recurrences in patients with ductal carcinoma in situ are usually detected on surveillance mammography, although one quarter may be detected on the basis of changes on physical examination of the breast or chest wall.[86-88] For this reason, patients should be scheduled for a base-line mammogram 6 to 12 months after initial therapy and at least annually thereafter. Distant breast-cancer metastases in the absence of regional recurrence are unusual. Local recurrences after breast-conserving surgery and radiotherapy are generally treated with mastectomy. Selected patients with local recurrences who have not previously received radiotherapy may be candidates for local excision and radiotherapy. The clinical outcome of ipsilateral tumor recurrence is governed by the nature of the recurrence. Patients with recurrent ductal carcinoma in situ have an excellent prognosis, with less than a 1 percent risk of further recurrence after salvage mastectomy. Patients with invasive recurrence after breast-conserving surgery for ductal carcinoma in situ have a prognosis similar to those with early-stage breast cancer, with a 15 to 20 percent risk of metastatic recurrence at eight years.[87-89]

CLINICAL MANAGEMENT

The standard management of ductal carcinoma in situ consists of coordinated, interdisciplinary care provided by radiologists, surgeons, pathologists, and oncologists; treatment recommendations are summarized in Table 2. Patients are first assessed to determine whether they are candidates for breast-conserving surgery. Women with multicentric ductal carcinoma in situ, as defined by the presence of two or more tumors in separate quadrants of the breast, and those with extensive or diffuse ductal carcinoma in situ or suspicious-appearing microcalcifications throughout the breast are candidates for mastectomy, as are women in whom negative margins or acceptable cosmesis cannot be achieved with the use of breast-conserving surgery. Similarly, women who are not candidates for radiotherapy because they have a collagen vascular disease such as scleroderma or active systemic lupus erythematosus, have previously undergone radiotherapy, or are pregnant should be offered mastectomy. Some women may prefer mastectomy to breast conservation in order to minimize the chance of ipsilateral recurrence or for other reasons. At present, there is no established role for the use of magnetic resonance imaging in screening patients for ductal carcinoma in situ or in determining whether breast-conserving surgery is an option.

Patients deemed to be appropriate candidates for breast conservation require complete surgical excision of the affected area. Careful orientation marking of the surgical specimen may facilitate subsequent reexcision, if necessary. The extent of ductal carcinoma in situ in the breast[90] and the existing margin determine the likelihood of identifying residual disease on reexcision. Nearly half of patients with margins that are less than 1 mm have residual ductal carcinoma in situ on reexcision.[91,92] However, the optimal margin width for the management of ductal carcinoma in situ is not known. At a minimum, there should be no tumor at the margin. Margins with a width of 1 mm or more are associated with a reduced risk of recurrence, a reasonable treatment goal.

Neither dissection of axillary lymph nodes nor mapping of sentinel lymph nodes is routinely warranted in patients with ductal carcinoma in situ, owing to the very low incidence of axillary metastases.[93] Three to 13 percent of patients with ductal carcinoma in situ, and a slightly greater percentage with ductal carcinoma in situ characterized by microinvasion, have isolated tumor cells in sentinel axillary lymph nodes.[94-97] The prognostic significance of these cells is not clear. Clinical experience suggests that patients have a much better outcome than would be predicted by such rates of nodal metastases, and the vast majority of instances represent micrometastases of unclear metastatic potential. However, sentinel-lymph-node mapping may be used in selected patients with a higher likelihood of occult invasive cancer — those with extensive, high-grade ductal carcinoma in situ or palpable masses — and those undergoing mastectomy, since sentinel-node mapping cannot be performed afterward if invasive tumor is identified.[98]

After breast-conserving surgery, radiotherapy is administered in tangential fields to the whole breast. The standard dose, 44 to 50 Gy delivered in fractions of 180 to 200 cGy on a daily basis, results in control of the tumor, and in most cases, the cosmetic outcome is rated as good to excellent. On the basis of extrapolation from data on the treatment of invasive breast cancer,[99,100] a radiation boost to the tumor bed may be added to whole-breast treatment, particularly for women with close surgical margins, although the benefits of such therapy for

---

Table 2. Standard Management of Ductal Carcinoma in Situ.

Mammography and other imaging

Preoperative magnification views to establish extent of ipsilateral disease

Contralateral-breast imaging to rule out concurrent bilateral disease

Radiography to confirm excision of microcalcifications

Postexcision breast imaging to confirm removal of suspicious-appearing areas

Annual surveillance to screen for recurrence and contralateral cancer

Pathological evaluation

Exclusion of invasive breast cancer

Characterization of nuclear grade, size and extent of tumor, presence or absence of comedonecrosis, and tumor architecture

Assessment, including measurement, of surgical margins

Determination of estrogen-receptor status in patients considering tamoxifen therapy after breast-conserving surgery

Breast surgery

Assessment for possible breast-conserving surgery on the basis of the extent of ductal carcinoma in situ or associated calcifications, suitability for subsequent radiotherapy, anticipated cosmetic result, and the patient's preference

Excisional biopsy, with careful orientation of the specimen, to remove ductal carcinoma in situ with negative margins at least 1 mm in width

Reexcision as necessary to obtain negative margins

Simple mastectomy, with or without reconstruction, if the patient is not a candidate for breast-conserving surgery or if the patient prefers mastectomy

Axillary surgery

Neither axillary-node dissection nor sentinel-lymph-node mapping routinely indicated

Consideration of sentinel axillary lymph node evaluation in women undergoing mastectomy for ducted carcinoma in situ or in women at higher risk for occult invasive disease (e.g., in a patient with a clinically palpable mass or areas of ductal carcinoma in situ over 4 cm)

Radiotherapy

Not indicated after mastectomy

Routinely administered after breast-conserving surgery to reduce risk of ipsilateral recurrence

Adjuvant hormonal therapy

Consideration of tamoxifen after breast-conserving surgery and radiotherapy to reduce risk of ipsilateral recurrence and contralateral disease, particularly in the case of estrogen-receptor–positive ductal carcinoma in situ

Investigational approaches

Omission of radiotherapy for a low-risk patient treated with excision alone (appropriate clinical and pathological criteria for selecting such patients are not uniformly established; no supporting data from prospective studies)

Evaluation of novel systemic adjuvant treatments

---

the management of ductal carcinoma in situ are not well characterized. Partial-breast irradiation has not been studied in patients with ductal carcinoma in situ. There is no proven role for postmastectomy or nodal irradiation in the treatment of ductal carcinoma in situ.

Methods of identifying patients with ductal carcinoma in situ who may not require radiotherapy after excision of the tumor are being investigated. A retrospective analysis has suggested that patients with low-grade, small tumors[101] or lesions with margins greater than 10 mm[102] have a very favorable prognosis, which may not be improved by radiotherapy. To date, this finding has not been confirmed in prospective studies of wide excision alone as therapy for ductal carcinoma in situ. In a study of women who had small areas of low- or intermediate-grade ductal carcinoma in situ, with negative reexcisions or margins of at least 1 cm, the recurrence rate was 12 percent five years after excision alone — a substantially higher rate than that predicted on the basis of retrospective analyses.[103] Thus, it is not yet possible to identify prospectively women who are at sufficiently low risk that radiotherapy may not be of some clinical advantage in preventing recurrences. After discussing the various options, patients may elect not to receive radiation treatment, but they must understand and accept the increased risk of recurrence that this choice probably entails.

Surveys of patients have shown that women with ductal carcinoma in situ have considerable deficits in their knowledge of the disease and that their lev-

els of psychological distress and fear of recurrent disease and death are similar to those among women with invasive breast cancer.[104,105] Clinicians can address their patients' misconceptions by providing accurate information and counseling.

Because ductal carcinoma in situ is a precursor to invasive breast cancer and shares many biologic features of invasive disease, it is increasingly recognized as a target for preventive measures. In the largest trials of the prevention of primary breast cancer among women at high risk for breast cancer by virtue of age, family history, or prior benign breast disease, tamoxifen reduced the risk of ductal carcinoma in situ by 50 to 70 percent.[106,107]

In summary, ductal carcinoma in situ is a preinvasive breast tumor commonly detected in women undergoing screening mammography. Ductal carcinoma in situ is heterogeneous, with a spectrum of biologic and clinical features affecting the likelihood of transformation to invasive breast cancer

and recurrence within the affected breast. The goal of treatment is to reduce the risk of recurrent disease in the breast, particularly invasive cancer. A variety of treatment options are available to patients, but there are no data showing that any one strategy provides superior survival. The treatment options vary with respect to the risk of a recurrence in the ipsilateral breast and side effects. Treatment choices are complicated by the varied clinical behavior of ductal carcinoma in situ. Patients and clinicians can use available data on likely benefits and potential side effects of therapy to make well-informed treatment decisions.

REFERENCES

1. Allred DC, Mohsin SK, Fuqua SAW. Histological and biological evolution of human premalignant breast disease. Endocr Relat Cancer 2001;8:47-61.

2. Radford DM, Phillips NHJ, Fair KL, Ritter JH, Holt M, Donis-Keller H. Allelic loss and the progression of breast cancer. Cancer Res 1995;55:5180-3. [Erratum, Cancer Res 1996;56:935.]

3. Stratton MR, Collins N, Lakhani SR, Sloane JP. Loss of heterozygosity in ductal carcinoma in situ of the breast. J Pathol 1995;175:195-201.

4. O'Connell P, Pekkel V, Fuqua SA, Osborne CK, Clark GM, Allred DC. Analysis of loss of heterozygosity in 399 premalignant breast lesions at 15 genetic loci. J Natl Cancer Inst 1998;90:697-703.

5. Aubele MM, Cummings MC, Mattis AE, et al. Accumulation of chromosomal imbalances from intraductal proliferative lesions to adjacent in situ and invasive ductal breast cancer. Diagn Mol Pathol 2000;9:14-9.

6. Farabegoli F, Champeme MH, Bieche I, et al. Genetic pathways in the evolution of breast ductal carcinoma in situ. J Pathol 2002;196:280-6.

7. Allred DC, Clark GM, Molina R, et al. Overexpression of HER-2/neu and its relationship with other prognostic factors change during the progression of in situ to invasive breast cancer. Hum Pathol 1992;23:974-9.

8. Rudas M, Neumayer R, Gnant MFX, Mittelbock M, Jakesz R, Reiner A. p53 Protein expression, cell proliferation and steroid hormone receptors in ductal and lobular in situ carcinomas of the breast. Eur J Cancer 1997;33:39-44.

9. Luzzi V, Holtschlag V, Watson MA. Expression profiling of ductal carcinoma in situ by laser capture microdissection and high-density oligonucleotide arrays. Am J Pathol 2001;158:2005-10.

10. Porter DA, Krop IE, Nasser S, et al. A SAGE (serial analysis of gene expression) view of breast tumor progression. Cancer Res 2001;61:5697-702.

11. Wulfkuhle JD, Sgroi DC, Krutzsch H, et al. Proteomics of human breast ductal carcinoma in situ. Cancer Res 2002;62:6740-9.

12. Porter D, Lahti-Domenici J, Keshaviah A, et al. Molecular markers in ductal carcinoma in situ of the breast. Mol Cancer Res 2003;1:362-75.

13. Ma XJ, Salunga R, Tuggle JT, et al. Gene expression profiles of human breast cancer progression. Proc Natl Acad Sci U S A 2003;100:5974-9.

14. Adeyinka A, Emberley E, Niu Y, et al. Analysis of gene expression in ductal carcinoma in situ of the breast. Clin Cancer Res 2002;8:3788-95.

15. Seth A, Kitching R, Landberg G, Xu J, Zubovits J, Burger AM. Gene expression profiling of ductal carcinomas in situ and invasive breast tumors. Anticancer Res 2003;23:2043-51.

16. Damiani S, Ludvikova M, Tomasic G, Bianchi S, Gown AM, Eusebi V. Myoepithelial cells and basal lamina in poorly differentiated in situ duct carcinoma of the breast: an immunocytochemical study. Virchows Arch 1999;434:227-34.

17. Guidi AJ, Schnitt SJ, Fischer L, et al. Vascular permeability factor (vascular endothelial growth factor) expression and angiogenesis in patients with ductal carcinoma in situ of the breast. Cancer 1997;80:1945-53.

18. Guidi AJ, Fischer L, Harris JR, Schnitt SJ.

Microvessel density and distribution of ductal carcinoma in situ of the breast. J Natl Cancer Inst 1994;86:614-9.

19. Allred DC, Wu Y, Tsimelzon A, Hilsenbeck SG, Osborne CK, O'Connell P. The progression of DCIS to IBC: a cDNA expression microarray study. Breast Cancer Res Treat 2002;76:Suppl 1:S81. abstract.

20. Allred DC. Biologic characteristics of ductal carcinoma in situ. In: Silverstein MJ, ed. Ductal carcinoma in situ of the breast. 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2002:37-48.

21. Lampejo OT, Barnes DM, Smith P, Millis RR. Evaluation of infiltrating ductal carcinomas with a DCIS component: correlation of the histologic type of the in situ component with grade of the infiltrating component. Semin Diagn Pathol 1994;11:215-22.

22. Gupta SK, Douglas-Jones AG, Fenn N, Morgan JM, Mansel RE. The clinical behavior of breast carcinoma is probably determined at the preinvasive stage (ductal carcinoma in situ). Cancer 1997;80:1740-5.

23. Warnberg F, Nordgren H, Bergkvist L, Holmberg L. Tumour markers in breast carcinoma correlate with grade rather than with invasiveness. Br J Cancer 2001;85:869-74.

24. Buerger H, Otterbach F, Simon R, et al. Different genetic pathways in the evolution of invasive breast cancer are associated with distinct morphological subtypes. J Pathol 1999;189:521-6.

25. Ernster VL, Barclay J, Kerlikowske K, Grady D, Henderson C. Incidence of and treatment for ductal carcinoma in situ of the breast. JAMA 1996;275:913-8.

26. Ernster VL, Ballard-Barbash R, Barlow WE, et al. Detection of ductal carcinoma in situ in women undergoing screening mam-

mography. J Natl Cancer Inst 2002;94:1546-54.

27. Olivotto IA, Bancej C, Goel V, et al. Waiting times from abnormal breast screen to diagnosis in 7 Canadian provinces. CMAJ 2001;165:277-83.

28. Kerlikowske K, Barclay J, Grady D, Sickles EA, Ernster V. Comparison of risk factors for ductal carcinoma in situ and invasive breast cancer. J Natl Cancer Inst 1997;89:76-82.

29. Claus EB, Stowe M, Carter D. Breast carcinoma in situ: risk factors and screening patterns. J Natl Cancer Inst 2001;93:1811-7.

30. Trentham-Dietz A, Newcomb PA, Storer BE, Remington PL. Risk factors for carcinoma in situ of the breast. Cancer Epidemiol Biomarkers Prev 2000;9:697-703.

31. Claus EB, Stowe M, Carter D. Family history of breast and ovarian cancer and the risk of breast carcinoma in situ. Breast Cancer Res Treat 2003;78:7-15.

32. Chen W, Schnitt S, Rosner BA, Colditz GA. Influence of postmenopausal hormone use (PMH) on breast cancer tumor characteristics. Prog Proc Am Soc Clin Oncol 2003; 22:845. abstract.

33. Gapstur SM, Morrow M, Sellers TA. Hormone replacement therapy and risk of breast cancer with a favorable histology: results of the Iowa Women's Health Study. JAMA 1999;281:2091-7.

34. Hittmair AP, Lininger RA, Tavassoli FA. Ductal carcinoma in situ (DCIS) in the male breast: a morphologic study of 84 cases of pure DCIS and 30 cases of DCIS associated with invasive carcinoma — a preliminary report. Cancer 1998;83:2139-49.

35. Stomper PC, Connolly JL, Meyer JE, Harris JR. Clinically occult ductal carcinoma in situ detected with mammography: analysis of 100 cases with radiologic-pathologic correlation. Radiology 1989;172:235-41.

36. Stomper PC, Connolly JL. Ductal carcinoma in situ of the breast: correlation between mammographic calcification and tumor subtype. AJR Am J Roentgenol 1992; 159:483-5.

37. Bassett L, Winchester DP, Caplan RB, et al. Stereotactic core-needle biopsy of the breast: a report of the Joint Task Force of the American College of Radiology, American College of Surgeons, and College of American Pathologists. Ca Cancer J Clin 1997;47:171-90.

38. Darling ML, Smith DN, Lester SC, et al. Atypical ductal hyperplasia and ductal carcinoma in situ as revealed by large-core needle breast biopsy: results of surgical excision. Am J Radiol 2000;175:1341-6.

39. Bonnett M, Wallis T, Rossmann M, et al. Histologic and radiographic analysis of ductal carcinoma in situ diagnosed using stereotactic incisional core breast biopsy. Mod Pathol 2002;15:95-101.

40. Schnitt SJ, Connolly JL, Tavassoli FA, et al. Interobserver reproducibility in the diagnosis of ductal proliferative breast lesions using standardized criteria. Am J Surg Pathol 1992;16:1133-43.

41. Fisher B, Costantino J, Redmond C, et al. Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer. N Engl J Med 1993;328:1581-6.

42. Fisher B, Dignam J, Wolmark N, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from the National Surgical Adjuvant Breast and Bowel Project B-17. J Clin Oncol 1998;16:441-52.

43. Fisher B, Land S, Mamounas E, Dignam J, Fisher ER, Wolmark N. Prevention of invasive breast cancer in women with ductal carcinoma in situ: an update of the National Surgical Adjuvant Breast and Bowel Project experience. Semin Oncol 2001;28:400-18.

44. Fisher ER, Costantino J, Fisher B, Palekar AS, Redmond C, Mamounas E. Pathological findings from the National Surgical Adjuvant Breast Project (NSABP) Protocol B-17: intraductal carcinoma (ductal carcinoma in situ). Cancer 1995;75:1310-9.

45. Fisher ER, Dignam J, Tan-Chiu E, et al. Pathological findings from the National Surgical Adjuvant Breast Project (NSABP) eight-year update of Protocol B-17: intraductal carcinoma. Cancer 1999;86:429-38.

46. Julien JP, Bijker N, Fentiman IS, et al. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. Lancet 2000;355:528-33.

47. Bijker N, Peterse JL, Duchateau L, et al. Risk factors for recurrence and metastasis after breast-conserving therapy for ductal carcinoma-in-situ: analysis of European Organization for Research and Treatment of Cancer Trial 10853. J Clin Oncol 2001;19:2263-71.

48. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. Lancet 1999;353:1993-2000.

49. Houghton J, George WD, Cuzick J, Duggan C, Fentiman IS, Spittle M. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomised controlled trial. Lancet 2003;362:95-102.

50. Kerlikowske K, Molinaro A, Cha I, et al. Characteristics associated with recurrence among women with ductal carcinoma in situ treated by lumpectomy. J Natl Cancer Inst 2003;95:1692-702.

51. Holland R, Hendriks JHCL, Verbeek ALM, Mravunac M, Schuurmans Stekhoven JH. Extent, distribution, and mammographic/histologic correlations of breast ductal carcinoma in situ. Lancet 1990;335:519-22.

52. Faverly DRG, Burgers L, Bult P, Holland R. Three dimensional imaging of mammary ductal carcinoma in situ: clinical implications. Semin Diagn Pathol 1994;11:193-8.

53. Singletary SE, Allred C, Ashley P, et al. Revision of the American Joint Committee on Cancer staging system for breast cancer. J Clin Oncol 2002;20:3628-36.

54. Lagios MD, Margolin FR, Westdahl PR, Rose MR. Mammographically detected duct carcinoma in situ: frequency of local recurrence following tylectomy and prognostic effect of nuclear grade on local recurrence. Cancer 1989;63:618-24.

55. Patchefsky AS, Schwartz GF, Finkelstein SD, et al. Heterogeneity of intraductal carcinoma of the breast. Cancer 1989;63:731-41.

56. Silver SA, Tavassoli FA. Mammary ductal carcinoma in situ with microinvasion. Cancer 1998;82:2382-90.

57. de Mascarel I, MacGrogan G, Mathoulin-Pelissier S, Soubeyran I, Picot V, Coindre JM. Breast ductal carcinoma in situ with microinvasion: a definition supported by a long-term study of 1248 serially sectioned ductal carcinomas. Cancer 2002;94:2134-42.

58. Betsill WL Jr, Rosen PP, Lieberman PH, Robbins GF. Intraductal carcinoma: long-term follow-up after treatment by biopsy alone. JAMA 1978;239:1863-7.

59. Page DL, Dupont WD, Rogers LW, Jensen RA, Schuyler PA. Continued local recurrence of carcinoma 15-25 years after a diagnosis of low grade ductal carcinoma in situ of the breast treated only by biopsy. Cancer 1995;76:1197-200.

60. Eusebi V, Feudale E, Foschini MP, et al. Long-term follow-up of in situ carcinoma of the breast. Semin Diagn Pathol 1994;11:223-35.

61. Fisher ER, Leeming R, Anderson S, Redmond C, Fisher B. Conservative management of intraductal carcinoma (DCIS) of the breast. J Surg Oncol 1991;47:139-47.

62. Ernster VL, Barclay J, Kerlikowske K, Wilkie H, Ballard-Barbash R. Mortality among women with ductal carcinoma in situ of the breast in the population-based Surveillance, Epidemiology and End Results program. Arch Intern Med 2000;160:953-8.

63. Cutuli B, Cohen-Solal-Le Nir C, de Lafontan B, et al. Ductal carcinoma in situ of the breast: results of conservative and radical treatments in 716 patients. Eur J Cancer 2001;37:2365-72.

64. Silverstein MJ, Barth A, Poller DN, et al. Ten-year results comparing mastectomy to excision and radiation therapy for ductal carcinoma in situ of the breast. Eur J Cancer 1995;31A:1425-7.

65. Habel LA, Moe RE, Daling JR, Holte S, Rossing MA, Weiss NS. Risk of contralateral breast cancer among women with carcinoma in situ of the breast. Ann Surg 1997;225:69-75.

66. Winchester DJ, Menck HR, Winchester DP. National treatment trends for ductal carcinoma in situ of the breast. Arch Surg 1997;132:660-5.

67. Baxter NN, Virnig BA, Durham SB, Tuttle TM. Patterns of care for DCIS: consistency with standard recommendations. Prog Proc Am Soc Clin Oncol 2003;22:27. abstract.

68. Fisher B, Bauer M, Margolese R, et al. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radia-

tion in the treatment of breast cancer. N Engl J Med 1985;312:665-73.

69. Fisher ER, Sass R, Fisher B, Wickerham L, Paik SM. Pathologic findings from the National Surgical Adjuvant Breast Project (protocol 6). I. Intraductal carcinoma (DCIS). Cancer 1986;57:197-208.

70. Lagios MD, Westdahl PR, Margolin FR, Rose MR. Duct carcinoma in situ: relationship of extent of noninvasive disease to the frequency of occult invasion, multicentricity, lymph node metastases, and short-term treatment failures. Cancer 1982;50:1309-14.

71. Recht A, Danoff BS, Solin LJ, et al. Intraductal carcinoma of the breast: results of treatment with excisional biopsy and irradiation. J Clin Oncol 1985;3:1339-43.

72. Bijker N, Peterse JL, Duchateau L, et al. Histologic type and marker expression of the primary tumour compared with its local recurrence after breast-conserving therapy for ductal carcinoma in situ. Br J Cancer 2001;84:539-44.

73. Waldman FM, DeVries S, Chew KL, Moore DH, Kerlikowske K, Ljung BM. Chromosomal alterations in ductal carcinomas in situ and their in situ recurrences. J Natl Cancer Inst 2000;92:313-20.

74. Solin LJ, Kurtz J, Fourquet A, et al. Fifteen-year results of breast-conserving surgery and definitive breast irradiation for the treatment of ductal carcinoma in situ of the breast. J Clin Oncol 1996;14:754-63.

75. Solin LJ, Fourquet A, Vicini FA, et al. Mammographically detected ductal carcinoma in situ of the breast treated with breast-conserving surgery and definitive breast irradiation: long-term outcome and prognostic significance of age and margin status. Int J Radiat Oncol Biol Phys 2001;50:991-1002.

76. Fisher B, Bryant J, Dignam JJ, et al. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. J Clin Oncol 2002;20:4141-9.

77. Allred DC, Bryant J, Land S, et al. Estrogen receptor expression as a predictive marker of effectiveness of tamoxifen in the treatment of DCIS: findings from NSABP Protocol B-24. Breast Cancer Res Treat 2002;76:Suppl 1:S36. abstract.

78. Boyages J, Delaney G, Taylor R. Predictors of local recurrence after treatment of ductal carcinoma in situ: a meta-analysis. Cancer 1999;85:616-28.

79. Silverstein MJ, Lagios MD, Craig PH, et al. A prognostic index for ductal carcinoma in situ of the breast. Cancer 1996;77:2267-74.

80. Tunon-de-Lara C, de-Mascarel I, MacGrogan G, et al. Analysis of 676 cases of ductal carcinoma in situ of the breast from 1971 to 1995: diagnosis and treatment — the experience of one institute. Am J Clin Oncol 2001;24:531-6.

81. Cutuli B, Cohen-Solal-le Nir C, de Lafontan B, et al. Breast-conserving therapy for ductal carcinoma in situ of the breast: the French Cancer Centers' experience. Int J Radiat Oncol Biol Phys 2002;53:868-79.

82. Hetelekidis S, Collins L, Silver B, et al. Predictors of local recurrence following excision alone for ductal carcinoma in situ. Cancer 1999;85:427-31.

83. Neuschatz AC, DiPetrillo T, Safaii H, Lowther D, Landa M, Wazer DE. Margin width as a determinant of local control with and without radiation therapy for ductal carcinoma in situ (DCIS) of the breast. Int J Cancer 2001;96:Suppl:97-104.

84. Vicini FA, Recht A. Age at diagnosis and outcome for women with ductal carcinoma-in-situ of the breast: a critical review of the literature. J Clin Oncol 2002;20:2736-44.

85. Vicini FA, Kestin LL, Goldstein NS, et al. Impact of young age on outcome in patients with ductal carcinoma-in-situ treated with breast-conserving therapy. J Clin Oncol 2000; 18:296-306.

86. Liberman L, Van Zee KJ, Dershaw DD, Morris EA, Abramson AF, Samli B. Mammographic features of local recurrence in women who have undergone breast-conserving therapy for ductal carcinoma in situ. AJR Am J Roentgenol 1997;168:489-93.

87. Solin LJ, Fourquet A, Vicini FA, et al. Salvage treatment for local recurrence after breast-conserving surgery and radiation as initial treatment for mammographically detected ductal carcinoma in situ of the breast. Cancer 2001;91:1090-7.

88. Cutuli B, Lemanski C, Le Blanc M, et al. Local recurrences after DCIS therapy: diagnosis, treatment and outcome. Breast Cancer Res Treat 2002;76:Suppl 1:S36. abstract.

89. Silverstein MJ, Lagios MD, Martino S, et al. Outcome after invasive local recurrence in patients with ductal carcinoma in situ of the breast. J Clin Oncol 1998;16:1367-73.

90. Holland R, Connolly JL, Gelman R, et al. The presence of an extensive intraductal component following a limited excision correlates with prominent residual disease in the remainder of the breast. J Clin Oncol 1990;8:113-8.

91. Silverstein MJ, Gierson ED, Colburn WJ, et al. Can intraductal breast carcinoma be excised completely by local excision? Clinical and pathologic predictors. Cancer 1994; 73:2985-9.

92. Neuschatz AC, DiPetrillo T, Steinhoff M, et al. The value of breast lumpectomy margin assessment as a predictor of residual tumor burden in ductal carcinoma in situ of the breast. Cancer 2002;94:1917-24.

93. Silverstein MJ, Rosser RJ, Gierson ED, et al. Axillary lymph node dissection for intraductal breast carcinoma — is it indicated? Cancer 1987;59:1819-24.

94. Zavotsky J, Hansen N, Brennan MB, Turner RR, Giuliano AE. Lymph node metastasis from ductal carcinoma in situ with microinvasion. Cancer 1999;85:2439-43.

95. Klauber-DeMore N, Tan LK, Liberman L, et al. Sentinel lymph node biopsy: is it indicated in patients with high-risk ductal carcinoma-in-situ and ductal carcinoma-in-situ with microinvasion? Ann Surg Oncol 2000; 7:636-42.

96. Pendas S, Dauway E, Giuliano R, Ku N, Cox CE, Reintgen DS. Sentinel node biopsy in ductal carcinoma in situ patients. Ann Surg Oncol 2000;7:15-20.

97. Intra M, Veronesi P, Mazzarol G, et al. Axillary sentinel lymph node biopsy in patients with pure ductal carcinoma in situ of the breast. Arch Surg 2003;138:309-13.

98. McMasters KM, Chao C, Wong SL, Martin RCG III, Edwards MJ. Sentinel lymph node biopsy in patients with ductal carcinoma in situ: a proposal. Cancer 2002;95:15-20.

99. Schnitt SJ, Abner A, Gelman R, et al. The relationship between microscopic margins of resection and the risk of local recurrence in patients with breast cancer treated with breast-conserving surgery and radiation therapy. Cancer 1994;74:1746-51.

100. Bartelink H, Horiot J-C, Poortmans P, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. N Engl J Med 2001;345:1378-87.

101. Silverstein MJ, Poller DN, Waisman JR, et al. Prognostic classification of breast ductal carcinoma-in-situ. Lancet 1995;345: 1154-7.

102. Silverstein MJ, Lagios MD, Groshen S, et al. The influence of margin width on local control of ductal carcinoma in situ of the breast. N Engl J Med 1999;340:1455-61.

103. Wong JS, Gadd MA, Gelman R, et al. Wide excision alone for ductal carcinoma in situ (DCIS) of the breast. Breast Cancer Res Treat 2003;82:Suppl 1:S10. abstract.

104. Bluman LG, Borstelmann NA, Rimer BK, Iglehart JD, Winer EP. Knowledge, satisfaction, and perceived cancer risk among women diagnosed with ductal carcinoma in situ. J Womens Health Gend Based Med 2001;10:589-98.

105. Rakovitch E, Franssen E, Kim J, et al. A comparison of risk perception and psychological morbidity in women with ductal carcinoma in situ and early invasive breast cancer. Breast Cancer Res Treat 2003;77: 285-93.

106. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998;90:1371-88.

107. Cuzick J, Forbes J, Edwards R, et al. First results from the International Breast Cancer Intervention Study (IBIS-I): a randomised prevention trial. Lancet 2002;360: 817-24.

Copyright © 2004 Massachusetts Medical Society.