

The management of ductal carcinoma *in situ* of the breast

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Abstract

Ductal carcinoma *in situ* (DCIS) of the breast is a heterogeneous group of lesions with diverse malignant potential. It is the most rapidly growing subgroup within the breast cancer family with more than 42 000 new cases diagnosed in the United States during 2000. Most new cases are nonpalpable and are discovered mammographically. Treatment is controversial and ranges from excision only, to excision with radiation therapy, to mastectomy. Prospective randomized trials reveal an approximate 50% reduction in local recurrence rate overall with the addition of radiation therapy to excisional surgery, but the published prospective data do not allow the selection of subgroups in whom the benefit from radiation therapy is so small that its risks outweigh its benefits. Nonrandomized single facility series suggest that age, family history, nuclear grade, comedo-type necrosis, tumor size and margin width are all important factors in predicting local recurrence and that one or more of these factors could be used to select subgroups of patients who do not benefit sufficiently from radiation therapy to merit its use. When all patients with ductal carcinoma *in situ* are considered, the overall mortality from breast cancer is extremely low, only about 1–2%. When conservative treatment fails, approximately 50% of all local recurrences are invasive breast cancer. In spite of this, the mortality rate following invasive local recurrence is relatively low, about 12% with eight years of actuarial follow-up. Genetic changes routinely precede morphological evidence of malignant transformation. Lessons learned from ongoing basic science research will help us to identify those DCIS lesions that are unlikely to progress and to prevent progression in the rest.

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Introduction

Ductal carcinoma *in situ* (DCIS) is a proliferation of presumably malignant epithelial cells within the ducto-lobular system of the breast without evidence, by light microscopy, of invasion through the basement membrane into the surrounding stroma. DCIS presents with a range of architectural forms, with differing growth rates, patterns, and cytological features. Patients with this heterogeneous group of lesions have an increased risk of developing an ipsilateral invasive breast cancer, generally within the same ductal system (quadrant) as the initial DCIS. When experts are asked whether DCIS is really breast cancer, most, but not all, answer yes.

For most of the last century, DCIS was a relatively uncommon lesion, representing less than 1% of all newly diagnosed cases of breast cancer (Nemoto *et al.* 1980). The introduction of high-quality mammography has dramatically increased the detection rate, and today DCIS is the most rapidly growing subtype of breast cancer with a more than 500% increase in new cases from 1983 to 1992 (Ernstner *et al.*

1996). This increase in incidence was observed for both black and white women as well as for women both under and over 50 years of age. During 2000, there was estimated to be more than 42 000 new cases of DCIS in the United States, representing 19% of all new cases of breast cancer (Greenlee *et al.* 2000). In centers that rely on mammography, this percentage could be as high as 30% to 50%. During the last 10 to 15 years, physicians have been overwhelmed with a large number of new cases of a disease about which little was previously known.

During the 1970s, DCIS was generally thought of as a single disease with a single treatment, mastectomy. Since DCIS was considered a more favorable disease when compared with infiltrating breast cancer, most surgeons treated patients with DCIS with a modified radical mastectomy rather than the Halsted radical mastectomy, which was the standard of care for patients with invasive breast carcinoma at that time.

For most of the 20th century, the majority of patients with DCIS were symptomatic, presenting with palpable

masses or bloody or serous nipple discharges. With the development and utilization of high-quality mammography during the 1980s, the number of new cases increased rapidly and the presentation changed. Today, most patients diagnosed with DCIS present with nonpalpable lesions and without symptoms.

Since significant numbers of patients with DCIS are a relatively recent phenomenon, there is little prospective randomized data in the literature to aid in the complex treatment decision-making process. There is a variety of treatments available ranging from excision only to excision plus radiation therapy to mastectomy with or without immediate reconstruction. The notion of DCIS as a single disease entity is not valid. DCIS is now understood to be a heterogeneous group of lesions with diverse malignant potential and it is unlikely that there will be a single treatment for this wide range of lesions.

Classification of DCIS

Numerous pathological classifications exist. Older ones are based on histological architecture; newer ones on nuclear grade, necrosis, cytonuclear differentiation, or combinations of these factors. A DCIS pathology consensus conference was held in 1997 (Consensus Conference Committee 1997). While the group could not agree upon a single unified classification for DCIS, they did agree about a number of basic pathology issues, such as the need to record margin width, tumor extent, nuclear grade, architecture, cell polarization, etc. By recording these data, any of the newer classifications can be used.

DCIS is generally separated into its five most common architectural subtypes (papillary, micropapillary, cribriform, solid, and comedo). The first four are often grouped together as noncomedo DCIS and compared with the remaining comedo lesions. The comedo/noncomedo grouping occurred because, in general, comedo DCIS is associated with high nuclear grade, aneuploidy (Aasmundstad & Haugen 1992), a higher proliferation rate (Meyer 1986), HER2/neu (c-erbB2) gene amplification or protein over-expression (Van de Vijver *et al.* 1988, Bartkova *et al.* 1990, Barnes *et al.* 1991), and a more aggressive clinical behavior (Lagios *et al.* 1989, Fisher *et al.* 1993, Schwartz 1994). Noncomedo lesions tend to be the opposite. Unfortunately, a division by architecture alone is an oversimplification because any architectural subtype may present with any nuclear grade with or without comedo-type necrosis. In addition, high nuclear grade noncomedo lesions may express biological markers similar to high-grade comedo lesions and behave just like high-grade comedo lesions. Complicating matters even further, mixtures of various architectural subtypes within a single biopsy specimen occur in approximately 70% of all lesions. Finally, pathologists simply do not agree on a uniform definition of what constitutes a comedo lesion. Many pathologists require

the DCIS cells to be high nuclear grade and their growth pattern to be solid, but some pathologists allow intermediate nuclear grade lesions with significant comedo necrosis to be signed out as comedo DCIS; some may even allow low nuclear grade lesions with comedo-type necrosis to be called comedo DCIS. Others consider a cribriform or micropapillary architectural pattern with significant comedo necrosis to be comedo DCIS. In addition, pathologists do not agree on exactly how much comedo DCIS needs to be present. Some pathologists say any amount of comedo DCIS makes it a comedo lesion, others require as much as 75% of the lesion to be of the comedo type.

Nuclear grade and comedo-type necrosis reflect the biological potential of the lesion and are currently used in most modern classifications. But histological classification, albeit biological, regardless of which one is used, can never be adequate by itself for determining proper treatment. A small high-grade aggressive appearing lesion may be adequately treated by excision alone if the margins are widely clear, whereas a large low-grade lesion with margin involvement may be better treated by mastectomy with or without immediate reconstruction. Clearly, factors in addition to morphological appearance which reflect the anatomical distribution of disease and the adequacy of surgical removal, must be considered when planning.

Percutaneous biopsy for DCIS

Since most current patients with DCIS will have their lesions discovered mammographically, percutaneous biopsy offers numerous advantages (Lieberman 2000). It is clearly less invasive, offers better cosmesis, and is less expensive than open surgical biopsy. In women with benign lesions, it will generally spare them open surgical biopsy. For patients with breast cancer, it will allow better preoperative planning. For example, large or multicentric lesions can be sampled. If positive, these patients are clearly poor candidates for breast preservation and plans can be made to proceed directly to mastectomy with or without immediate reconstruction. If a lesion amenable to breast conservation has been sampled, the patient can proceed directly to definitive surgery with axillary staging.

When stereotactic biopsy first became available, it became possible, using a specially designed table, with the patient in the prone position, to make a preoperative diagnosis with a 14-gauge core biopsy. This allowed preoperative consultation and planning and for most patients it meant only one trip to the operating room for definitive treatment. The main problem with the 14-gauge core biopsy was that because of the relatively small sample size, the final diagnosis was upstaged about 20% of the time, following definitive surgery. In other words, one patient in five, in whom the 14-gauge core diagnosis was DCIS, actually had invasive breast cancer. This generally meant a trip back to

the operating room on another day to dissect the axilla. The problem was similar with a 14-gauge stereotactic biopsy that yielded a diagnosis of atypical ductal hyperplasia (ADH). Again, about 20% of the time, at definitive surgery, these lesions turned out to be DCIS. Because of this, most radiologists routinely recommended open biopsy following 14-gauge core biopsy with a diagnosis of ADH.

By the late 1990s, this problem was remedied, to a major extent, with the development of a number of new larger core tissue acquisition systems for percutaneous minimally invasive breast biopsy. The 11-gauge vacuum-assisted tools take significantly larger cores of tissue when compared with the 14-gauge needle and afford the ability to sample tissue contiguously. Consequently, upgrading or changing the diagnosis at the time of definitive surgery is far less frequent, only about 5% in a large series.

Natural history

Insight regarding the natural history of this disease can be gained by carefully evaluating the outcome in patients with DCIS who have received no formal treatment. Betsill *et al.* (1978), Rosen *et al.* (1980), and Page *et al.* (1982, 1995) have published such series. The series of Page *et al.* sheds the most light on this subject. Their 1995 update followed these patients for an average of almost 30 years (Page *et al.* 1995). By carefully reviewing slides from the pathology archives, twenty-eight patients with low-grade DCIS who were biopsied during the 1950s and 1960s, but whose diagnosis of DCIS was not made until a subsequent review many years later, were identified. At the time of biopsy, they were not felt to have DCIS and so no attempt was made completely to excise the lesion. These patients were essentially untreated. Of the 28 patients, 7 (25%) developed invasive breast cancer within 10 years of their original biopsy. Another 2 developed invasive breast cancer 20–30 years after their initial biopsy. The absolute 30-year risk of invasive recurrence was 32%; for breast cancer specific mortality, it was 18%. These results suggest that over two-thirds of untreated DCIS will never progress to invasive cancer. It is important to remember that the lesions followed in these studies were the most benign members of the DCIS family: small, low-grade, and without comedo-type necrosis. The lesions were initially diagnosed as a benign condition by the pathologist of the day. In fact, most DCIS lesions are less benign and the actual incidence of invasive breast cancer after untreated DCIS is probably significantly higher. However, there clearly are some lesions that are histopathologically defined as DCIS that will never progress, which raises the question of whether DCIS is truly cancer.

The fully expressed malignant phenotype consists of at least five factors: unlimited growth, genomic elasticity (resistance to treatment), angiogenesis, invasion and metastasis (Lippman 1993, Dickson & Lippman 1995). DCIS

lacks the latter two factors: the ability to invade and metastasize. When we understand why some DCIS lesions become invasive and metastasize and why others do not, we will have made a major step forward in our understanding of the neoplastic process.

The patient with DCIS has a noninvasive borderline lesion, which is currently not a threat to her life. This must be emphasized when discussing options with the patient. Data from both prospective and retrospective studies all document a breast cancer-specific mortality in the range of 1–2% at up to 10 years (Silverstein *et al.* 1995a, Fisher *et al.* 1999b, Julien *et al.* 2000). No published series has demonstrated a statistically significant difference in breast cancer-specific mortality, regardless of treatment (Ashikari *et al.* 1971, Rosner *et al.* 1980, Fisher *et al.* 1993, Fisher *et al.* 1999b, Julien *et al.* 2000). In other words, no matter how the patient is treated, excision alone, excision plus radiation therapy, or mastectomy, the single most important outcome (breast cancer-specific survival) is statistically the same for all treatment subgroups.

Treatment of DCIS

The treatment selection process has become more complex and extremely controversial in recent years. For most of the 20th century, the treatment for DCIS was mastectomy. Even as breast preservation began to be accepted in the 1980s for invasive breast cancer, the treatment for DCIS, an earlier and more favorable lesion than invasive breast cancer, continued to be mastectomy. The reason was that many patients with invasive breast cancer had been prospectively randomized into mastectomy versus breast preservation protocols in the 1970s, a time when there were relatively few cases of DCIS and no ongoing prospective randomized trials for patients with DCIS.

With the dramatic increase of new DCIS cases, numerous prospective randomized trials, comparing excision alone versus excision plus radiation therapy, began to take form in the mid to late 1980s. Simultaneously, several groups began to collect data on their own series of patients treated with either mastectomy or breast conservation. The current treatment for DCIS is based on data from both the prospective randomized trials and the retrospective individual series.

While multi-institutional prospective randomized trials are generally considered to be the 'gold standard' of clinical research because they are randomized (avoiding selection bias) and the results are generally applicable (the results were generated at many institutions with a variety of treating physicians), they do have their limitations. Typically, multi-institutional prospective randomized trials are designed to answer very specific questions. The requirements are made simple enough to be easily met in a wide range of institutions. The data collected is limited to the question

under investigation. The problem is that the simplified requirements and limited data collection do not allow expansion of the question asked.

In contrast, retrospective series are not designed to ask specific questions, but rather accumulate all information on a group of patients. In general, more detailed information is available, allowing a variety of questions to be addressed. The limitations are that patients are not randomly assigned to treatment groups, allowing the possibility of selection bias. Further, the data is based on the work of a single investigator or group of investigators and therefore may not be generally applicable.

Results from the randomized trials

The first prospective, randomized trial to be published was performed by the National Surgical Adjuvant Breast and Bowel Project (NSABP, protocol B-17) (Fisher *et al.* 1993). More than 800 patients with DCIS excised with clear surgical margins (defined by the NSABP as non-transection of the lesion) were randomized into two groups: excision only versus excision plus radiation therapy. The study was designed to ask the question whether radiation therapy was important after breast conserving surgery, and the main endpoint of the study was ipsilateral breast tumor recurrence, either invasive or noninvasive (DCIS).

At 8 years, 27% of patients treated with excision only had recurred locally, whereas only 12% of those treated with excision plus irradiation had recurred. The decrease in local recurrence of both DCIS and invasive breast cancer was statistically significant for the irradiated patients (Fisher *et al.* 1998b). The 8-year data confirmed the 5-year results, and the NSABP continues to recommend post-operative radiation therapy for all patients with DCIS who chose to save their breasts.

The initial 1993 NSABP study (Fisher *et al.* 1993) was criticized for a number of reasons, including the NSABP's definition of clear margins, no requirement for specimen radiography, no requirement for post-biopsy/pre-radiation therapy mammography to exclude residual disease, no requirement for the inking or marking of margins, no requirement for size estimation and, most importantly, no requirement for complete tissue processing without which invasive foci and margin involvement cannot be excluded.

More recently, the European Organization for Research and Treatment of Cancer (EORTC) published the results of its prospective randomized DCIS study (Julien *et al.* 2000), a trial with a similar randomization to B-17. This trial (EORTC protocol 10853) included 1010 patients: at 4 years, 9% of patients treated with excision plus radiation therapy had recurred locally compared with 16% of patients treated with excision alone.

The EORTC trial corroborated the main conclusion of the B-17 study: radiation therapy decreases local recurrence

rates of both invasive and noninvasive disease in conservatively treated patients with DCIS (Julien *et al.* 2000). The EORTC study, unfortunately, is subject to the same criticism that was leveled at the initial B-17 publication: a lack of a subset analysis that would permit physicians to estimate local recurrence rates for various subgroups of patients (Lagios & Page 1993, Page & Lagios 1995), for example, high grade (nuclear grade 3) versus low grade lesions; wide excision margins versus narrow margins; those with comedo-type necrosis versus those without, etc. Currently there are too few recurrences in the EORTC trial for such a subset analysis, but a subsequent central pathology review is forthcoming. A third study, performed in the United Kingdom has been published in abstract form and again confirms the results seen in the NSABP and EORTC trials (George *et al.* 2000).

A unique finding in the B-17 trial was the 3.5-fold reduction in invasive local recurrences following radiation therapy (Fisher *et al.* 1993, 1998b), an observation not seen in the EORTC trial or any other study of breast conservation employing radiation therapy (Silverstein *et al.* 1996, 1999, Solin *et al.* 1996). While DCIS recurrences were reduced by 47% in the NSABP trial if radiation therapy was given, invasive recurrences were reduced by 71% (Fisher *et al.* 1998b). In contrast, the EORTC trial demonstrated an essentially equal reduction for both *in situ* and invasive local recurrences following radiation therapy. The NSABP has used the marked decrease in invasive local recurrence as the principal rationale for their recommendation that all conservatively treated patients with DCIS receive postoperative breast irradiation.

The EORTC trial noted an increased rate of contralateral breast cancer in irradiated patients at just over 4 years. Although perhaps a chance finding, the difference reached statistical significance ($P=0.01$). One possible cause for this increase in contralateral breast cancer is the EORTC requirement for a compensatory filter or wedge during breast radiotherapy. The use of a wedge or filter on the medial tangential field has been reported to give a higher scatter dose to the contralateral breast (Fraass *et al.* 1985, Muller-Runkel & Kalokhe 1990). However, in a case-control study following over 41 000 women diagnosed with breast cancer between 1935 and 1982, the relative risk (RR) of developing a second breast cancer associated with radiation therapy was only 1.19. The risk increased to 1.33 if the women survived at least 10 years after treatment, suggesting a latent period of approximately 10 years for radiation-induced contralateral breast cancers to develop. The increased risk was seen only in women under the age of 45 years when treated (RR=1.59) and not among older women (RR=1.01) (Boice *et al.* 1992). Given this data, it seems unlikely that the increased incidence of contralateral breast cancer seen at 4.25 years in the EORTC trial can be attributed to the radiation therapy.

The early favorable results of B-17, in favor of radiation therapy for patients with DCIS, led the NSABP to perform protocol B-24 (Fisher *et al.* 1999a). In this trial, 1804 patients with DCIS were treated with excision and radiation therapy, then randomized to receive either tamoxifen or placebo. At 5 years, 8.6% of patients treated with placebo had recurred locally, whereas only 6.4% of those treated with tamoxifen had recurred (Fisher *et al.* 1999a). The results of B-17, B-24 and P1 (the NSABP chemoprevention study) (Fisher *et al.* 1998a) led the NSABP to recommend both radiation therapy and tamoxifen for all patients with DCIS treated with breast preservation (Wolmark 1999).

Results from retrospective series

The largest of the published retrospective series is the series from Van Nuys. Updated through February 2000, a total of 551 patients were treated with either excision alone (323) or excision with radiation therapy (228). The treatments were determined for the most part by date of presentation: those treated before 1989 received radiation, those treated after usually were not radiated. At eight years the incidence of local recurrence was 16.5% in the excision alone group and 24% in the radiated group. The difference was not statistically significant. Other published series have also reported recurrence rates in the range of those observed in the EORTC and NSABP trials (Van Zee *et al.* 1999, Weng *et al.* 1999, Ringberg *et al.* 2000). In fact, all published series have shown recurrence rates of about 10–17% for patients treated with excision with radiation, and 15–27% for those treated with excision alone. While the available data clearly supports a role for radiation therapy in breast conservation therapy for DCIS, at least two thirds of patients will not recur regardless of whether or not they receive radiation. Radiation therapy really benefits only those patients who recur only if not receiving radiation, that is less than 15% of all patients. The important question is how to select those patients most likely to benefit from radiation therapy.

Why not give radiation therapy to all conservatively treated patients with DCIS?

Radiation therapy is expensive, time consuming, and accompanied by side effects in a small percentage of patients (Recht 1997). Radiation fibrosis of the breast is a somewhat more common side effect. New technologies with more uniform dose distribution may reduce this. Radiation fibrosis, when it occurs, changes the texture of the breast and skin, may make mammographic follow-up more difficult, and may result in delayed diagnosis if there is a local recurrence. Should there be a recurrence at a later date, radiation therapy cannot be used again (although some have tried this), and mastectomy is required. Should there be significant skin and

vascular changes following radiation therapy, skin-sparing mastectomy, if needed in the future, is clearly more difficult to perform. Finally, the most compelling reason not to use radiation therapy for all patients with DCIS is that no difference has been shown in the single most important end-point, breast cancer-specific mortality, regardless of treatment. The NSABP's 1999 update reported four breast cancer deaths among the excision-only group and seven among the excision plus radiation therapy group (Fisher *et al.* 1999b). The EORTC study also failed to show a difference in breast cancer-specific mortality between the two treatment arms.

Recently, the Early Breast Cancer Trialists' Collaborative Group (2000) published a meta-analysis of the 10- and 20-year results from 40 unconfounded randomized trials of radiotherapy for early breast cancer. Radiotherapy regimens routinely produced a reduction in local recurrence along with a reduction, in the range of 2–4%, in 20-year breast cancer-specific mortality. However, cardiovascular mortality was increased in those who received radiotherapy. Because of this, the absolute survival gain with radiotherapy was only 1.2% (Kurtz 2000). The studies reported in the meta-analysis were conducted between 1961 and 1990. More modern radiotherapy techniques are designed to minimize cardiopulmonary exposure but long-term cardiovascular mortality data do not exist. Physicians must be sure that the benefits of radiation therapy significantly outweigh the potential side effects, complications, inconvenience, and costs for a given subgroup of patients, particularly those with relatively nonlethal malignancies such as DCIS.

The axilla in patients with DCIS

There is now uniform agreement that for patients with DCIS, the axilla does not need treatment (Silverstein *et al.* 1987, Hansen & Giuliano 1997). For patients with DCIS undergoing breast conservation, it should not be irradiated and no form of axillary sampling or dissection need be performed. For patients treated with excision plus post-operative radiation therapy, the lower axilla is included by the tangential fields to the breast.

For patients with DCIS lesions large enough to merit mastectomy, a sentinel node biopsy (Krag *et al.* 1993, Giuliano *et al.* 1995, Albertini *et al.* 1996, Hansen & Giuliano 1997) using a vital blue dye, radioactive tracer or both can be performed at the time of mastectomy. This is done only to avoid the need for additional surgery for axillary staging in the event that permanent sections of the mastectomy specimen reveal one or more foci of invasion. If invasion is documented, no matter how small, the lesion is no longer considered DCIS but rather it is an invasive breast cancer. The sentinel node or nodes are evaluated by hematoxylin and eosin (H & E) staining followed by

immunohistochemical staining for cytokeratin when routine H & E stains are negative.

Preliminary data are now available on the results of sentinel node biopsy in patients with DCIS. Nodal positivity ranges from 5% to 13% by immunohistochemistry for patients with high-risk DCIS (Klauber-DeMore *et al.* 2000). High-risk DCIS is generally defined as lesions with high nuclear grade, large size, palpability, or those requiring mastectomy. The general consensus is that the positive nodes result from undetected microinvasive disease. The clinical significance of these micrometastatic deposits is unclear, and most clinicians do not alter therapy based on the finding of immunohistochemically positive nodes in patients with DCIS.

Factors influencing the incidence of local recurrence

The NSABP trial was not designed to identify subgroups with a greater or lesser risk of recurrence. However, after the trial closed a central (retrospective) review of pathology was performed looking at nine different factors: histological type, nuclear grade, focality, comedo-type necrosis, stromal response, lymphoid infiltrate, cancerization of lobules, margins of resection, and tumor size. This histopathological data was published in 1995 (Fisher *et al.* 1995) and updated in 1999 (Fisher *et al.* 1999b). No pathological material was available for review by the central pathologist in 23% of the cases in the 1999 update (Fisher *et al.* 1999b).

The NSABP considered a margin 'clear' if the tumor was not transected. In other words, only a fat cell or a collagen fiber between the DCIS and the inked margin was required to consider that margin clear. Many margins were obviously significantly wider than that, as the NSABP surgeons certainly did not set out to achieve the smallest possible margins. Rather, the B-17 protocol was designed for simplicity and reproducibility. The margin was either clear or not clear; the DCIS was either transected or not transected. Further, there was no requirement in the NSABP B-17 protocol for estimating and reporting tumor size. In the initial NSABP report, more than 40% of patients had no size recorded. It was only later, after a retrospective central review (Fisher *et al.* 1995, 1999b) that approximately 90% of the tumors were reported to be 10 mm or smaller. The retrospective size analysis measured the largest dimension on a single slide.

Given these limitations, the NSABP was able to identify high nuclear grade, moderate to marked comedonecrosis, margin status, and solid histological type as factors that predict recurrence on univariate analysis. Multivariate analysis indicated only comedonecrosis and margin status as independent predictors of recurrence (Fisher *et al.* 1995). In the 1999 update, only comedonecrosis was found independently to predict recurrence (Fisher *et al.* 1999b).

The bulk of our information regarding risk factors for local recurrence is derived from retrospective series. In a study from the Oschner Clinic, family history and young age were found to be predictors of local recurrence. Women with a family history had a 10.3% local recurrence rate, whereas those with no family history had a recurrence rate of 2.3% ($P=0.05$). Women under 50 had a recurrence rate of 9.1% compared with 2.4% in women over 50 ($P=0.10$). Women who were under 50 and had a positive family history had a local recurrence rate of 20% ($P=0.03$) (Szelei-Stevens *et al.* 2000). The impact of age on the outcome following treatment of DCIS was confirmed in the series from William Beaumont Hospital. Women younger than 45 years had a 10-year ipsilateral failure rate of 26.1%, compared with 8.6% in older patients ($P=0.03$). Furthermore, women in the younger age group had a much higher incidence of invasive local recurrence (19.9% vs 3.2%) (Vicini *et al.* 2000). The authors suggested that the higher recurrence rate might be related to smaller resection volumes in the younger women, and a greater preponderance of lesions with high nuclear grade and comedonecrosis (Goldstein *et al.* 2000b, Vicini *et al.* 2000). Pathological analysis of the series from William Beaumont Hospital identified young age, the number of slides with DCIS, the number of ducts or lobules containing malignant cells within 5 mm of the margin, and the absence of pathological calcifications as factors associated with recurrence following treatment of DCIS (Goldstein *et al.* 2000a, Kestin *et al.* 2000). On multivariate analysis, all 4 were independently predictive of local recurrence when evaluating all patients with DCIS (Goldstein *et al.* 2000a), but only the absence of pathological calcifications was an independent predictor when limiting the study to those lesions detected by mammography (Kestin *et al.* 2000). The Memorial series identified age, comedonecrosis, nuclear grade, and margin status as factors associated with recurrence, but only margin status (negative vs close or positive) was independently predictive (Van Zee *et al.* 1999).

A population-based study of 309 patients with DCIS from Sweden evaluated the effect of nuclear grade, growth pattern (diffuse vs not diffuse), necrosis, size, resection margins, presence of pathological calcifications, and focality on the incidence of ipsilateral local recurrence. Nuclear grade, margins <1 mm, and comedonecrosis were significantly associated with recurrence in the group not receiving radiation therapy. Non-diffuse growth pattern showed a trend towards lower recurrence rates ($P=0.065$). The groups with the lowest relapse rate in the non-irradiated group were those with both non-high grade and nondiffuse growth pattern lesions, and those with non-high grade lesions and margins ≥ 1 mm, with recurrence rates <10% (Ringberg *et al.* 2000).

In the Van Nuys series, margins were inked on all specimens and margin size was measured to the nearest mm by ocular micrometry. Lesions were three-dimensionally

reconstructed for the size determination. In general, the largest diameter on a single slide was smaller than the size recorded. Multivariate analysis indicated that high nuclear grade, comedonecrosis, tumor size and margin width were all independent predictors of recurrence. Combining nuclear grade and comedonecrosis together results in a pathological classification with 3 groups: high grade with or without necrosis, non-high grade with necrosis, non-high grade without necrosis (Silverstein *et al.* 1995b). Pathological class is also an independent predictor of local recurrence. The Van Nuys Prognostic Index (VNPI) is a numerical algorithm based on tumor features and recurrence data from the Van Nuys series of DCIS patients (Silverstein *et al.* 1996, Silverstein 1997, 1998). The VNPI quantifies the measurable prognostic factors of pathological class, tumor size and margin width, separating DCIS patients into three clearly defined risk groups. It was designed to be usable with the resources of any hospital and to permit a more rational approach to the treatment of DCIS. The VNPI was meant to be used in conjunction with and not instead of, clinical experience and prospective randomized data. As with all such aids to treatment planning, the VNPI will need to be independently validated.

Table 1 The Van Nuys Prognostic Index scoring system. One to three points are given for each of three different predictors of local breast recurrence (size, margin width, and pathological classification). Scores for each of the predictors are totaled to yield a VNPI score ranging from a low of 3 to a high of 9

	1	2	3
Size (mm)	≤15	>15–40	>40
Margins (mm)	≥10	1–<10	<1
Pathological classification	Non-high grade without necrosis	Non-high grade with necrosis	High grade with or without necrosis

Modified and reproduced with permission from Silverstein *et al.* (1996).

Table 1 shows the VNPI scoring system. Scores from 1 to 3 were given for each of the three different predictors of local breast recurrence (tumor size, margin width, and pathological classification). The scores for each predictor for each individual patient were totaled to yield a VNPI score ranging from a low of 3 to a high of 9 for a group of 551 patients with DCIS treated with breast preservation both with and without radiation therapy (the Van Nuys series through February 2000). Patients treated with mastectomy were not included since local recurrence is rare following mastectomy.

Figure 1 shows all 551 conservatively treated patients divided into 3 subgroups by score (3 or 4 vs 5, 6 or 7 vs 8 or 9). The probability of local recurrence is significantly different for each subgroup. More importantly, patients with a low VNPI score (3 or 4) showed no difference in local

recurrence-free survival at 10 years regardless of whether or not they received radiation therapy (Fig. 2) and can be considered for treatment with excision only. Patients with intermediate scores (5, 6, or 7) showed a statistically significant decrease in local recurrence rates with radiation therapy (Fig. 3) and should be considered for treatment with radiation therapy. Conservatively treated patients with VNPI scores of 8 or 9 had unacceptably high local recurrence rates, regardless of irradiation (Fig. 4), and mastectomy is the procedure of choice for these patients.

Margin width is the distance between DCIS and the closest inked margin and reflects the completeness of excision. Although the multivariate analysis used to derive the VNPI suggests approximately equal importance for the three significant factors (margin width, tumor size and biological classification), the fact that DCIS can be thought of in Halstedian terms (it is a local disease and complete excision should cure the patient) suggests that margin width should be the single most important factor in terms of local recurrence.

Serial subgross evaluation of more than 100 breasts after mastectomy for DCIS suggests that when margin widths exceed 10 mm the likelihood of residual disease is relatively small, in the range of 10–15% (Faverly *et al.* 1994, Holland & Faverly 1997). Based on the Van Nuys series, at 8 years patients with margins less than 1 mm had a 58% local recurrence rate, those with margins 1 mm to less than 10 mm had a 20% local recurrence rate, and for those with 10 mm or greater margins, the local recurrence rate was only 3% (Silverstein *et al.* 1999). Margin width is a continuum: the wider the margin width, the less likely there is to be a local recurrence (Silverstein 1998). Further, our data suggest that there is little to be gained from post-operative breast irradiation when all margins are greater than 10 mm, regardless of nuclear grade, tumor size, or the presence of comedo-type necrosis (Silverstein *et al.* 1999) (Table 2).

Taken together, the data from both prospective and retrospective studies suggest that young age, family history, nuclear grade, comedonecrosis, tumor size (estimated either by 3–dimensional reconstruction or by assessing the number of slides with DCIS) and margin status (negative vs margin width measured by ocular micrometry, vs assessing the number of ducts or lobules containing malignant cells within 5 mm of the inked margin) are all predictive of local recurrence. Further, at least some of these factors, including tumor size, margin status, nuclear grade, and comedonecrosis, can be used to identify patients that are at such low risk for recurrence that radiation therapy is unnecessary.

Outcome after local invasive recurrence

Local recurrence after treatment for DCIS is demoralizing and, if invasive, it is a threat to life. Approximately 50% of

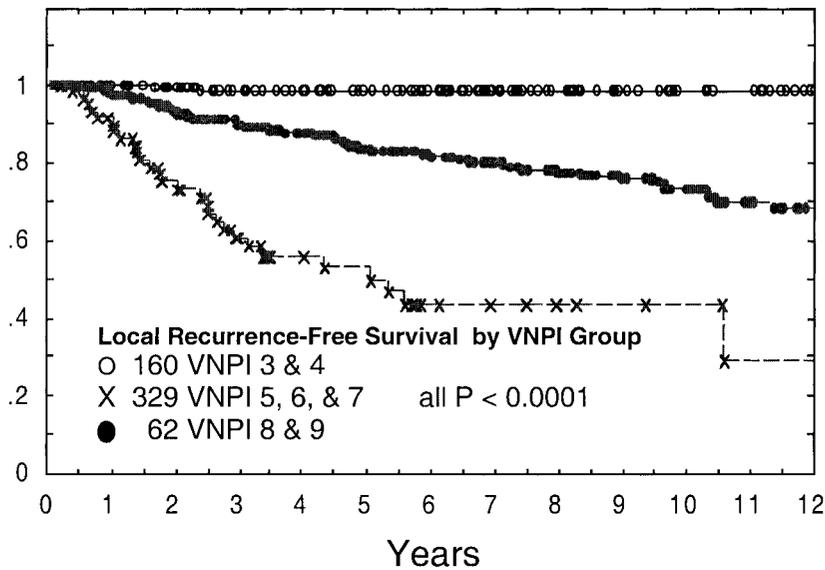


Figure 1 Probability of local recurrence-free survival for 551 breast conservation patients grouped by Van Nuys Prognostic Index score (3 or 4 vs 5, 6 or 7 vs 8 or 9) (all $P < 0.0001$).

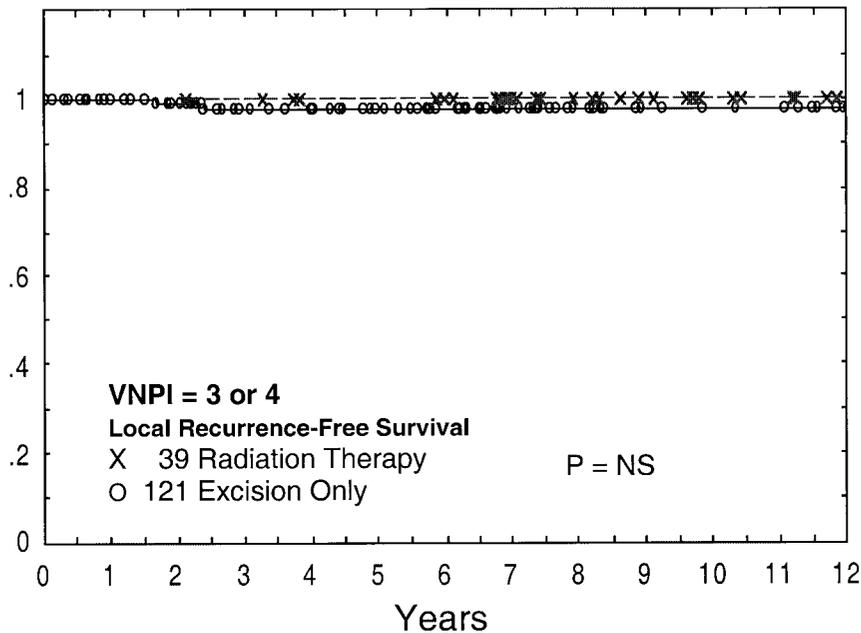


Figure 2 Probability of local recurrence-free survival by treatment for 160 breast conservation patients with Van Nuys Prognostic Index scores of 3 or 4 (P =not significant (NS)).

all local recurrences are invasive (Solin *et al.* 1994, 1996, Silverstein *et al.* 1995a, 1998, Fisher *et al.* 1998b, Julien *et al.* 2000). For the last decade, local recurrence (both invasive and noninvasive) has been used as the marker of treatment failure for patients with DCIS.

Table 3 updates the outcome after local recurrence through February 2000 for 866 patients in the Van Nuys

series with a total of 98 local recurrences, 45 (46%) invasive and 53 (54%) noninvasive. No patient with a noninvasive recurrence developed distant metastases or died of breast cancer. For the 45 patients with invasive recurrences, 51% presented with Stage IIA or more disease at the time of local recurrence, 8 developed distant metastases and 5 died of breast cancer. The breast cancer-specific mortality rate at 8

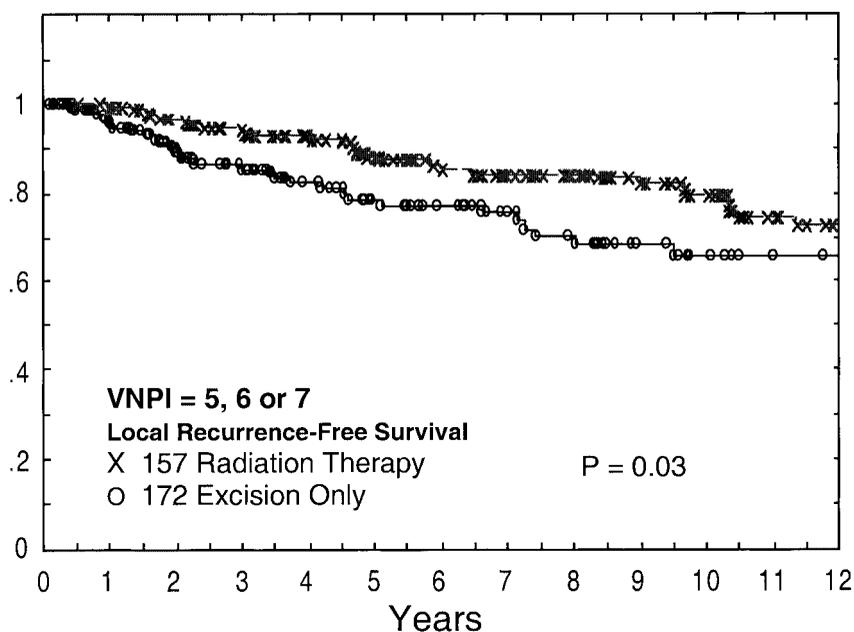


Figure 3 Probability of local recurrence-free survival by treatment for 329 breast conservation patients with Van Nuys Prognostic Index scores of 5, 6 or 7 ($P=0.03$).

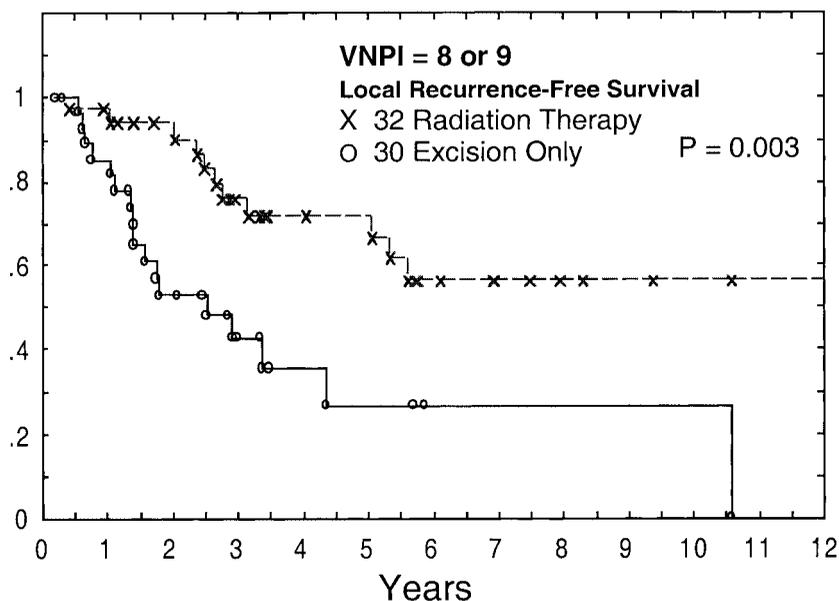


Figure 4 Probability of local recurrence-free survival by treatment for 62 breast conservation patients with Van Nuys Prognostic Index scores of 8 or 9 ($P=0.003$).

years for the subgroup of patients with invasive local recurrences was 12.4%, the distant disease rate for this subgroup was 21.9%, rates similar to the ones reported by others. Invasive recurrence after treatment for DCIS is a significant event, converting a patient with previous Stage 0 disease to a patient, on average, with Stage IIA breast cancer

(range Stage I to IV). Treatment for a patient with an invasive recurrence should be based on the stage of the recurrent disease.

In spite of these five mortalities, one must not lose sight of the fact that, overall, DCIS is an extremely favorable disease. When the entire Van Nuys series of 866 patients is

Table 2 Association of radiation therapy with recurrence stratified by comedo-type necrosis, nuclear grade, and tumor size

Margin	Un-adjusted analysis			Stratified by:	Adjusted analysis		
	RR ¹	95% CI ²	P value ³		RR ¹	95% CI ²	P value ⁴
≥10 mm	1.14	(0.10, 12.64)	0.916	Necrosis	1.22	(0.11, 13.93)	0.872
				Nuclear grade	1.08	(0.09, 12.70)	0.949
				Size	1.69	(0.15, 18.79)	0.663
1–9 mm	1.49	(0.76, 2.90)	0.243	Necrosis	1.84	(0.93, 3.61)	0.075
				Nuclear grade	1.75	(0.87, 3.56)	0.114
				Size	1.87	(0.93, 3.78)	0.078
< 1 mm	2.54	(1.25, 5.18)	0.010	Necrosis	2.56	(1.25, 5.26)	0.014
				Nuclear grade	2.30	(1.12, 4.76)	0.029
				Size	2.52	(1.23, 5.14)	0.015

¹Relative risk of recurrence in non-radiation therapy group compared to the patients who received radiation; ²95% confidence interval for the relative risk; ³based on likelihood ratio test from the Cox proportional hazard model; ⁴based on likelihood ratio test from the Cox proportional hazard model stratifying for either necrosis (Yes, No), nuclear grade (categorized as 1,2,3), or tumor size (<10 mm, ≥10 mm).

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Table 3 Outcome after local recurrence: 866 patients with DCIS analyzed by treatment. All recurrences and mortality probabilities are Kaplan-Meier estimates at 8 years

	Mastectomy	Excision + radiation	Excision only
Number of patients (n = 866)	315	228	323
Total recurrences (n = 98)	2	43	53
Invasive recurrences (n = 45)	2	22	21
Distant metastases (n = 8)	1	6	1
Breast cancer deaths (n = 5)	0	4	1
Local recurrence probability	<1%	16.5%	24%
Distance recurrence probability	<1%	2.9%	<1%
Breast cancer-specific mortality	0	2.4%	<1%
Overall mortality (all causes)	7%	6%	8%

considered, the actuarial probability of an invasive recurrence at 8 years is 6.4% and the probability of a breast cancer specific mortality is only 1.1%. It is, however, a tragedy when a patient with DCIS recurs with invasive breast cancer and then goes on to die of metastatic disease.

Current therapy for DCIS

Currently there is a wide range of acceptable treatments for the patient with DCIS. Treatment varies from simple excision to numerous forms of wider excision (segmental resection, quadrant resection, etc.), all of which may or may not be followed by radiation therapy. If the patient is a poor candidate for breast preservation, then mastectomy, with or without immediate reconstruction, will be recommended. Since DCIS is a biologically heterogeneous group of lesions rather than a single entity and because patients have a wide variety of personal needs and agendas that must be considered throughout the treatment selection process, it is clear that no single approach will be appropriate for all forms of the disease or for all patients.

The most benign appearing forms of DCIS (for example, low nuclear grade, small celled without necrosis, estrogen and progesterone receptor positive, c-erbB2 negative, etc.), if untreated, may never cause clinical disease. Long-term actuarial analyses reveal that approximately one third of untreated low-grade lesions develop into invasive breast cancer after 25–30 years of follow-up (Page *et al.* 1995). About half of these patients go on to die of breast cancer. In other words, only one patient in six with untreated low-grade DCIS goes on to die from breast cancer. This finding again raises an issue discussed earlier regarding whether or not DCIS, in particular low-grade DCIS, should be considered breast cancer. Alternatively, the most aggressive appearing forms of DCIS (high nuclear grade, large celled with comedo-type necrosis, c-erbB2 positive, etc.), if left untreated are much more likely to develop into invasive carcinomas in significantly shorter periods of time.

With the development of high-quality screening mammography, it has become common to see an asymptomatic patient in whom routine mammography has revealed an area of microcalcifications. This is currently the

most common presentation for women with DCIS. In this era it is rare to see a patient present with symptomatic DCIS. Diagnosis is made by stereotactic core biopsy of the calcifications preferably using one of the new larger core tissue acquisition systems for percutaneous minimally invasive breast biopsy such as the 11-gauge vacuum-assisted Mammotome probe (Ethicon Endo-Surgery, Cincinnati, OH, USA).

Once the diagnosis of DCIS is made, the patient is thoroughly counseled about the nature of the disease, paying particular attention to the size and distribution of her disease as seen mammographically. If she is a good candidate for breast preservation (an area of DCIS that can be removed completely with clear margins, without dramatically deforming the breast) and she is anxious to preserve her breast, a wide excision is performed. Based on the biological characteristics of the lesion, its size and extent, and the adequacy of the surgical margins, radiation therapy may or may not be recommended. This decision is based on the individual patient's risk of local recurrence. Those with minimal risk of local recurrence can avoid radiation, while those with an intermediate risk would likely benefit from radiation, and those with very high risk should probably undergo mastectomy. Re-excision can be attempted to reduce the patient's risk of local recurrence before making the decision to irradiate. Some DCIS lesions extend well beyond their mammographic signs and may be extremely difficult to excise completely. These patients are probably better served with mastectomy with or without reconstruction.

In patients whose lesions are too large mammographically to yield clear margins and an acceptable cosmetic result, mastectomy should be recommended. If the patient wishes immediate reconstruction, skin-sparing mastectomy and autologous reconstruction, generally with a TRAM flap is our preference.

The future

The most important questions today are which lesions, if untreated, are going to become invasive breast cancer? How long will it take for this to happen? Are there biological markers that can be used to predict ultimate invasion? Which DCIS lesions, if treated conservatively, have such high rates of local recurrence, regardless of radiation therapy, that mastectomy should be the preferred initial treatment? In patients who do not require mastectomy, which lesions can be treated with excision alone and which lesions need post-operative breast irradiation? Simple questions – difficult answers. More research is needed to understand the biological behavior of DCIS in order adequately to address these issues.

The current treatment approach to noninvasive breast cancer is phenotypic rather than genotypic. It is based on morphology rather than etiology. Genetic changes routinely

precede morphological evidence of malignant transformation. Lobular carcinoma *in situ* and DCIS are lesions in which the complete malignant phenotype of unlimited growth, angiogenesis, genomic elasticity, invasion, and metastasis has not been fully expressed. With sufficient time, many DCIS lesions will learn how to invade and metastasize. Lessons learned from ongoing basic science research will help us to identify those lesions that are unlikely to progress and to prevent progression in the rest.

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