Ductal Carcinoma In Situ of the Breast: Controversial Issues

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ABSTRACT

Ductal carcinoma in situ (DCIS) of the breast is a heterogeneous group of lesions with diverse malignant potential and a range of controversial treatment options. It is the most rapidly growing subgroup in the breast cancer family, with more than 36,000 new cases diagnosed in the United States during 1997. Most new cases are nonpalpable and discovered mammographically. In this overview, a variety of controversial issues are discussed, including: whether or not DCIS should be considered cancer, the fallacy of grouping lesions by their pathologic architecture, an algorithm to aid in the complex treatment-selection process, the profound importance of excision margins, and the outcome following invasive local recurrence, in terms of distant recurrence and mortality. Current approaches to DCIS are based on morphology rather than etiology. In all likelihood, genetic changes precede morphologic evidence of malignant transformation. Medicine must learn how to recognize these genetic changes, exploit them, and, in the future, prevent them. *The Oncologist* *1998;3:94-103*

INTRODUCTION

For most of this century, ductal carcinoma in situ (DCIS) of the breast was a relatively uncommon disease, representing less than 1% of all newly diagnosed cases of breast cancer [1]. Today, it is the most rapidly growing subgroup in the breast cancer family. *Ernster et al*. [2] reported a 557% increase in new cases of DCIS from 1983 to 1992. During 1997, more than 36,000 new cases of DCIS (17% of all new breast cancers) were diagnosed in the United States [3]. Suddenly, we have been inundated with a large number of new cases of a disease that we knew little about.

During the 1970s, most cases of DCIS, because of its rarity and because the heterogeneity of the disease was not widely appreciated, were grouped together. DCIS was generally thought of as a single disease with a single treatment, namely, mastectomy. Fifteen years ago, most patients with DCIS presented with a palpable mass, or, less frequently, with a bloody or serous nipple discharge. In other words, patients were symptomatic, most discovering their own lesions.

With the development of high-quality mammography, the number of new cases increased rapidly, and the presentation changed. Most patients currently diagnosed present with asymptomatic, nonpalpable lesions. From 1979 to 1981, only 16% of patients diagnosed with DCIS at The Van Nuys Breast Center had nonpalpable lesions. During the last five years, 92% of all newly diagnosed patients had nonpalpable lesions, most of which were detected mammographically [4]. High-quality mammography is capable of finding a range of nonpalpable, asymptomatic, noninvasive lesions, many smaller, of lower nuclear grade, and with subtler mammographic findings than had been seen in the past. The concept of DCIS as a single disease entity is clearly not valid. DCIS is a heterogeneous group of lesions with diverse malignant potential.

SHOULD PATIENTS WITH DCIS BE TOLD THAT THEY HAVE BREAST CANCER?

There is no easy way to tell any woman that she has breast cancer. But is DCIS really breast cancer? When one thinks of cancer, one generally thinks of a disease that, if untreated, runs an unrelenting course toward death. This is certainly not the natural history of DCIS.

The fully expressed malignant phenotype consists of at least five factors: unlimited growth, genomic elasticity

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(resistance to treatment), angiogenesis, invasion, and metastasis [5, 6]. DCIS, as best we can determine, lacks the ability to invade and metastasize. In all likelihood, when we understand why some DCIS lesions become invasive and metastasize and why others do not, our understanding of the neoplastic process will have been dramatically advanced.

When counseling a patient with DCIS, it must be emphasized that she has a borderline, noninvasive lesion which, at this time, is not a threat to her life. In the Van Nuys Series through December 1997 which consists of 733 patients with DCIS, the absolute breast cancer-specific mortality rate is 0.7%. The eight-year actuarial breast-cancer-specific mortality rate is 0% for mastectomy patients, 1.4% for all patients, and 2.1% for breast-preservation patients. Numerous other DCIS series [7-9] confirm an extremely low mortality rate for DCIS.

One of the most frequent concerns expressed by patients, once a diagnosis of cancer has been made, is the fear that the cancer has spread. The patient with DCIS whose excision specimens have been completely and sequentially processed can be assured that no invasion was seen microscopically and that the likelihood of systemic spread is small.

The patient with DCIS needs to be educated that the term "breast cancer" encompasses a wide variety of lesions with a large variance in aggressiveness and lethal potential. The patient with DCIS must be, and needs to be, reassured that she has a minimal lesion and that she may need some additional treatment, which might include further surgery or radiation therapy or both. She needs to know that she will not need chemotherapy, that her hair will not fall out, and that it is highly unlikely that she will die from this lesion. She will, of course, also need careful clinical follow-up.

Pathology of DCIS

A variety of classifications based on histologic architecture, nuclear grade, necrosis, cytonuclear differentiation, or various combinations of these factors are currently being used. In April 1997, a DCIS Pathology Consensus Conference was held at Jefferson Medical College in Philadelphia, Pennsylvania. There was agreement regarding a number of basic pathology issues, such as the need to record margin width, tumor extent, nuclear grade, architecture, cell polarization, etc., but there was no consensus on a single unified classification for DCIS [10].

Pathologists generally divide DCIS into five architectural subtypes (papillary, micropapillary, cribriform, solid, and comedo). It has become quite common to group the first four together as noncomedo DCIS and to compare them with the remaining comedo lesions. This was done because, in general, comedo DCIS is often associated with high nuclear grade, aneuploidy [11], a higher proliferation rate [12], *HER2/neu* (*c-erbB2*) gene amplification or protein overexpression [13, 14], and clinically more aggressive behavior [15, 16]. Noncomedo lesions tend to be the opposite. However, a division by architecture is an oversimplification because any architectural subtype may present with any nuclear grade with or without comedo-type necrosis. It is not uncommon for high nuclear grade noncomedo lesions to express biologic markers similar to high-grade comedo lesions and to behave like high-grade comedo lesions. Furthermore, mixtures of various architectural subtypes within a single biopsy specimen are common. In the Van Nuys Series, approximately 70% of all lesions had significant amounts of two or more different architectural subtypes. Adding to the confusion, there is no uniform agreement among pathologists of exactly how much comedo DCIS needs to be present to consider the lesion a comedo DCIS.

To complicate matters further, before a lesion is called comedo DCIS, many pathologists require the cells to be high nuclear grade and their growth pattern to be solid. However, some pathologists will allow intermediate nuclear grade lesions with significant comedo necrosis to be signed out as comedo DCIS; some may even allow low nuclear grade lesions to be called comedo DCIS. Others will allow a cribriform or micropapillary architectural pattern with significant comedo necrosis to be called comedo DCIS.

My point is simple: architecture is simply a poor way to classify DCIS. It is like comparing two similar-looking prisons by their design. But one houses murderers, the other tax evaders. As we judge the risk that those prisons pose to our neighborhoods, it is not the external architecture that is important, but rather it is their contents that are key. Current DCIS classification systems should be based on factors that reflect the biologic potential of each individual lesion—in other words, the cellular content rather than the arrangement of the cells.

Nuclear grade, comedo-type necrosis, tumor size, and margin width are all important predictors of the probability of local recurrence after breast-conserving treatment [8, 15, 17-22].

Two of these factors, nuclear grade and comedo-type necrosis, were used to develop the simple, reproducible [23] Van Nuys Classification [17]. In the Van Nuys Classification, high nuclear grade lesions, with or without comedo-type necrosis, are grouped into the worst prognostic category (group 3). Patients with non-high-grade lesions (nuclear grade 1 or 2) are then separated by the presence of necrosis (group 2, an intermediate group) or the absence of necrosis (group 1, the best prognostic group) (Fig. 1). This pathologic classification yields three different subgroups of DCIS patients with significantly different rates of local recurrence [17]. But histologic classification, regardless of which one is used, will never be adequate by itself for determining proper treatment. A small aggressive-appearing lesion may be adequately treated by

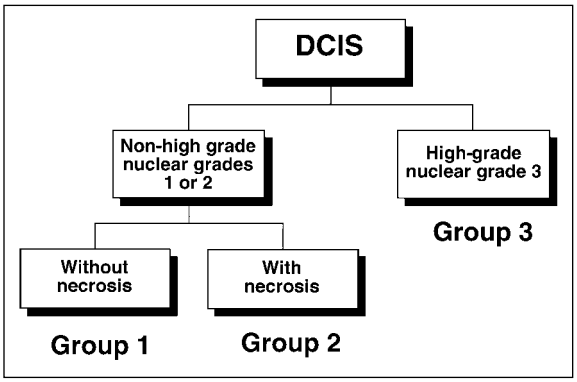

Figure 1. Pathologic classification. *DCIS patients are sorted into high nuclear grade and non-high nuclear grade. Non-high nuclear grade cases are then sorted by the presence or absence of comedo-type necrosis. Lesions in Group 3 (high nuclear grade) may or may not show comedo-type necrosis. Reprinted with permission [17].*

excision alone if the margins are widely clear, whereas a large but unaggressive-appearing lesion with margin involvement may be better treated by mastectomy with immediate reconstruction. Clearly, factors in addition to morphologic appearance must be considered when planning treatment [18, 21]. Please refer to the Van Nuys Prognostic Index, below.

Treatment of DCIS

As our knowledge of DCIS has evolved, the treatment decision-making process has become complex and controversial, with a wide range of treatment options. There are numerous ongoing prospective randomized trials that are attempting to simplify the treatment-selection process [24]. Only the one performed by the National Surgical Adjuvant Breast Project (NSABP) (protocol B-17) has been published [7]. The results of B-17 were updated in 1995 [22] and 1998 [25]. In this study, more than 800 patients with DCIS excised with clear surgical margins were randomized into two groups: excision-only versus excision-plus-radiation therapy. The endpoint of the study was local recurrence, invasive or noninvasive (DCIS).

The NSABP defines a surgical margin as clear when the tumor has not been transected. In other words, only a few fat cells or collagen fibers need be present between DCIS and the inked margins to consider that margin clear. After eight years of follow-up, there was a statistically significant decrease in local recurrence of both DCIS and invasive breast cancer in patients treated with radiation therapy. The overall local recurrence rate for patients treated by excision only was 27% at eight years. For patients treated with excision plus irradiation, it was 12%, a 15% difference in favor of those treated with radiation therapy [25]. These updated data led the NSABP to stand by their 1993 position and to continue to recommend postoperative radiation therapy for all patients with DCIS who chose to save their breasts. B-17 has been criticized for a number of reasons [26, 27], the most important being a lack of pathologic subset analysis in the initial report. Other problems with B-17 include: the lack of size measurements in more than 40% of cases when originally reported in 1993, no requirement for mammographic/pathologic correlation or specimen radiography, no uniform guidelines for tissue processing or size estimation, and the NSABP's controversial definition of what constitutes a clear margin. Margins were defined in such a way that outcome differences analyzed by clear versus involved margins could easily be obscured. The problem with size was rectified in 1998, when the NSABP performed a retrospective analysis and reported that 90% of their cases were 10 mm in diameter or smaller [25].

In defense of the NSABP, their trial was designed in the mid-1980s, at a time when researchers were asking a single broad question: does radiation therapy benefit patients with DCIS treated with breast preservation? The NSABP has answered that question, and the answer is unequivocally "yes". The NSABP study was not, however, designed to answer the more difficult questions that we ask today. For example, exactly which subgroups benefit from radiation therapy and by how much? If the benefit in a defined subgroup is only a few percent, the advantage gained by radiation therapy may be offset by its cost and disadvantages.

Radiation therapy is expensive and time-consuming and is accompanied by significant side effects in a small percentage of patients (cardiac, pulmonary, etc.) [28]. Radiation fibrosis of the breast is a more common side effect, particularly with the type of radiation therapy given during the 1980s. This complication changes the texture of the breast and skin, makes mammographic follow-up somewhat more difficult, and may result in delayed diagnosis if there is a local recurrence. The use of radiation therapy for DCIS precludes its use if an invasive recurrence develops at a later date. The use of radiation therapy with its accompanying skin and vascular changes makes skin-sparing mastectomy, if needed in the future, more difficult to perform. Clinicians must be secure that the benefits of radiation therapy, in terms of improved recurrence-free survival, significantly outweigh the side effects, complications, inconvenience, and costs for a given subgroup of patients.

Consider the following two patients, both of whom meet NSABP B-17 criteria and would receive postoperative radiation therapy if treated according to current NSABP recommendations. The first is a woman with a 15 mm low-grade DCIS, widely excised with a minimum of 20 mm margins in all directions. Compare her with the second patient, a woman

with a 17 mm high-grade lesion in which DCIS approaches within 0.1 mm of the inked margin but does not involve it. According to the NSABP, both of these patients should be treated with radiation therapy, and neither one needs re-excision. At my facility, the first patient would receive no additional therapy. She would be carefully followed with physical examination and mammography every six months. The second patient would undergo a wide re-excision before a final treatment decision was made. If significant residual disease approaching the new margins were found, a recommendation for mastectomy and immediate reconstruction would be made; if widely clear new margins with little or no residual DCIS were found, a recommendation for breast conservation would be given. The Van Nuys Prognostic Index, discussed below, explains why I would make those recommendations.

Therapy for DCIS ranges from simple excision to various forms of wider excision (segmental resection, quadrant resection, etc.), all of which may or may not be followed by radiation therapy. If breast preservation is not an option, then mastectomy, with or without immediate reconstruction, is generally performed. Since DCIS is a heterogeneous group of lesions rather than a single entity and because patients have a wide variety of personal needs that must be considered during treatment selection, it is obvious 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. Less than 50% of low-grade lesions develop into invasive breast cancer over a 25- to 30-year period [29]. This finding goes back to an issue raised earlier as to whether or not DCIS, and in particular, low-grade DCIS, should be classified as 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 time periods.

The most important question today is: which lesions, if untreated, are going to become invasive breast cancer? And how long will it take for this to happen? Are there biologic markers that can be used to predict this? If treated conservatively, which lesions have such high rates of local recurrence, regardless of radiation therapy, that mastectomy is the preferred initial treatment? If mastectomy is not required, which patients can be treated with excision alone and which ones need postoperative radiation therapy? The questions are simple; the answers are not.

The Van Nuys Prognostic Index (VNPI)

The VNPI is a numerical algorithm based on tumor features and recurrence data from a large series of DCIS patients [18, 30]. It permits quantification of easily measured prognostic factors, in a reproducible fashion, 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 designed 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.

As mentioned above, histologic classification by itself yields insufficient information for determining proper treatment. Two additional factors, tumor size and margin width, are also independent predictors of local recurrence in patients with conservatively treated DCIS [8, 15, 17-22]. It may be possible, by using a combination of these three factors, to select subgroups of patients who do not require irradiation if breast conservation is elected, or to select patients whose recurrence rate is so high that even with breast irradiation, mastectomy is preferable.

As previously discussed, nuclear grade and comedo-type necrosis were used to develop the Van Nuys Pathologic Classification [17]. Nuclear grade and comedo-type necrosis reflect the biology of the DCIS, but are inadequate as the sole guidelines in the treatment selection process. Tumor size and margin width reflect the distribution of the disease and the surgeon's ability to adequately excise the disease. The VNPI [18, 30] was developed by combining these three factors.

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 pathologic classification). The scores for each predictor for each individual patient were totaled to yield a VNPI score ranging from a

Table 1. The Van Nuys Prognostic Index scoring system. One to three points are awarded for each of three different predictors of local breast recurrence (size, margin width, and pathologic 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. Reprinted with permission [18].

Score	1	2	3
Size (mm)	≤ 15	16-40	≥ 41
Margins (mm)	≥ 10	1-9	< 1
Pathologic classification	Non-high grade without necrosis (nuclear grades 1 & 2)	Non-high grade with necrosis (nuclear grades 1 & 2)	High grade with or without (necrosis (nuclear grade 3)

low of 3 to a high of 9 for a group of 461 patients with DCIS treated with regard to breast preservation (our series updated through 1997). Figure 2 shows all 461 patients divided into three subgroups by score (3 or 4 versus 5, 6, or 7 versus 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. 3) 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. 4). Conservatively treated patients with VNPI scores of 8 or 9 had unacceptably high local recurrence rates regardless of irradiation (Fig. 5) and should be considered for mastectomy.

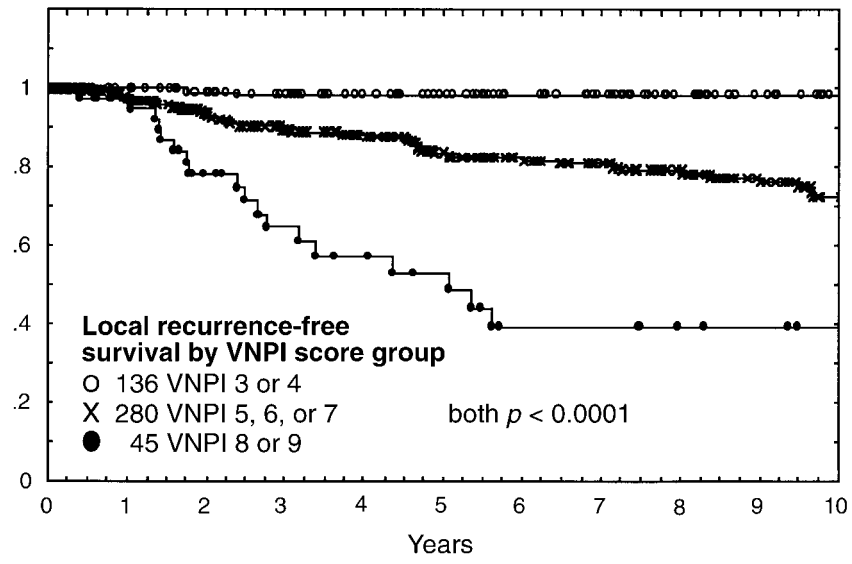

Figure 2. Probability of local recurrence-free survival for 461 breast conservation patients grouped by VNPI score (3 or 4 versus 5, 6, or 7 versus 8 or 9) (all p < 0.0001).

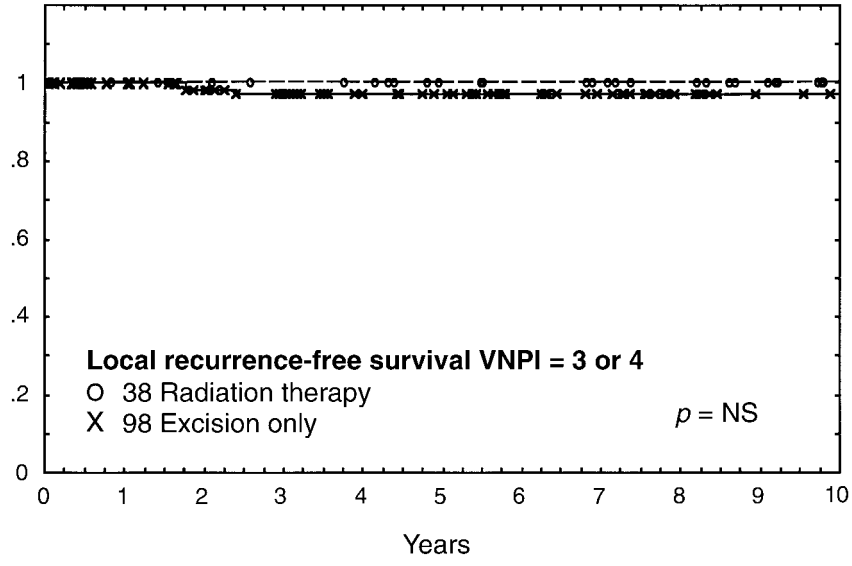

Figure 3. Probability of local recurrence-free survival by treatment for 136 breast conservation patients with VNPI scores of 3 or 4 (p = NS).

Margin Width

Margin width, the distance between DCIS and the closest inked margin, 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 classification), the fact that DCIS can be thought of in Halstedian terms suggests that margin width should indeed be the single most important factor. In other words, since DCIS is a noninvasive lesion without the ability to invade and metastasize (two critically important components of the fully expressed malignant phenotype), complete excision should cure the lesion. At this point in time, the best way to access complete excision is by determining margin width. The serial subgross work of *Holland* and *Faverly* [31] suggests that when margin widths exceed 10 mm, the likelihood of residual disease is relatively small. Supporting data from The Van Nuys Breast Center (Table 2) reveal that there is little benefit from postexcisional radiation therapy if margins are greater than 10 mm, regardless of nuclear grade [32] or the presence of comedo-type necrosis [33]. These data are presented in graphic form in Figures 6 and 7.

Comedonecrosis and nuclear grade reflect tumor biology and are significant only when there is a high likelihood of residual disease (for example, close or involved margins). Preoperative planning with the use of stereotactic biopsy followed by wide excision with

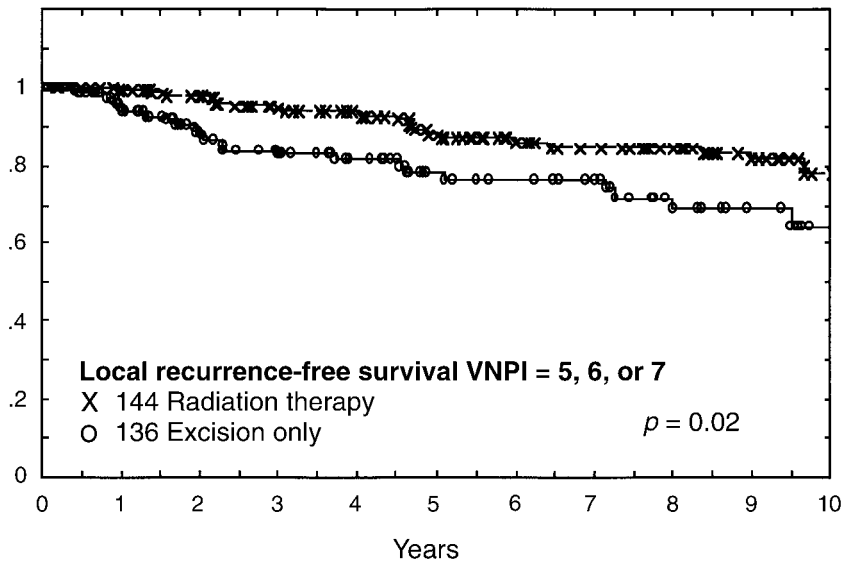

Figure 4. Probability of local recurrence-free survival by treatment for 280 breast conservation patients with VNPI scores of 5, 6 or 7 (p = 0.02).

multiple bracketing wires (Fig. 8) is the best way to achieve widely clear margins and thereby avoid the need for postoperative radiation therapy [4].

Outcome after Local Recurrence Following Conservative Treatment for DCIS

Local recurrence after treatment for DCIS is demoralizing and, if invasive, it is a threat to life. In most reported series, approximately 50% of all local recurrences are invasive [19, 34-37]. For the last decade, local recurrence (both invasive and noninvasive) has been used as the marker of treatment failure for patients with DCIS. As patient accrual increases and follow-up lengthens, more appropriate endpoints might now be invasive local recurrence and breast cancer-specific mortality caused by invasive local recurrence [35].

Table 3 updates the outcome after local recurrence through 1997 for 733 patients in the Van Nuys DCIS series with a total of 75 local recurrences, 35 invasive and 40 noninvasive. All of the patients with noninvasive recurrences did well without any distant disease and with no (0%) breast cancer mortality.

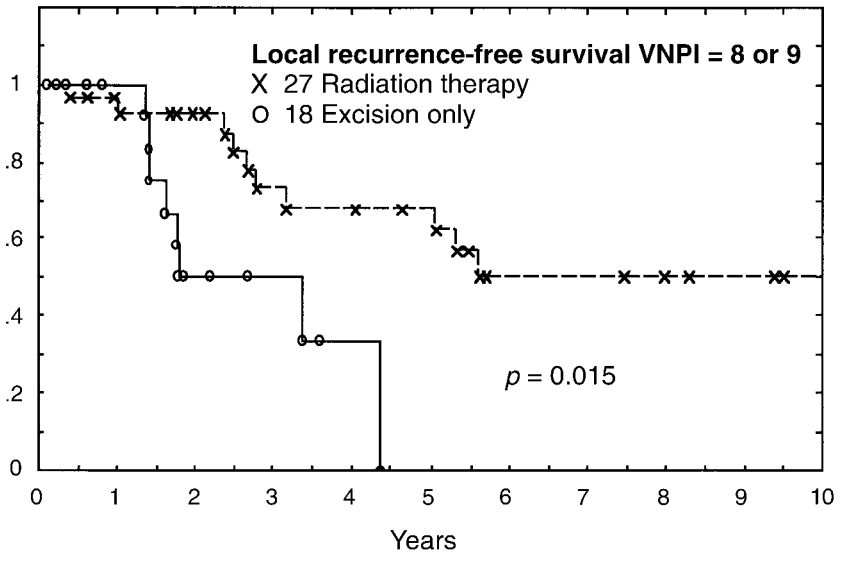

Figure 5. Probability of local recurrence-free survival by treatment for 45 breast conservation patients with VNPI scores of 8 or 9 (p = 0.015).

Among the 35 patients with invasive recurrences, more than half (51%) presented with stage 2A or more disease at the time of local recurrence (Fig. 9), seven developed distant disease, and five died of breast cancer. The median follow-up for the 35 patients with invasive recurrences was more than nine years. The breast cancer mortality rate at eight years calculated by the Kaplan-Meier method for the subgroup of patients with invasive local recurrences was 14%; the distant disease rate for this subgroup was 27%, rates similar to the ones reported by *Solin et al*. [36, 37]. Invasive recurrence after treatment for DCIS is a significant event, generally converting a patient with previous Stage 0 disease to a patient with stage 2A breast cancer (range: stages 1 to 4).

Treatment for a patient with an invasive recurrence should be based on the stage of the disease at the time of recurrence. Patients initially treated by mastectomy generally require excision of the recurrence followed by radiation therapy to the chest wall and chemotherapy. Patients previously treated by excision and radiation therapy generally require mastectomy followed by chemotherapy if the invasive recurrence is high grade, greater than 1 cm in diameter, or has poor prognostic markers. Patients previously treated by excision only can be re-excised; if clear margins are obtained, they can be

Table 2. Eight-year probability of local recurrence by treatment and then further subdivided by margin width and additionally by the presence of comedo-type necrosis.

	Excision + radiation	Excision only	*p* value
Number of patients (*n* = 461)	209	252	
Local recurrence rate (all patients)	16%	22%	0.04
Margins ≥ 10 mm (*n* = 131)	4%	5%	NS
Margins = 1-9 mm (*n* = 223)	12%	19%	0.05
Margins < 1 mm (*n* = 107)	29%	63%	0.002
Eight-year actuarial local recurrence rate by nuclear grade and margin width:			
Nuclear grade 1 (low nuclear grade) (*n* = 100)			
Margins ≥ 10 mm (*n* = 33)	0%	0%	NS
Margins = 1-9 mm (*n* = 59)	6%	7%	NS
Margins < 1 mm (*n* = 8)	25%	50%	NS
Nuclear grade 2 (intermediate nuclear grade) (*n* = 176)			
Margins ≥ 10 mm (*n* = 42)	10%	0%	NS
Margins = 1-9 mm (*n* = 93)	7%	11%	NS
Margins < 1 mm (*n* = 41)	23%	44%	NS
Nuclear grade 3 (high nuclear grade) (*n* = 185)			
Margins ≥ 10 mm (*n* = 56)	0%	6%	NS
Margins = 1-9 mm (*n* = 71)	25%	39%	NS
Margins < 1 mm (*n* = 58)	36%	73%	0.01
Eight-year actuarial local recurrence rate by comedonecrosis and margin width:			
Comedonecrosis present (*n* = 286)			
Margins ≥ 10 mm (*n* = 78)	7%	3%	NS
Margins = 1-9 mm (*n* = 124)	16%	30%	0.04
Margins < 1 mm (*n* = 84)	31%	68%	0.003
Comedonecrosis absent (*n* = 175)			
Margins ≥ 10 mm (*n* = 53)	0%	7%	NS
Margins = 1-9 mm (*n* = 99)	9%	10%	NS
Margins < 1 mm (*n* = 23)	20%	33%	NS

considered for breast preservation with radiation therapy. Many, however, will likely opt for mastectomy. The decision to add adjuvant chemotherapy should be based on tumor factors and axillary node status.

In spite of the few mortalities in our series, one must not lose sight that DCIS is overall an extremely favorable disease. When our entire series of 733 patients is considered, the probability of an invasive recurrence at eight years is 6%, and the probability of a breast cancer-specific mortality is only 1.4%. It is, however, a tragedy when a patient with DCIS recurs with invasive breast cancer and then goes on to die of metastatic disease.

Patients with DCIS treated with breast preservation should be followed closely. At our center, they are examined physically every six months, forever. Mammography is performed every six months, on the ipsilateral breast and annually on the contralateral breast.

When breast cancer mortality, rather than local recurrence, is the end-point, patients with DCIS do exceptionally well, regardless of treatment (all *p* = NS). For the 75 patients who recurred, the eight-year breast cancer-specific mortality after salvage treatment was 9%. For the 35 patients with invasive recurrences, the eight-year breast cancer-specific mortality was 14%. These results indicate that most patients who recur can be salvaged. For the small subgroup of patients who recur with invasive breast cancer, mortality rate, on average, is similar to that of patients with stage 2A primary breast cancer.

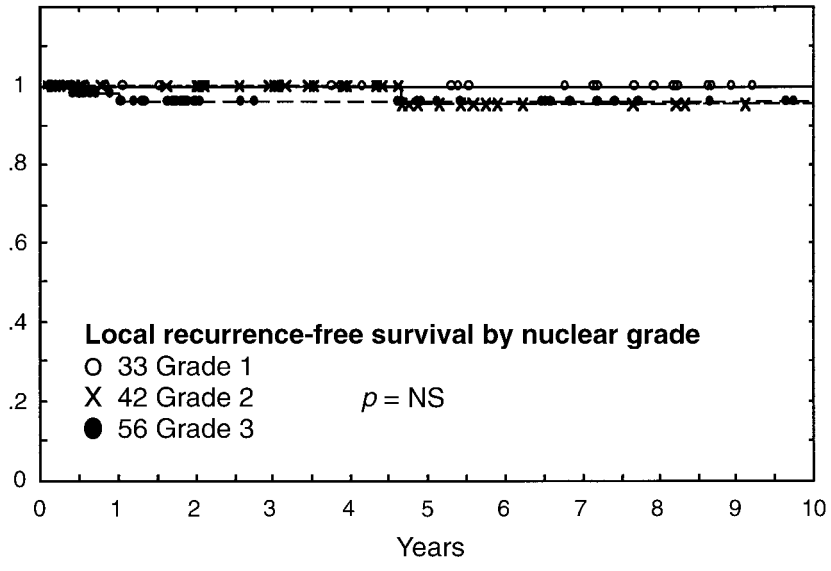

Figure 6. Probability of local recurrence-free survival by nuclear grade for 131 breast conservation patients with 10 mm or greater margins. *With adequate margins (10 mm or more), the local recurrence rate is similar for all patients regardless of nuclear grade or whether radiation therapy was given postoperatively.*

Treatment of the Axilla in Patients with DCIS

There is now general agreement that for patients with DCIS, the axilla does not need treatment [38, 39]. At my facility, the axilla is not treated

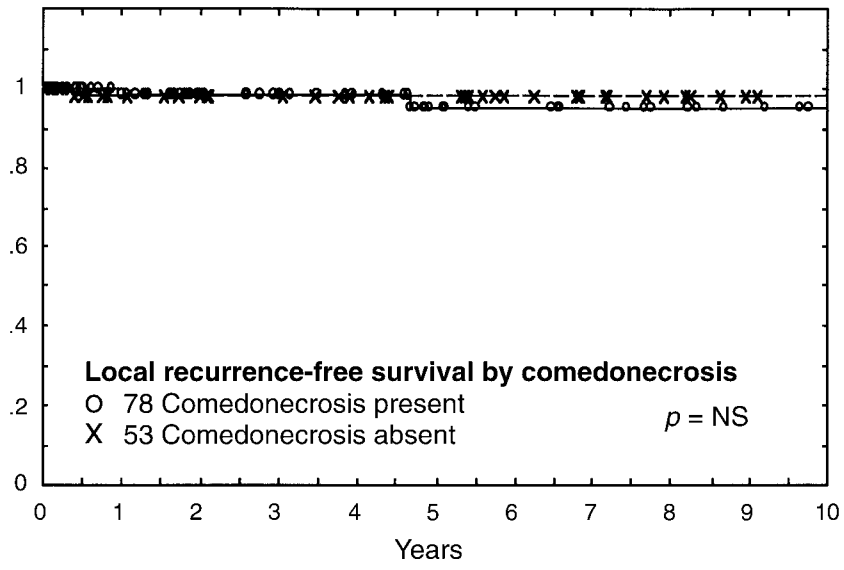

Figure 7. Probability of local recurrence-free survival by the presence or absence of comedo-type necrosis for 131 breast conservation patients with 10 mm or greater margins. *With adequate margins (10 mm or more), the local recurrence rate is similar for all patients regardless of comedonecrosis or whether radiation therapy was given postoperatively.*

Table 3. Outcome after local recurrence: 733 patients with DCIS analyzed by treatment. All recurrences and mortality probabilities are Kaplan-Meier estimates at eight years.

	Mastectomy	Excision + radiation	Excision only
Number of patients (n = 733)	272	209	252
Total recurrences (n = 75)	2	36	37
Invasive recurrences (n = 35)	2	18	15
Distant metastases (n = 7)	1	5	1
Breast cancer deaths (n = 5)	0	4	1
Average DCIS size (mm)	40	18	14
Local recurrence probability	< 1%	16%	21%
Distant recurrence probability	< 1%	3%	1%
Breast cancer-specific mortality	0%	3%	< 1%
Overall mortality (all causes)	6%	7%	9%

for patients with DCIS undergoing breast conservation. It is not irradiated, and no form of axillary sampling or dissection is performed. For patients treated with excision plus postoperative radiation therapy, the lower axilla is included by the tangential fields to the breast.

For patients undergoing mastectomy, we generally perform a sentinel node biopsy using a vital blue dye, radioactive tracer, or both at the time of mastectomy [40-42]. This is done in the event that permanent sectioning of the mastectomy specimen reveals one or more foci of invasion. If invasion is documented, no matter how small, the lesion is no longer considered DCIS, but rather an invasive cancer. The sentinel node or nodes are evaluated by hematoxylin and eosin (H & E) staining followed by immunohistochemistry for cytokeratin when routine H & E stains are negative.

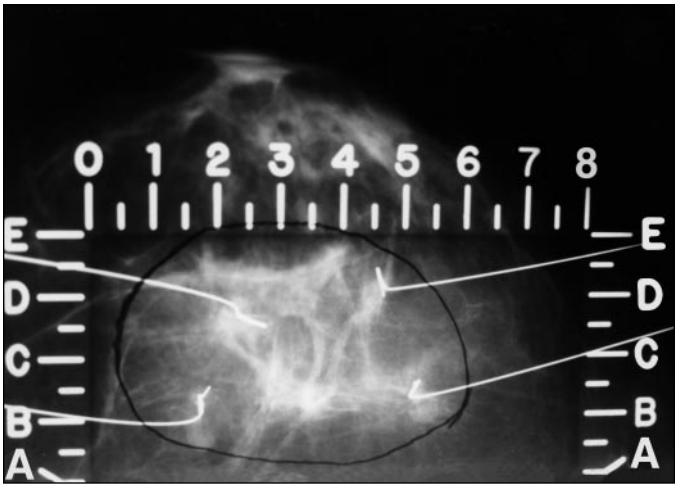

Figure 8. Craniocaudal mammogram taken after insertion of four bracketing wires around an area of architectural distortion.

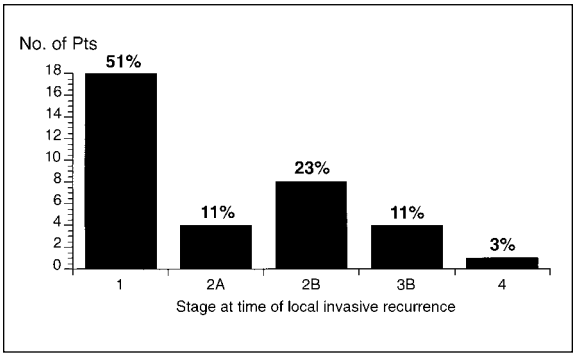

Figure 9. The number and percentage of patients in the Van Nuys DCIS Series with each stage of disease at the time of diagnosis of invasive recurrence. *Reprinted with permission [35].*

The Future

Our current treatment approach to DCIS is based on morphology rather than etiology, on phenotype rather than genotype. But morphologically normal-appearing tissue surrounding areas of DCIS may reveal losses of heterozygosity as in the primary tumor [43-46]. It is highly likely that genetic changes precede morphologic evidence of malignant transformation. Using basic science, medicine must learn how to recognize these genetic changes and exploit them, and, ultimately, prevent them. DCIS is a lesion in which the complete malignant phenotype of unlimited growth, angiogenesis, genomic elasticity, invasion, and metastasis have not been fully expressed. With sufficient time, most noninvasive lesions will learn how to invade and metastasize. We must learn how to prevent this.

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