Use of Predictors of Recurrence to Plan Therapy for DCIS of the Breast

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Despite the results of the National Surgical Adjuvant Breast and Bowel Project B-17, there continues to be debate regarding the most appropriate treatment for patients with ductal carcinoma in situ (DCIS) of the breast. Numerous clinical, pathologic, and laboratory factors can aid clinicians and patients wrestling with the difficult decision-making process.

Introduction

"Her agony came from the fact that mastectomy would be curative and it was hard to turn that down. A lesser procedure, while preserving her breast and her femininity, offered her somewhat less chance for a complete cure--but exactly how much less was unknown. Perhaps only a small amount less. It didn't seem worth losing her breast for a few percentage points. Yet, maybe it was. It was the most difficult decision of her life. But medicine had failed her. The data upon which to base her judgment was weak, and we had shifted the burden of that judgment to her."[1]

That paragraph was written in 1991 about a woman with ductal carcinoma in situ (DCIS) of the breast and her arduous journey through the medical system as she searched for the "correct" treatment. There were a number of "correct" treatments then for her particular form of DCIS, but each was flawed in one way or another, confounding her thoughts and making her decision more difficult. But that was 1991. Today, we know much more about DCIS. But is the decision-making process any easier?

The results of the National Surgical Adjuvant Breast Project (NSABP) Protocol B-17 were published in 1993[2] and updated in 1995[3] and 1997[3a]. This prospective, randomized clinical trial was designed to resolve the controversy over the treatment of DCIS. More than 800 patients with DCIS excised with clear surgical margins were randomized to one of two treatments: excision only or excision plus radiation therapy. At 5 years, there was a statistically significant decrease in local recurrence of both DCIS and invasive breast cancer in patients treated with radiation therapy. These data led the NSABP to recommend postexcision radiation therapy for all patients with DCIS who chose to save their breasts--a recommendation that some consider too broad.[4,5]

The NSABP B-17 study was criticized for a number of reasons, including its definition of clear margins (which the NSABP defined as a tumor that is not transected), determination of size by central review of the pathology report, the absence of size measurements for more than 40% of cases, and, perhaps most important, the lack of pathologic subset analysis in the initial report.[4,5] In defense of the NSABP, the trial did exactly what it was designed to do; namely, it proved that radiation therapy was effective for patients with DCIS. It was not designed to answer the questions about patient subgroups that we ask today.

Consider the following two patients, both of whom merit radiation therapy based on the results of NSABP B-17. The first patient is a woman with a 12-mm low-grade lesion that has been widely excised with a minimum of 15-mm margins in all directions. Compare her with the second patient, a woman with a 35-mm high-grade lesion with DCIS approaching to within 0.2 mm of the inked margin but not involving it. According to the NSABP, both of these patients should be treated with radiation therapy.

At our facilities, based on data that will be presented below, the first patient would receive no additional therapy. Rather, she would be carefully followed with physical examination every 6 months and mammography every 6 to 12 months. The second patient would undergo a wide reexcision prior to making a final treatment decision. Significant residual disease approaching the new margins would earn a recommendation for mastectomy and immediate reconstruction; widely clear new margins with little or no residual DCIS would warrant consideration for radiation therapy. Thus, despite the results of NSABP B-17, there continues to be debate regarding the DCIS decision-making process, which is not much clearer now than it was in 1991.
Numerous clinical, pathologic, and laboratory factors can aid clinicians and patients wrestling with the difficult treatment decision-making process. Our research has shown that nuclear grade, the presence of comedo-type necrosis (coagulative necrosis), tumor size, and margin width are all key factors in predicting local recurrence in patients with DCIS.[6-8] By using a combination of these factors, it may be possible to identify subgroups of patients who do not require irradiation, if breast conservation is elected; it also may be possible to identify patients whose recurrence rate is potentially so high, even with breast irradiation, that mastectomy is preferable.

Changing Patterns of Disease

Ductal carcinoma in situ is a biologically and histologically heterogeneous group of lesions.[9,10] With the appreciation and acceptance of this heterogeneity, DCIS has become confusing for both patients and physicians. Currently, it is not uncommon for DCIS patients to seek second, third, and even fourth opinions and to receive a diverse spectrum of advice ranging from biopsy only to wide excision, segmental resection, quadrant resection, mastectomy, or even bilateral mastectomy. As an adjunct to all these treatments except mastectomy, radiation therapy may be advised. Patients seeking treatment advice will find physicians willing to support most of these options.[1]

The second opinion-givers are usually oncologists specializing in medicine, surgery, or radiation therapy. Some patients, however, seek advice from their gynecologists, internists, or family practitioners. Many women also turn for counsel to family, friends, and other women who have had breast cancer, most of whom have had invasive disease. Table 1 shows the changing nature of DCIS during the last decade. Before the widespread use of mammography, DCIS was diagnosed infrequently, representing less than 1% of all breast cancer cases.[11,12] Today, DCIS is common, accounting for approximately 12% to 15% of all newly diagnosed cases[13] and as many as 20% to 40% of cases at institutions that effectively utilize mammography.[14,15] In 1997, more than 36,000 new cases of DCIS are expected to be diagnosed in the United States.[16]

Previously, most patients with DCIS presented with clinical symptoms, such as a breast mass, bloody or serous nipple discharge, or Paget's disease and frequently had extensive disease.[11,17-19] Today, most lesions are smaller, nonpalpable, subclinical, and detected by mammography alone. Until recently, the treatment for most patients with DCIS was mastectomy. Currently, many patients are being treated with breast preservation. Fifteen years ago, when mastectomy was common, reconstruction was infrequent and, if performed, was generally done as a delayed procedure with implants. Today, reconstruction for patients with DCIS treated by mastectomy is common and is usually done immediately, at the time of mastectomy, and often with autologous tissue.

In the past, when a mastectomy was performed, large amounts of skin were discarded. Now, it is considered safe to perform a skin-sparing mastectomy for DCIS.[20-23] We must keep in mind, however, that in patients with extensive disease, recurrences may develop after mastectomy (with or without reconstruction) in the scant residual breast tissue. The thicker the skin flaps, the more residual breast tissue is left behind and the more likely there is to be a recurrence.

In the past, there was no confusion. All breast cancers were considered the same and mastectomy was the only treatment. Today, we know that all breast cancers are different. There are many treatments and a great deal of confusion.

Factors Responsible for the Changes

These changes were brought about by numerous factors. The most important of these are increased utilization of mammography, improvements in mammographic technique, and the acceptance of breast-conservation therapy for invasive breast cancer.

Mammography--The acceptance of mammography not only changed the way we detect DCIS, it also altered the nature of the disease that we detected by allowing us to enter the neoplastic continuum at an earlier time. Every institution employing mammography has witnessed a relatively large increase in the number of small, mammographically detected cases of DCIS. This can be appreciated by charting the impact that mammography has had on the number and type of DCIS cases at one of our facilities, the Breast Center in Van Nuys, California.[24]

From 1979 to 1981, the Van Nuys group treated a total of only 15 patients with DCIS, an average of 5 per year. Only two lesions (13%) were nonpalpable. Two new mammography units and a full-time, experienced mammographer were added in 1982, and immediately the number of new DCIS cases increased to more than 30 per year, most of them nonpalpable. With the addition of a third mammography machine in 1987, almost 40 new cases per year were diagnosed. In 1994, a fourth mammography machine and a stereotactic biopsy unit were added. Analysis of the Van Nuys series
through June 1996 (more than 500 patients) revealed that 81% of lesions were nonpalpable. If we consider only those lesions that were diagnosed after 1991, 92% were nonpalpable.

**Breast Conservation**—The second factor that affected how we think about DCIS was the acceptance of breast-conservation therapy (lumpectomy, axillary node dissection, and radiation therapy) for patients with invasive breast cancer. Until 1980, the treatment for most patients with any form of breast cancer was mastectomy. Since then, numerous prospective randomized trials have revealed that survival in patients with invasive breast cancer treated with lumpectomy and radiation therapy is equivalent to that in women who undergo mastectomy.[25-32] Based on these results, it was difficult to continue treating noninvasive disease with mastectomy while treating more aggressive invasive breast cancer with breast preservation.

Patients often ask the question, “You mean if I waited until my cancer was invasive, I could have saved my breast?” The answer is not that simple. Although there is clearly a relationship between DCIS and invasive breast cancer, the two entities are different heterogeneous groups of diseases with some overlap. It is extremely common to see both DCIS and invasive breast cancer within a single specimen. Authorities agree that DCIS is an obligate precursor to invasive breast cancer, but there is speculation that DCIS may be less amenable to control with irradiation. Thus, while patients with invasive breast cancers that are 4 cm or smaller and have little or no intraductal component can readily be treated by lumpectomy and radiation therapy, the same may not be true for patients with pure DCIS or for those with invasive breast cancer with an extensive intraductal component. Nevertheless, current data suggest that many patients with DCIS can be successfully treated with breast preservation (with or without radiation therapy). In the sections that follow, we will show how easily available data can be used to predict which patients are more likely to suffer a recurrence after breast conservation. Knowing the probability of local recurrence can help simplify the complex treatment selection process.

**Classifying DCIS**

There is no single universally accepted histopathologic classification for ductal carcinoma in situ.

**Tumor Architecture**

Pathologists traditionally divide DCIS into five or six architectural subtypes (papillary, micropapillary, cribriform, clinging, solid, and comedo), often grouping the first five together as noncomedo lesions and comparing them with comedo DCIS.[14,33,34] Comedo DCIS is frequently associated with high nuclear grade,[14,33-35] aneuploidy,[36] a higher proliferation rate,[37] HER-2/neu (c-erb-B2) gene amplification or protein overexpression,[38-43] and more clinically aggressive behavior.[8,44-46] Noncomedo lesions tend to have the opposite features. However, such a division by architecture, comedo vs noncomedo, is an oversimplification and has not been shown to correlate with outcome in all cases.

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 markers similar to high-grade comedo lesions. Such lesions may require more aggressive treatment. Furthermore, mixtures of various architectural subtypes within a single biopsy specimen are common. In our series, 68% of all lesions had significant amounts of two or more architectural subtypes (Figure 1). Adding to the confusion, there is no uniform agreement among pathologists on exactly how much comedo DCIS needs to be present to consider the lesion a comedo DCIS. Architecture, without a strict set of universally agreed upon criteria (which currently do not exist), is a poor way to classify DCIS.

**Nuclear Grade**

Nuclear grade is a more dependable biologic indicator than architecture and has emerged as a key histopathologic factor for identifying aggressive tumor behavior.[8,11,33,34,46-49] In a multivariate analysis of the Van Nuys series that was limited to DCIS patients treated with excision plus radiation therapy, nuclear grade was the only significant factor that predicted for local recurrence of both DCIS and invasive breast cancer.[7] This result led us to perform a more detailed analysis of all patients in our series who underwent breast preservation (excision alone or excision plus radiation therapy).[6,50] We analyzed 15 prognostic factors by univariate analysis (log-rank test). All statistically significant predictors of local recurrence by univariate analysis were then evaluated using a Cox multivariate regression analysis with backward elimination.

As shown in Table 2, six factors—nuclear grade, margin width, tumor size, presence of necrosis, comedo architecture, and HER-2/neu overexpression—were significant predictors of local recurrence...
on univariate analysis, but only three--nuclear grade, tumor size, and margin width--remained significant on multivariate analysis. The presence of comedo-type necrosis also approached significance on multivariate analysis (P = .09). The remaining nine factors (estrogen receptor, progesterone receptor, S-phase, ploidy, p53, microcalcifications, palpability, year of diagnosis, and age) were not significant predictors of local recurrence by univariate analysis.

Van Nuys Pathologic Classification

With this in mind, in May 1995, the Van Nuys group introduced a new pathologic classification of DCIS, the Van Nuys Pathologic Classification, based on two statistically important predictors of local recurrence: the presence or absence of high nuclear grade and comedo-type necrosis.[49] We believe that both of these factors reflect tumor biology.

To use the Van Nuys Pathologic Classification (Figure 2), all high-grade lesions, regardless of the presence or absence of comedo-type necrosis, are placed into the worst prognostic group (group 3) (Figures 3a and 3b). The remaining non-high grade lesions (nuclear grades 1 or 2) are then separated by the presence of any amount of comedo-type necrosis (group 2; Figures 4a-4c) or the absence of comedo necrosis (group 1; Figures 5a and 5b). This results in three easily identifiable groups with significantly different outcomes as measured by local tumor recurrence (Figure 6).

High nuclear grade was chosen as the most important factor in the Van Nuys classification because of the results of our multivariate analysis (Table 2) and because there is general agreement that the recurrence rate after breast conservation is higher in patients with high-grade lesions than in those patients with low-grade lesions.[8,11,30,34,47,39,51] Comedo-type necrosis was chosen because its presence also suggests a poor prognosis.[14,44-46,52,53] Both high nuclear grade and comedo-type necrosis are easily and consistently recognized by practicing pathologists.[54]

In our pathologic classification, no requirement is made for a minimum or specific amount of high-grade DCIS or comedo-type necrosis. Occasional desquamated or individually necrotic cells are ignored and are not scored as comedo-type necrosis. Since publication, the reproducibility of the Van Nuys Pathologic Classification, as compared with other proposed classification systems, has been independently confirmed by Gupta and colleagues.[55]

The most difficult part of nuclear grading is the intermediate-grade lesion. The subtleties of the intermediate-grade lesion are not important to our classification; only nuclear grade 3 needs to be recognized. This is a fairly straightforward task for most pathologists.[49] The cells must be large and pleomorphic, lack architectural differentiation and polarity, have prominent nucleoli and coarse clumped chromatin, and generally show mitoses[14,33,34,52] (Figures 3a and 3b). This pathologic classification, when combined with tumor size and margin width, is an integral part of the Van Nuys Prognostic Index, a system that will be explained in detail below.

Which Treatment Option?

For most patients who have DCIS, there is no single correct treatment approach. Patients generally have to make a choice among several options--a decision that, although seemingly simple, is not. As the treatment alternatives increase and become more complicated, frustration will increase for both patient and physician.[1]

There is no easy way to tell a patient that she has breast cancer. But is DCIS really breast cancer? When we think of cancer, we think of a disease that, if untreated, can run an unrelenting course toward death. That is certainly not the case with DCIS. The cancer phenotype consists of at least five factors: unlimited growth, genomic elasticity (resistance to treatment), angiogenesis, invasion, and metastasis.[56,57] Ductal carcinoma in situ lacks the latter two characteristics. In all likelihood, when we understand why some DCIS lesions develop the ability to invade and metastasize and why others do not, we will have opened the door to a far better understanding of the neoplastic process.

When counseling a patient with DCIS, one must emphasize that she has a borderline, or "preinvasive," lesion, which, at this time, is not a threat to her life. In the Van Nuys series of 504 patients with DCIS, absolute mortality is 0.6% (there have been three breast cancer-related deaths). The 10-year actuarial breast cancer-specific mortality is 0% for mastectomy patients, 1% for all patients, and 2% for breast-preservation patients. Numerous other DCIS series[2,7,14,17,58-63] confirm the extremely low mortality of DCIS.

One of the most common concerns expressed by patients once a diagnosis of cancer has been made is the fear that the cancer has spread. The DCIS patient can be assured that no invasion was seen microscopically and that the likelihood of systemic spread is minimal.

The patient with DCIS should be educated that the term "breast cancer" encompasses a wide variety of lesions with a wide range of aggressiveness and potential lethality. She needs to be reassured
that she has a minimal lesion and that she may require some additional treatment, which may include further surgery and/or radiation therapy. The patient needs to know that she will not require 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.

**The Van Nuys Prognostic Index**

It is clear that breast irradiation reduces the local recurrence rate at 5 years by about half (from about 20% to about 10%). Does this mean that all conservatively treated patients with DCIS should receive postoperative radiation therapy? Series with longer follow-up[64,65] suggest that as time passes, recurrences continue to accrue in patients treated with radiation therapy. This raises speculation that, at least in some patients, radiation merely delays, rather than prevents, an inevitable recurrence.

The median time for local recurrence for excision-only patients in our series was 1.7 years, whereas for patients treated with excision plus radiation therapy, it was 4.7 years. There is now sufficient, easily available, information that can aid clinicians in differentiating patients who may benefit from postexcision radiation therapy from those who may not. These same data can identify patients who are better served by mastectomy because their recurrence rates with breast conservation are unacceptably high with or without radiation therapy.

Our research[6-8,14,49,51,66], as well as that of other investigators,[44,46,52,67,68] has shown that various combinations of nuclear grade, the presence of comedo-type necrosis, tumor size, and margin status are all important predictors of local recurrence in conservatively treated patients with DCIS. We believe that it is possible, by using a combination of these prognostic factors, to distinguish subgroups of patients who do not require radiation therapy in addition to complete excision and also patients whose recurrence rate is theoretically so high, even with breast irradiation, that mastectomy is preferable.

The first two of these prognostic factors (nuclear grade and necrosis) were used to develop the Van Nuys Pathologic Classification[49] described above (which henceforth will be referred to as pathologic classification). Nuclear grade and comedo-type necrosis reflect the biology of the lesion, but neither is adequate as the sole guideline for treatment decision-making. Tumor size and margin width reflect the extent of disease, the adequacy of surgical treatment, and the likelihood of residual disease and therefore, are extremely important. The results of the multivariate analysis confirm the critical importance of these variables.

**How Tumors Are Scored**

The Van Nuys Prognostic Index (VNPI)[50,69,70] was devised by combining these three statistically significant predictors of local tumor recurrence in patients with DCIS: tumor size, margin width, and pathologic classification. A score, ranging from 1 for lesions with the best prognosis to 3 for lesions with the worst prognosis, was assigned for each of the three predictors. The objective with all three predictors was to create three statistically different subgroups for each, using local recurrence as the marker of treatment failure. Cut-off points (for example, what size or margin width constitutes low, intermediate, or high risk of local recurrence) were determined by statistical modeling, using the log-rank test with an optimum P-value approach.

**Size Score**--A score of 1 was given for small tumors (15 mm or less in diameter); a score of 2, for intermediate-sized tumors (16 to 40 mm); and a score of 3, large tumors (41 mm or more).

**Margin Score**--A score of 1 was used to denote widely clear tumor-free margins (10 mm or more). This was most commonly achieved by reexcision with the finding of no residual DCIS or only focal residual DCIS in the biopsy cavity. A score of 2 was used for intermediate margins (1 to 9 mm) and a score of 3, for involved or close margins (less than 1 mm).

**Pathologic Classification Score**--A score of 3 was given for tumors classified as group 3 (all high-grade lesions); a score of 2, for tumors classified as group 2 (non-high-grade lesion with comedo-type necrosis); and a score of 1, for tumors classified as group 1 (non-high-grade lesion without comedo-type necrosis).[49]

**Calculating the VNPI**

The VNPI formula was determined by using the beta values, obtained from the initial multivariate analysis.[6,70] The beta values reflect the relative contribution of each factor to the estimation of the likelihood of local recurrence[7,70,71]; these values were similar for all three factors. This method yielded a relatively user-unfriendly formula with 27 possible VNPI scores. The 27 subgroups naturally divided into three prognostic subgroups with low, intermediate, and high risks, respectively, of recurrence.
Because the beta values for the three factors were similar, additional analyses revealed that the formula could be simplified, without compromising validity, by omitting the beta weighting, suggested by the multivariate analysis, and by readjusting the numerical range for each of the three subgroups. Thus, the final formula for the VNPI became:

\[
VNPI = \text{Pathologic classification score} + \text{Margin score} + \text{Size score}
\]

This formula yielded a total of seven groups with whole-number scores ranging from 3 to 9. The best possible VNPI score was 3, a score of 1 for each predictor (eg, a 5-mm low-grade lesion with widely clear margins [10 mm or more] would earn this score). The worst possible score was 9, a score of 3 for each predictor (eg, a 50-mm high-grade lesion with close or involved margins [less than 1 mm] would warrant such a score). Table 3 summarizes the scoring for the VNPI. When patients were subdivided into those with scores of 3 or 4, those with scores of 5, 6, or 7, and those with scores of 8 or 9, the results were identical to the more complicated beta-weighted version and the VNPI was much easier to use.

**Validating the VNPI**

The VNPI was initially tested on 254 breast-conservation patients from The Breast Center, and these results were presented at the annual meeting of the American Society of Clinical Oncology (ASCO) in April 1995.[6] The index was subsequently validated by analyzing a series of patients treated with excision-only compiled by Lagios et al.[8,51,66] The validation yielded almost identical local disease-free survival curves for all VNPI subgroups when 83 Breast Center excision-only patients, who met the strict criteria of Lagios et al,[51] were compared with the 79 patients of Lagios et al.[8,66] The results of the combined series were presented at the 18th Annual San Antonio Breast Cancer Symposium[50] in December 1995.

The VNPI was next tested in a group of 42 DCIS patients treated by the Breast Center's radiation oncologists (Western Tumor Radiation Therapy Group) but not operated upon by the center's surgeons. All pathology was centrally reviewed by the Breast Center's pathologist. The results again revealed almost identical outcomes when the two groups of radiation therapy patients were compared by VNPI scores.

With two outside groups of patients validating the VNPI, we feel comfortable presenting data through mid-1996 by combining all three groups for a total of 394 patients (273 breast-preservation patients from the Breast Center, 79 excision-only patients from Lagios et al, and 42 excision-plus-radiation therapy patients from the Western Tumor Radiation Therapy Group).

**Results of an Analysis Using the VNPI**

The local recurrence-free survival for all 394 patients is shown by pathologic classification in Figure 6, by tumor size in Figure 7, and by margin width in Figure 8. The differences among the three survival curves for each of the three predictors that constitute the VNPI are statistically significant. Figure 9 shows the local recurrence-free survival rate for each of the seven VNPI groups, 3 through 9. Figure 10 groups patients with low (VNPI = 3 or 4), intermediate (VNPI = 5, 6, or 7), or high (VNPI = 8 or 9) recurrence rates together. Each of these three groups is statistically different from the other two with respect to local recurrence-free survival.

As shown in Figure 11, breast irradiation does not significantly decrease local recurrence in patients with low VNPI scores (3 or 4). Patients with intermediate VNPI scores (5, 6, or 7) derive some benefit from irradiation (Figure 12). Among this group, there is a 13% average decrease in local recurrence rate in irradiated patients, which is statistically significant compared to those treated by excision alone (P = .027). Patients with high VNPI scores (8 or 9) benefit the most from the addition of radiation therapy to their treatment regimen (Figure 13). However, even though the difference between the two groups is significant (P = .025), patients with a VNPI score of 8 or 9 have an extremely high rate of recurrence, regardless of whether of not they receive radiation therapy.

**Discussion**

Although mastectomy is curative for approximately 98% to 99% of patients with DCIS,[7,17,58,59,62,63,72-74] mastectomy represents overtreatment for most cases detected by current methods. When breast conservation is elected, radiation therapy statistically decreases the likelihood of local recurrence when compared with excision alone.[2,3] However, radiation therapy, like mastectomy, may also represent overtreatment for a significant number of patients who opt for breast preservation.

Subsets of patients who are not likely to derive a significant benefit from radiation therapy can be identified, eg, those with VNPI scores of 3 or 4 in the series presented here, low-grade lesions in the series of Lagios et al,[8,66] small noncomedo lesions with uninvolved margins in the series of
Schwartz, et al,[44] or the well-differentiated lesions of Zafrani et al.[68] Such patients may account for 30% to 40% of all currently diagnosed patients with DCIS.[8,44,49,66,68]

The recommendation by the NSABP that radiation therapy is appropriate for all patients with DCIS who are treated with breast preservation does not take into account the heterogeneity of DCIS or the significant differences in subsets demonstrated by our data,[7,8,14,49,51,66] the data of others,[3,44,46,52,53,67,68] and, more recently, the NSABP's own data.[3]

Radiation therapy, like all treatments, has side effects. Radiation changes the texture of the breast and may make subsequent mammography more difficult to interpret. Perhaps most importantly, its use precludes additional radiation therapy and breast conservation should invasive breast cancer develop at a later date. The risks and benefits of radiation therapy must be carefully weighed and compared to those of other options prior to making a treatment recommendation. The use of radiation therapy should then be advocated only for those patients likely to obtain a benefit.  

Treatment Recommendations Based on VNPI Scores

Patients in this series with VNPI scores of 8 or 9 pose a special problem. While these patients derive the greatest relative benefit from postexcision radiation therapy, their local recurrence rate continues to be unacceptably high, more than 60% at 5 years. Therefore, a recommendation for mastectomy should be considered.

Treatment recommendations for the intermediate group (patients with VNPI scores of 5, 6, or 7) are the most difficult to make. For patients with intermediate VNPI scores and margin scores of 2 or 3, reexcision may decrease the risk of local recurrence by lowering their VNPI score ("downscoring"). If the score remains intermediate after reexcision, radiation therapy should be considered. However, some patients with scores of 7 may be better treated with mastectomy (eg, a patient with a large grade 2 lesion without necrosis that shows involved margins after reexcision). Some patients with scores of 5 may elect no further treatment (eg, a patient with widely clear margins, small tumor size, but high nuclear grade).

These are independent judgments that must be made by the patient and her physician. We are hopeful that the VNPI will be a helpful adjunct as these difficult decisions are discussed. If the VNPI, or some similar system, is not used, there are few data in the literature to aid clinicians in the complex DCIS treatment selection process.

Potential Flaws and Benefits of the VNPI System

There is a strong selection or treatment bias among the patients used to develop the VNPI. In all cases, the treatment was selected by the individual patient and her physician, not by random assignment. However, treatment selection does not bias the results since the VNPI compares patients with different scores, not different treatments. Although the patient and her clinician control treatment selection, neither can control final margins, tumor size, or pathologic classification. The fact that some patients opted for suboptimal treatments that were not recommended (eg, 33 patients with VNPI scores of 8 or 9 who selected breast conservation were all advised to undergo mastectomy) was helpful in developing and evaluating the VNPI.

Counseling patients with DCIS in a rational manner can be extremely difficult when the range of treatment options is extreme. The VNPI permits the physician to carry out a scientifically based discussion with the patient, using the parameters of the lesion obtained after an initial excision. Thus, in some cases, a patient can choose reexcision, in an effort to downscore her lesion. Successful downsccoring of a patient with a VNPI score of 8 or 9 could result in a substantial reduction in the risk of local recurrence, perhaps changing a recommendation from mastectomy to breast preservation with radiation therapy. Similarly, patients with close or involved margins who have VNPI scores of 5 or 6 after initial excision could opt for reexcision. Successful downsccoring by achieving widely clear margins could result in a final VNPI score of 3 or 4, leading to a recommendation for careful clinical follow-up without radiation therapy.

Downscoring can be accomplished only by reexcising lesions in patients with margin scores of 2 or 3. Reexcision will not lower the pathologic classification score or reduce the size of the tumor. In some cases, reexcision will upscore the tumor, increasing the VNPI score by revealing a larger tumor size, a higher nuclear grade, the presence of previously undetected comedo necrosis, or an involved margin.

The VNPI is the first attempt to quantify known important prognostic factors in DCIS, making them clinically useful in the treatment decision-making process. It may be useful to clinicians because it divides DCIS into three groups with different risks for local recurrence after breast-conservation therapy. Although there is an obvious treatment choice for each group (Table 4)—excision only for patients with scores of 3 or 4, excision plus radiation therapy for patients with scores of 5, 6, or 7, and mastectomy for patients with scores of 8 or 9—the VNPI is offered only as a guideline, a starting
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place for discussions with patients. The case histories below illustrate how the VNPI was used to aid
the treatment selection process.

Conclusions

Based on the research to date, including our studies, the following general conclusions can be made
about DCIS and the role of the VNPI in helping the physician and patient navigate the complex
treatment decision-making process:

1. **DCIS is relatively common and its frequency is increasing.** Most of this increase is due to better
mammographic detection and greater familiarity with minimal lesions among pathologists.
2. **Not all microscopic DCIS will progress to clinical cancer, but if a patient has DCIS and is not
   treated, she is far more likely to develop an ipsilateral invasive breast cancer than is a woman
   without DCIS.**
3. **The separation of DCIS into two groups by architecture (comedo vs noncomedo) is an
   oversimplification and does not reflect the biologic heterogeneity of the disease.** This conventional
classification may mask the biologic potential of the lesion, which may be better recognized by using
a classification based on nuclear grade and comedo-type necrosis.
4. **High-grade DCIS is more aggressive and malignant in its histologic appearance and is more likely
to be associated with subsequent invasive cancer than is non-high-grade DCIS.** High-grade DCIS is
more likely than non-high-grade DCIS to have a high S-phase, overexpress HER-2/neu (c-erb-B2),
and show increased thymidine labeling. Also, when treated conservatively, high-grade DCIS is more
likely to recur locally than is non-high-grade DCIS.
5. **Most cases of DCIS detected today will be nonpalpable.** Such cases will be detected by
mammography, with microcalcifications as the most common finding. It is not uncommon for DCIS to
be larger than expected by mammography, to involve more than a quadrant of the breast, and to be
unifocal (rather than multicentric) in its distribution.
6. **Preoperative evaluation should include film-screen mammography with compression
magnification.** The surgeon and radiologist should plan the excision procedure carefully. The first
attempt at excision is the best chance for achieving complete excision with a good cosmetic result.
Reexcisions are more likely to yield poor cosmetic results. In patients with suspicious mammographic
lesions, consideration should be given to stereotactic core biopsy to make a definitive diagnosis prior
to initial wide excision.
7. **The successful treatment of a patient with DCIS, whether by breast conservation or mastectomy,
   presupposes that a competent and interested pathologist will be part of the team.** It is best to plan
the resection with the pathologist, radiologist, and surgeon all having input into the discussion.
The data presented in this paper are based on complete, sequential tissue processing and
mammographic/pathologic correlation. It is important that any facility in which DCIS patients are
treated have this capability.
8. **Following the establishment of the diagnosis, the patient should be apprised of the risks and
   advantages of all alternative procedures.** If she wants to preserve her breast, the surgeon and
radiologist should plan the procedure carefully, using multiple wires to map out the extent of the
lesion. Once the multiple-wire-directed excisional biopsy has been done, two factors can be
evaluated: cosmesis and histopathology. If the cosmetic result is acceptable and the margins are
clear, breast conservation can proceed. If the patient has a VNPI score of 3 or 4, the option of no
further therapy can be considered.
If the patient's VNPI score is 5, 6, or 7, reexcision may be possible. If reexcision cannot be done or if
the postexcision score remains in the mid-range, breast irradiation should be considered. Occasional
patients with VNPI scores of 5 may be treated with excision alone, while some patients with VNPI
scores of 7 may be better served by mastectomy. Individual judgment is required for all patients
with intermediate scores.
For patients with VNPI scores of 8 or 9, a mastectomy with immediate reconstruction is usually
recommended.
9. **If the initial biopsy margins are involved, consideration can be given to a reexcision procedure, but
   it may yield a poor cosmetic result, and margins may continue to be involved.** At this point,
mastectomy (with or without immediate reconstruction) should be considered. Reconstruction can be
accomplished with a variety of techniques, including an expander, an implant, and a transrectus
abdominus myocutaneous (TRAM) flap. In general, immediate reconstruction in combination with a
skin-sparing mastectomy is preferable. It eliminates at least one future surgical procedure and
usually results in a happier patient with a better cosmetic result.
For women with larger lesions (relative to breast size) that cannot be totally excised, mastectomy remains the treatment of choice. However, the NSABP is conducting a prospective study (Protocol B-24) that is randomizing patients to one of two treatments: excision plus breast irradiation with or without tamoxifen (Nolvadex). In this study, positive margins and residual calcifications are allowed. The results of this study are eagerly awaited.

Future Prospects

Clearly, the validity of the VNPI must be independently confirmed by other groups with large series of DCIS patients and sufficient data to complete the subset analysis as outlined here. Prospective confirmation, however, would be better. In the future, other factors, such as molecular markers, may be integrated into the VNPI or other prognostic indices when they are shown to statistically influence the likelihood of local recurrence after breast-conservation therapy. Our knowledge of DCIS genetics and molecular biology is increasing at a remarkably rapid rate. Future studies may identify markers that will allow us to distinguish DCIS with an invasive potential from DCIS that is merely a microscopic finding. When it becomes possible to make such a distinction, the treatment selection process will become much simpler.

References:


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