Current Management of Patients with Ductal Carcinoma-in-Situ

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ABSTRACT

Because of the wider use of screening mammography, ductal carcinoma-in-situ, or DCIS, once rare, is now diagnosed with increasing frequency. Important questions remain unresolved regarding the natural history, classification, and management of DCIS. Many physicians have assumed that DCIS is diffuse and regularly progresses to invasive cancer; therefore, they routinely recommend mastectomy. However, as we learn more about this lesion, it is now clear that in many cases the lesion is focal in extent, "premalignant," and curable with local procedures short of mastectomy. In this review, we describe the current state of knowledge regarding the presentation, pathology, natural history, and management of DCIS. The Oncologist 1997;2:76-82

INTRODUCTION

The widespread use of screening mammography has led to a significant increase in the detection and diagnosis of a heterogeneous group of intraductal proliferative lesions collectively termed ductal carcinoma-in-situ, or DCIS [1, 2]. Upon light microscopic examination, DCIS represents a proliferation of presumably malignant cells confined to the mammary ducts and lobules without demonstrable evidence of invasion through the basement membrane into the surrounding stroma. In the past, because of the unclear natural history of DCIS and the assumption that the DCIS regularly progresses to invasive cancer, physicians routinely recommended mastectomy for this condition. The presence of the term “carcinoma” in DCIS has tended to create the impression for both patients and physicians that the potential of the lesion for invasion and metastasis is known and certain. As we learn more about this lesion and its malignant potential, many are concerned that this lesion is focal in nature, “premalignant,” and curable with local procedures. This approach is more consistent with the fact that many women with invasive cancer are cured with breast-conserving therapy. Currently, there is a great deal of interest in the use of excision with or without breast irradiation for patients with DCIS. In this review, we describe the current state of knowledge regarding the presentation, pathology, natural history, and management of DCIS.

PRESENTATION

Before the development of modern mammographic techniques and the widespread use of screening mammography, women with DCIS typically presented with a palpable “gross” mass or an abnormal discharge from the nipple. Today, the presentation of DCIS is typically an abnormal mammogram; palpable lesions now account for only a small percentage of diagnosed DCIS cases. The characteristic appearance on the mammogram is a cluster of microcalcifications. While most DCIS lesions are detected by mammography, the preoperative specificity is only 50%-60% in distinguishing benign from malignant entities [3-6]. Many clusters of microcalcifications are associated with benign breast lesions such as sclerosing adenosis, and some clusters reveal invasive cancer on biopsy. DCIS can also present as an incidental finding in breast tissue removed for an unrelated lesion, such as a fibroadenoma. Finally, DCIS can be found in association with Paget’s disease of the nipple.

PATHOLOGY

The histologic classification of DCIS has evolved over time. The traditional classification of DCIS was based on the architectural pattern of the lesion. In this system, the two main descriptive categories are the comedo subtype and the noncomedo subtypes, such as cribriform, micropapillary, papillary, and solid. Comedo lesions are characterized by...
prominent necrosis in the involved spaces and tumor cells demonstrating pleomorphic nuclei and numerous mitoses. In contrast, noncomedo subtypes characteristically have low nuclear grade without prominent necrosis.

Comedo lesions differ from noncomedo lesions in a number of important ways. Comedo lesions more often demonstrate microinvasion beyond the basement membrane [7, 8]. Comedo lesions also demonstrate a significantly higher degree of microvessel density (angiogenesis) than noncomedo lesions [9], and thymidine-labeling studies have shown a higher proliferative rate for the comedo subtype than for noncomedo lesions. In addition, the comedo lesions more often exhibit overexpression of HER2/neu, cyclin D1, and p53 oncogenes, and the absence of estrogen receptor and bcl-2 expression, than do noncomedo lesions [9-15]. Mammographically, comedo lesions often present with casting (linear) or coarse granular calcifications, and standard 2-view mammography generally accurately predicts the microscopic size of the lesion based upon the extent of the microcalcifications. In contrast, the noncomedo lesions more often demonstrate fine granular microcalcifications, and standard 2-view mammography often underestimates the size of the lesion based on the extent of microcalcifications; however, this can be improved by the use of magnification views [16].

Recently, pathologists have questioned the usefulness of classifying DCIS based on architecture and have proposed new classifications based on nuclear grade and the presence or absence of necrosis. There are a number of problems with classification based on architecture. Lesions can display a spectrum of architectural patterns with or without the presence of necrosis. Also, this system does not account for nuclear grade, which is believed to be a better prognostic factor. Three alternative classification schemes proposed by Lagios [17], Silverstein [18] and the EORTC [19] are displayed in Table 1. At this time, it is uncertain which of these classifications is the most useful clinically. Ultimately, a comprehensive system that includes both molecular markers of biologic behavior and histologic features will likely provide the most meaningful basis for diagnosis and treatment.

Predictive factors for response to hormone therapy in invasive breast cancer such as estrogen and progesterone receptor protein status have not been proven of benefit for DCIS and, therefore, pathologists do not routinely perform these assays. However, this is currently an area of active clinical investigation.

In the majority of cases, the diagnosis of DCIS can be readily established. Problems can arise, however, in differentiating DCIS from lesions on both ends of the spectrum. On the benign end, it can sometimes be difficult to distinguish DCIS from atypical ductal hyperplasia and on the opposite end, it can be difficult to distinguish some cases of DCIS from DCIS with foci of stromal invasion. In addition, DCIS can resemble lobular carcinoma in situ (LCIS) [20]. For problematic cases, it may be of value to refer slides to a dedicated breast pathologist.

Careful pathologic and mammographic examination is important in determining the distribution of DCIS in the breast and in making the important distinction between multicentric and multifocal lesions. Multicentric lesions are those in which there are foci of DCIS clearly distinct from the index focus. Multifocality refers to foci of DCIS present in close proximity to the index lesion. The difference between these two descriptors has a great impact upon the treatment of the individual patient. True multicentricity has now been shown to be uncommon. Holland and colleagues conducted a detailed examination of pathologic specimens coupled with mammographic correlation in order to demonstrate that additional foci previously considered to constitute multicentric disease were almost always present in relation to the index focus [16]. Therefore, previously suspected multicentricity proved actually to be multifocality. Breast conservation therapy is more feasible in cases of multifocal than in multicentric disease.

DCIS does not metastasize to the adjacent lymph nodes. However, approximately one percent of patients diagnosed with DCIS will display axillary lymph node involvement [21]. The presence of involvement in the lymph nodes indicates that there is undetected invasive disease within the breast. Lagios and colleagues found that the extent of the lesion is related to the likelihood that a pathologist will find either stromal invasion or axillary lymph node involvement. When DCIS lesions were less than 25 mm, no cases of invasion were uncovered. However, in 48% of the lesions larger than 55 mm, stromal invasion was seen. Only two patients in this group demonstrated axillary lymph node involvement; both women had areas of invasive disease [22].

### Table 1. DCIS classification: examples of newly proposed classification systems

<table>
<thead>
<tr>
<th>Lagios et al. [17]</th>
<th>Silverstein et al. [18]</th>
<th>EORTC [19]</th>
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<tbody>
<tr>
<td>Low grade</td>
<td>Non-high grade without necrosis</td>
<td>Well differentiated</td>
</tr>
<tr>
<td>Intermediate grade</td>
<td>Non-high grade with necrosis</td>
<td>Intermediately differentiated</td>
</tr>
<tr>
<td>High grade</td>
<td>High grade</td>
<td>Poorly differentiated</td>
</tr>
</tbody>
</table>

**Natural History of DCIS and Its Malignant Potential**

A critical question regarding DCIS is its risk of progression to invasive cancer. Because surgeons have traditionally performed mastectomy for these lesions, little information exists on the malignant potential of DCIS.
Ideally, a prospective trial could definitively answer the question of what happens to DCIS left untreated. However, this trial would be ethically impossible to conduct with the information that we have from two retrospective reviews of low-grade DCIS in breast biopsies initially diagnosed as “benign.” These retrospective studies provide long-term follow-up of a small number of patients who did not receive definitive treatment for their DCIS [23-25]. Page and colleagues identified 28 patients with noncomedo DCIS previously considered to be benign and treated with biopsy alone. They observed progression to invasive disease in nine women, or 32%. The interval to progression ranged from 3 to 31 years. The mean follow-up interval among women who did not develop breast cancer was 24 years [23, 24]. Rosen and colleagues identified 15 patients with low-grade, noncomedo DCIS previously considered to be benign, and eight (53%) progressed to invasive disease. The average interval after biopsy was 9.7 years. In the latter study, however, fifteen additional patients, a number equal to those studied, were lost to follow-up [25]. In both studies, most of the invasive cancers occurred at or near the original biopsy site. These studies demonstrate that low-grade DCIS is associated with a persistent risk of invasive cancer through 15-25 years of follow-up if not adequately treated, but that many do not progress [24].

Another study affords additional information. Alpers and colleagues studied 44 women choosing to undergo bilateral mastectomy for invasive cancer of one breast. Pathologic examination of the contralateral breast tissue revealed that 48% also contained microscopic evidence of DCIS [26]. This percentage greatly exceeds the expected rate of development of contralateral invasive breast cancer, which is approximately 10%-15% over 20 years. Therefore, it seems clear that some, but not all, examples of DCIS will progress to invasive breast cancer.

**MANAGEMENT**

Local treatment for DCIS has ranged from excision alone to excision plus radiation therapy to mastectomy. Comparison of the published retrospective series has proven difficult, as patient populations and surgical, radiation, pathologic, and mammographic evaluation techniques have varied across the published series. Mastectomy, the most radical treatment for DCIS, affords women close to a 100% cure rate whether the DCIS is detected grossly or mammographically [27-29]. Many factors have led physicians and patients to consider breast-conservation therapy in lieu of the more radical treatment. First, screening mammography commonly detects small, low-grade lesions for which mastectomy appears to be overly aggressive treatment [30]. Second, as physicians now routinely offer the option of breast conservation to women with invasive breast cancers, it seems paradoxical to offer mastectomy routinely for a “precancerous” lesion. And last, as discussed above, recent studies have shown that DCIS is uncommonly a multicentric process [31] that would require mastectomy.

On the opposite end of the treatment options for DCIS, many investigators have performed retrospective studies of excision alone (Table 2) [17, 32-35]. Non-randomized studies of relatively selected patients have demonstrated an 8%-18% recurrence rate with excision alone. The percentage of invasive recurrences ranged from 20% to 46% [17, 32-35].

The non-randomized studies using excision alone have shown that patients with comedo subtype DCIS consistently demonstrate a greater risk of local recurrence than patients with noncomedo DCIS [17, 34]. There are two series which included detailed mammographic and pathologic evaluation; both demonstrate a very low rate of recurrence for noncomedo lesions. In the Lagios series at 106 months follow-up, the recurrence rate was 33% among patients with the comedo subtype of DCIS compared with 2% for women with the low-grade, noncomedo subtype [17]. In the Schwartz series, at 47 months follow-up, the rate of recurrence was 38% in the patients with a comedo subtype and 3% for the noncomedo subtype [34]. However, since the time to local recurrence for low-grade DCIS can be prolonged, these women must be followed for an extended period of time before they can be considered cured.

In an effort to reduce the rate of local recurrence, yet still conserve the breast, many investigators have examined excision followed by radiation therapy as local treatment (Table 3) [35-43]. The recurrence rates after excision and radiation therapy in these retrospective series appear to be lower than those observed with wide excision alone. However, the percentage

<table>
<thead>
<tr>
<th>Investigator</th>
<th># Patients</th>
<th>Mean follow-up (mos.)</th>
<th>% Recurrence (#)</th>
<th>% Invasive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnesson</td>
<td>38</td>
<td>60</td>
<td>13 (5)</td>
<td>40</td>
</tr>
<tr>
<td>Carpenter</td>
<td>28</td>
<td>38</td>
<td>18 (5)</td>
<td>20</td>
</tr>
<tr>
<td>Lagios</td>
<td>79</td>
<td>124</td>
<td>16 (13)</td>
<td>46</td>
</tr>
<tr>
<td>Schwartz</td>
<td>72</td>
<td>49</td>
<td>15 (11)</td>
<td>27</td>
</tr>
<tr>
<td>Silverstein</td>
<td>26</td>
<td>56</td>
<td>8 (2)</td>
<td>50</td>
</tr>
</tbody>
</table>
of recurrences containing invasive disease appears to be approximately the same.

While radiation therapy has been demonstrated to be effective in treating invasive cancers, its role in treating DCIS is less well-established. There are a number of considerations regarding the potential use of radiation therapy after excision. Some cases of DCIS are of dubious clinical significance, and radiation therapy is unlikely to be of any benefit. Also, some cases are extensive, and conventional doses of radiation therapy will be insufficient to control the DCIS. Thus, radiation therapy is unlikely to be useful in some cases. A critical element in the appropriate use of wide excision alone is an established method of insuring that a lesion has been adequately excised. Patients with DCIS and negative margins on an initial excision commonly have residual DCIS on further breast resection [44]. At present, there is no definition of “negative margins” that assures complete removal of a lesion. In addition, when radiation therapy is employed following conservative surgery for invasive cancer, it is presumably used to eradicate residual multifocal invasive cancer and DCIS. Thus, the use of radiation therapy following conservative surgery for invasive cancer is not dissimilar from the approach of using radiation therapy with pure DCIS following conservative surgery. These considerations are useful to pose hypotheses which can only be resolved by large randomized clinical trials.

At present, there is only one randomized controlled trial with published results comparing treatment consisting of excision and radiation therapy to excision alone. The National Surgical Adjuvant Breast Project (NSABP) B-17 trial demonstrated that radiation therapy reduced the five-year rate of local recurrences in women with DCIS [45]. The study randomized a total of 790 women to two treatment arms: 391 women underwent excision alone (or “lumpectomy”) and 399 women underwent excision followed by breast irradiation (50 Gy). At 43 months follow-up, the ipsilateral breast recurrence rate was 7% in the lumpectomy-plus-radiation therapy group compared with 16% in the lumpectomy-alone group. The event-free survival rate was significantly better in patients receiving radiation therapy (84% versus 74%; p = 0.001). This difference is mainly attributed to the 59% reduction in ipsilateral breast recurrences in the group receiving radiation therapy (Table 4).

In contrast to the findings in the retrospective series, the addition of radiation therapy, in particular, significantly reduced the rate of invasive recurrences. The five-year cumulative incidence rate of invasive recurrence decreased from 10.5% to 2.9% with the addition of radiation therapy. The five-year cumulative incidence rate of recurrent DCIS decreased from 10.4% to 7.5% with the addition of radiation therapy. Upon analysis of the pathologic variables predictive for local failure, Fisher and colleagues found that moderate to marked comedo necrosis and uncertain or inevaluable surgical margins were predictors of a higher risk of local recurrence [46]. Longer follow-up in the B-17 study and the published results of other trials are necessary to establish more fully the rates of local recurrence of low- and high-grade DCIS, both with and without radiation therapy. It is theoretically possible that radiation therapy only delays the time to recurrence. Nevertheless, the current results of the NSABP B-17 trial suggest that radiation therapy is useful in all cases of DCIS [46].

**TREATMENT RECOMMENDATIONS FOR THE INDIVIDUAL PATIENT**

At this time, most women have a choice of treatment for DCIS. For those desiring near certainty of cure, mastectomy...
is appropriate. An alternative to the routine use of mastectomy is detailed mammographic and pathologic assessment and a wide resection of the lesion with or without radiation therapy. The indications for each are outlined below. Certain procedures are important in all cases of DCIS evaluated for breast-conserving treatment. Magnification views aid in identifying the full extent of the lesion and should be routinely used. One important goal of surgery is to remove all suspicious microcalcifications. Specimen mammograms and post-biopsy mammograms are extremely helpful in confirming their removal. The pathologic specimen must also be evaluated methodically. This should include orienting, inking, and measuring the specimen before sectioning. Accurate measurement of the DCIS lesion often proves difficult with mammograms alone, therefore the pathologist can aid in this detail by reporting the number of blocks in which DCIS is present and the maximal extent on a given slide. In addition, the pathologist should describe the relationship between the DCIS and the microcalcifications. Of critical importance is a description of whether DCIS involves the inked margin of resection. In the event of margin involvement, the pathologist can play a key role in identifying the location of involvement. Given the current information, we believe that patients should only be offered breast-conserving treatment if negative margins of resection are achieved. Thus, mammographers, pathologists, surgeons, and radiation oncologists must work together to assess the extent of the lesion and the adequacy of the excision.

It is possible to estimate for the patient the risks of pursuing breast-conserving treatment including radiation therapy, following detailed mammographic and pathologic assessment. In the absence of definitive information from randomized trials comparing mastectomy with breast conservation therapy, a reasonable estimate of local recurrence rates for breast conservation therapy is approximately 10% at 10 years. (It may be feasible to achieve even lower rates.) Half of these recurrences will be in the form of invasive cancer, that is, about a 5% risk at 10 years. If one estimates that there is approximately a 30%-40% risk of dying from an invasive breast cancer, this translates into about a 2% risk of breast cancer death for women who elect breast conservation therapy for DCIS. This is not dissimilar from the 1% risk for women treated with mastectomy for DCIS. It should be noted, however, that not all DCIS recurrences are within 10 years of treatment. Therefore, it will be necessary to reevaluate these risks once longer follow-up becomes available. However, these rough calculations demonstrate that it is not unreasonable to elect breast-conserving therapy in limited cases of DCIS.

It is not certain that all patients require radiation therapy following conservative surgery. Given the results of the studies by Lagios [17] and Schwartz [34], we believe it is reasonable to use excision alone in patients with small low-grade DCIS having clearly negative margins. If there is considerable residual DCIS on reexcision or positive margins, mastectomy is recommended. Intermediate lesions can be treated with excision followed by radiation therapy.

A new system called the Van Nuys Prognostic Index (VNPI) [47] has been proposed to aid in the treatment decision process for DCIS. Using the VNPI, a patient’s lesion is assigned one to three points for each of the following three predictors of local recurrence: pathologic classification, size, and margin width (Table 5). The pathologic classification consisted of (1) non-high grade without necrosis, (2) non-high grade with necrosis and (3) high grade with or without necrosis. Size is classified as (1) less than or equal to 15 mm, (2) 16 to 44 mm, or (3) greater than or equal to 45 mm. Margins are scored as (1) greater than or equal to 10 mm, (2) 1 to 9 mm or (3) less than 1 mm. The total of the 3 scores for each of the predictors yields a VNPI score ranging from 3 to 9. The authors claim that the total score can be translated into a treatment recommendation. Using data retrospectively compiled from two institutions of patients treated between 1972 and 1995, Silverstein and colleagues analyzed 333 patients treated for DCIS with mastectomy, conservative surgery alone, or conservative surgery plus radiation therapy and assigned them VNPI scores. Median follow-up was 79 months. Based upon outcome from this study, the following treatment recommendations are given: lesions with VNPI 3 and 4 can be treated with excision alone; those with VNPI 5, 6, and 7 are well managed with excision plus radiation therapy; and lesions with VNPI 8 and 9 should be treated with mastectomy.

There are a number of caveats that limit the use of the VNPI at this time. The VNPI groupings are based upon data-derived subset analysis, and such results are not always generalizable outside of the initial data set. The VNPI needs external

<table>
<thead>
<tr>
<th>Pathologic classification:</th>
<th>Score:</th>
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<tbody>
<tr>
<td>Non-high grade without necrosis</td>
<td>1</td>
</tr>
<tr>
<td>Non-high grade with necrosis</td>
<td>2</td>
</tr>
<tr>
<td>High grade with or without necrosis</td>
<td>3</td>
</tr>
<tr>
<td>Size:</td>
<td></td>
</tr>
<tr>
<td>≤ 15 mm</td>
<td>1</td>
</tr>
<tr>
<td>16 to 44 mm</td>
<td>2</td>
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<tr>
<td>≥ 45 mm</td>
<td>3</td>
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<tr>
<td>Margins:</td>
<td></td>
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<tr>
<td>≥ 10 mm</td>
<td>1</td>
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<tr>
<td>1 to 9 mm</td>
<td>2</td>
</tr>
<tr>
<td>&lt; 1 mm</td>
<td>3</td>
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</table>
validation and longer follow-up of some groups. In addition, the VNPI is based upon retrospective comparisons of groups treated with different diagnostic, pathologic, and therapeutic techniques. Another concern is that the VNPI calls for a specific type of pathologic processing involving sectioning of the entire specimen with microscopic evaluation of each section. Using this processing, one can best assess the size of the lesion and margin status. However, this processing is costly and not commonly employed. Using more standard methods of processing, it is not possible to assess size with certainty. A final concern is the use of an index which implies equivalence of the three factors in the equation and which may obscure important interactions between the factors.

Finally, not all patients will be appropriate candidates for breast conservation therapy. Physicians must consider the extent and histopathology of the lesion, the patient’s medical history, and the desired cosmetic outcome. Most importantly, physicians need to listen to the concerns and wishes of the patient in discussing treatment options. For patients treated with mastectomy, breast reconstruction (either immediate or delayed) is an important option to discuss. Axillary lymph node dissection is not a standard of care for patients treated with mastectomy, breast reconstruction (either immediate or delayed) is an important option to discuss. Axillary lymph node dissection is not a standard of care at this time; however in some cases of extensive, high-grade DCIS, the surgeon might deem it prudent. At this time, neither adjuvant chemotherapy nor tamoxifen have been proven to play a role in the treatment of DCIS.

Summary
Numerous ongoing trials are attempting to answer the unresolved questions regarding the treatment of DCIS. The NSABP B-24 trial is testing the use of tamoxifen with wide excision and radiation therapy in an effort to reduce local recurrences. It is possible that other medical treatments may be useful in this setting. Several European trials are investigating the roles of adjuvant radiation therapy and of tamoxifen in addition to wide excision. Ongoing trials are attempting to identify patients with low-grade DCIS and negative surgical margins who might be the ideal candidates for wide excision alone. Currently, the Harvard Cooperative Oncology Group has developed two protocols for treatment of either low-grade (grades 1 or 2) or high-grade (grade 3) DCIS with wide excision alone. The purpose of these protocols is to determine if patients with either low- or high-grade DCIS who meet strict surgical and mammographic criteria can be effectively treated with excision alone without an excessive risk of local recurrence. The criteria for entry include: (A) pure DCIS without evidence of microinvasion or invasive cancer; (B) mammographic size less than or equal to 2.5 cm (by best imaging study); (C) histologic margins 1 cm or greater, and (D) complete removal of calcifications demonstrated on specimen or post-excision mammograms. The endpoint of the study will be a recurrence in the breast, either preinvasive or within five years after excision. Because of the prolonged time to local recurrence after breast-conserving treatment for DCIS, a key to the upcoming trials will be long follow-up time. This is especially true in assessing the breast cancer mortality associated with each option.

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References


