APPENDIX

Updated management in the treatment of breast ductal carcinoma in situ (DCIS)

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- Earlier form of breast cancer
- Calcification
- Immunohistochemistry
- Van Nuys Prognostic Index
- Biologic markers
- Recommended treatment

Abstract

The definition of DCIS has evolved with our enhanced ability to detect earlier forms of breast cancer.

Of mammographically detected cases of DCIS, approximately 75% presents as calcifications alone, 10% as soft-tissue abnormalities, and 12% as combinations.

Weighing the prognostic factors of grade, extent and marging width has been accomplished in the Van Nuys Prognostic Index which provides summary scores varying from 3 to 9 for DCIS.

The morphologic diversity of DCIS is also reflected in the pattern of expression of a number of important biologic markers.

Recommended treatment for ductal carcinoma in situ*

*Localized carcinoma (< 4 cm)***

Wide local excision ensure that mammographic lesion has been completel excised with clear histopathologic margins.

Re-excise if margins are involved consider mastectomy if carcinoma >4 cm in size or if micropapillary

Consider postoperative radiotherapy if comedo type carcinoma

Consider tamoxifen, 20 mg a day

*Widespread carcinoma (>4 cm)***

Mastectomy (with or without breast reconstruction)

Consider tamoxifen

* Outside trials of experimental treatments.

** Extent of carcinoma can be estimated in 80% of patients by measuring extent of malignant microcalcification on mammograms.

Areas of investigation currently being studied in clinical trials

Natural course of screen detected ductal carcinoma in situ treated by wide excision.

Role of tamoxifen in reducing recurrence after complete excision of localized ductal carcinoma in situ.

Role of radiotherapy in reducing recurrence after complete excision of localized ductal carcinoma in situ.

Updated management in the treatment of breast ductal carcinoma in situ (DCIS)

Ductal carcinoma in situ (DCIS) was first defined by Broders in 1932[1] as a condition in which "malignant epithelial cells and their progeny are found in or near positions occupied by their ancestors before the ancestors underwent malignant transformation". Before the advent of screening mammography[2], this entity remained little more than an uncommon curiosity in females, and it remains an uncommon curiosity in males.

For the surgeon treating patients with breast cancer in the modern era, the role of breast-conserving therapy for invasive cancer has, until recently, represented the greatest of many controversies. With the increased recognition of ductal carcinoma in situ (DCIS) as a distinct, frequent, and significant clinicopathological entity, the focus of debate has shifted. The optimal treatment of patients with DCIS has become the subject of intense study and vigorous debate [3].

Definition

The definition of DCIS has evolved with our enhanced ability to detect earlier forms of breast cancer. Currently, DCIS is defined as a malignancy of the epithelial cells lining the lactiferous ducts, without penetration to these cells of the ductal basement membrane (by conventional light microscopy; electron micrographs will frequently reveal basement membrane invasion that does not appear to be clinically significant). There is by definition no invasion into the periductal stromal tissue. As a result, pure DCIS theoretically carries with it no risk of metastasis.

The natural history of low-grade DCIS can extend greater than 4 decades, with invasive breast carcinoma developing at the same site as the previous DCIS in the majority of patients. This natural history differs markedly from that of patients with high-grade DCIS [4].

DCIS must be clearly distinguished from lobular carcinoma in situ (LCIS), which arises from the epithelial cells lining the breast lobules. It is now generally accepted that LCIS should be viewed as a "marker" of increased risk for the subsequent development of invasive breast cancer; in itself, LCIS is now thought to require no intervention other than long-term careful follow-up. This differs from DCIS, which requires adequate local treatment [5].

Incidence

The apparent incidence of DCIS varies considerably with the population examined. Up to 15% of consecutive autopsies performed on women with no history of breast cancer reveal the presence of DCIS. This incidence is, in fact, much higher than the reported clinical incidence, suggesting that the disease may not always progress and that some women may live exist with their DCIS for many years.

DCIS in females: 9% - 25%
DCIS in males: 3% - 15%

Presentation of DCIS

Today, the asymptomatic DCIS detected by mammography is probably not the same lesion we encountered before the 1970s that presented as a mass, nipple discharge, or Paget's disease[6,7]. As such, it may not be appropriate to extrapolate our experience with symptomatic DCIS to asymptomatic DCIS. On the other hand, in terms of asymptomatic DCIS, which is the most common entity we see today, we have little long-term follow-up or experience. Therefore, we are faced with the dilemma of either treating patients using strategies based on long-term follow-up of a disease that may be unlike that which presents today or using strategies based on relatively short-term follow-up of asymptomatic DCIS.

Mammographic Findings

Of mammographically detected cases of DCIS, approximately 75% presents as calcifications alone, 10% as soft-tissue abnormalities, and 12% as combinations. Factoring in those cases that are mammographically occult lowers these cases slightly to account for the approximately 5% of cases that present clinically (either with Paget's disease, nipple discharge, or a palpable mass).

Calcifications are of varying types: linear, branching, granular, or heterogeneous. The calcifications originate from intraluminal debris (dystrophic), from necrotic tumor cells remaining in the ductal epithelium that have not yet coalesced to form casts, or from tumor cell secretions. Comedo DCIS is more likely to be associated with so-called casting calcifications (i.e., linear with or without branching). In a series of 66 consecutive of DCIS with this pattern of calcifications analyzed by Stomper and Connolly[8], 78% were comedo. Noncomedo types, particularly cribriform, have a high likelihood of granularity (94% in the series of Stomper and Connolly). However, in the noncomedo types, as with the comedo subtypes, there is considerable overlap[8]. Soft-tissue abnormalities range from well-circumscribed masses to architectural distortion to developing densities. These mammographic findings pathologically are the result of either the tumor itself or periductal fibrosis elicited by the tumor [9-16].

Ultrasound findings

Recently advances in US equipment and refinement of breast imaging techniques have improved the detection and characterization of small breast lesions. Nagashima[17] detected breast lesions by associated with microcalcifications in 54 of 73 patients (74%) and the pathological examination revealed breast cancer in all of the corresponding specimens.

Table 1: Classification of ductal carcinoma in situ

Histology	Cytology	Necrosis	Clacification
Comedo	High grade	Extensive	Branched
Intermediate	Intermediate	Limited	Limited
Non-comedo*	Low grade	Absent	Microfoci, inconsistent

* Cribriform, solid, or micropapillary

There are several published classifications of DCIS which utilize nuclear grade and necrosis as the major distinguishing features of specific subtypes. The separations achieved by these classifications are different, and in part may impact on interpretation of outcome results (Table 1). DCIS characterized by grade III nuclear morphology and necrosis is uniformly classified as high grade.

Tot [18] postulate that ductal carcinoma in situ and consequently breast carcinoma in general, is a lobar disease, as the simultaneously or asynchronously appearing often multiple, in situ tumor foci are localized within a single lobe.

Ductal carcinoma in situ is considered to be a preinvasive malignant lesion. Premalignant lesions are atypical ductal hyperplasia, atypical lobular hyperplasia, and lobular carcinoma in situ [19].

Immunohistochemical analysis of ductal carcinoma in situ (DCIS) and invasive ductal carcinoma (UDS) showed that the loss of Claudin-7 (CLDN-7) expression correlated with histological grade in both DCIS ($p<0.001$; $n = 38$) and/IDS ($p = 0/014$, $n = 31$), occurring predominately in high-grade (Nuclear and Elston grade 4) lesions [20].

Van Nuys Prognostic Index (VNPI) [21]

Weighing the prognostic factors of grade, extent and marging width has been accomplished in the Van Nuys Prognostic Index which provides summary scores varying from 3 to 9 for DCIS. In this system tumor grading is weighed: 1 for low grade (group I) lesions defined as NG I and II without necrosis; 2 for intermediate grade (group II) lesions defined as NG I or II

with necrosis; and 3 for high grade (group I-II) lesions, defined as NG III. Size is weighed 1, 2, and 3 as 15 mm or less; 16-40 mm, and 41 mm or more respectively. Margin width is weighed: 1 for margins 10 mm or more, or with a negative re-excision; 2 for margins between 1 and 9 mm; and 3 for margins less than 1 mm. Adding these individual scores produces prognostic groups with summary scores of 3 and 4, 5 - 7 and 8 - 9. Local recurrence rates are lowest for VNPI scores of 3 and 4 (5%), and highest for scores 8 and 9 (60%). Radiation therapy provides no benefit for VNPI scores of 3 or 4, a 13% benefit for scores 5, 6 or 7 and a large benefit for VNPI scores 8 and 9. However, despite the large difference in local recurrence rate in the VNPI 8 and 9 group, dependent on irradiation, both irradiated and non-irradiated patients have such large recurrence rates that radiation therapy is not a practical therapeutic option. Analysis of the data based on margins, however, shows that the different grades of DCIS all resected with a 10 mm margin or greater, are not statistically significant. An adequate margin eliminates the clinical differences in outcome and the benefit of irradiation for all subgroups.

Rodrigues et al [22] stated that residual DCIS and/or IC was present in 58% of patients whose primary tumors were DCIS only or invasive carcinoma <6 mm (Tia), whereas invasive carcinomas > or = 6 mm had RD in only 28%. Twenty-three patients (64%) with extensive DCIS had RD, <0.001). Ductal carcinoma in situ was within 0 RD was present in 26 (50%), whereas 18 of 56 patients (32%) with IC close to the margin had RD ($P < 0.05$). Grade of DCIS and IC was not related to presence of RD. Residual carcinoma was present in 38% of repeat-excision specimens with close but not transected margins in this study.

Biologic markers of DCIS [3, 23]

The morphologic diversity of DCIS is also reflected in the pattern of expression of a number of important biologic markers. Comedo DCIS is usually negative for estrogen receptors, which are more often expressed in DCIS with low nuclear grades. Similarly, overexpression of the c-erbB-2 oncogene is seen almost exclusively in comedo-type DCIS and correlates with the extent of disease. In fact, overexpression is more common in DCIS than in invasive carcinomas, and there is usually concordance between the invasive and intraductal components of an individual tumor.

Alterations of p53 tumor suppressor genes occur in intraductal carcinomas, and are seen mostly in the large-cell, high-nuclear-grade, estrogen receptor-negative, comedo subtype. Concordant expression is often seen between the in situ and invasive components.

Aneuploidy, or abnormalities of the DNA content, is also encountered more commonly in DCIS of high and intermediate nuclear grade, and in fact, correlates with negative estrogen receptor status and c-erb-B-2 overexpression.

It has recently been shown that the density of the microvasculature is a measure of angiogenesis activity and a useful prognostic indicator in breast cancer. An increase in microvessel density has been observed immediately around ducts involved with DCIS. One study also observed a diffuse increase in stromal microvasculature in comedo DCIS, but not in the other subtypes. These observations have important implications regarding the role of angiogenesis in neoplastic progression of DCIS.

Because negative estrogen receptor status, aneuploidy, alterations of c-erb-B-2 oncogene and p53 tumor suppressor gene, and increased angiogenesis activity are adverse prognostic parameters for invasive breast carcinoma, their predilection for comedo-type DCIS is in keeping with the propensity of this subtype to recur and its potential as an obligate preinvasive lesion.

Table 2: Features of ductal and lobular carcinoma in situ

	Ductal carcinoma	Lobular carcinoma
Average age	Late 50's	Late 40's

Menopausal status	70% postmenopausal	70% premenopausal
Clinical signs	Breast mass, Paget's disease, nipple discharge	Non
Mammographic signs	Microcalcification	Non
Risk of subsequent carcinoma	30%-50% at 10-18 years	25%-30% at 15-20 years
Site of subsequent carcinoma:		
Same breast	99%	50%-60%
Other breast	1%	40%-50%

MacDonald et al [24] emphasize that margin width has been shown previously to be the most import predictor of local treatment failures after breast conservation for ductal carcinoma in situ. They found that local recurrence for patients with margins less than 10 mm was 5.39 times as much as that for patients with margins of 10 mm or more (95% confidence interval, 2.68 – 10.64).

Treatment

Over the years, the treatment of DCIS followed the treatments for invasive breast cancer until the era of breast conservation. When lumpectomy with radiation therapy became a standard therapy for invasive breast cancer, there was disagreement in the medical community regarding how to best proceed with treatment of DCIS. The opinions ranged from the idea that all DCIS should be treated by mastectomy because this was a more diffuse disease of the breast, to the idea that treatment should be the same as for invasive breast cancer with lumpectomy and radiation therapy, to the idea that because this was an early cancer perhaps lumpectomy alone without radiation therapy was sufficient intervention [3].

Follow-up from single institution retrospective studies and prospective clinical trials is just now providing sufficient data to help identify the most appropriate treatment(s) for DCIS. Even though a randomized comparison between lumpectomy and mastectomy has never been undertaken because breast conservation has proven to be an effective treatment in invasive cancer, the medical community has determined that it is also an appropriate treatment in noninvasive cancer.

Sahoo et al [25] analyzed 103 patients with DCIS who were treated with breast conservation therapy. All patients were treated uniformly with external beam radiation (median dose 46 Gy) with a boost to the tumor bed (median dose 14 Gy). The median follow-up was 63 months. 5-year local control rate was 89%. The median time to local recurrence was 55 months.

This is justifiable because even among the patients who underwent mastectomy, a small number of patients develop systemic disease and die in the absence of local recurrence. It is conceivable that a certain percentage of DCIS is actually a systemic disease at inception and is probably inappropriately categorized as DCIS [26-29].

Mittendorf et al [30] demonstrated the technique of sentinel lymph node biopsy in DCIS. They concluded that the rate of axillary disease in patients with pure completely resected DCIS is low. Therefore, sentinel lymph node biopsy is not indicated in all patients with this biopsy diagnosis.

Regarding the necessity for breast radiation therapy in breast conservation, a review of all patients in the medical literature treated by breast conservation without radiation therapy and breast conservation with radiation therapy shows that overall breast conservation without radiation therapy is expected to produce an approximately 18.7% local recurrence rate, about half of which is invasive cancer. On the other hand, breast conservation with radiation therapy is expected to produce a 9.0% local recurrence rate, with approximately half recurring as invasive cancer. Death from breast cancer in DCIS patients is only sporadically reported in the literature, which may be the result of the short follow-up currently available. A conclusion that may be drawn from this retrospective review is that radiation therapy prevents local recurrence, specifically prevents invasive cancer recurrence, and causes a reduction in the rate of invasive recurrence from 18.7% to 9.0% of patients treated.

Hayman et al [31] emphasized the principal benefit associated with adding radiation therapy to breast conserving survey for DCIS seems to be its ability to reduce invasive recurrences.

Patients who have recurrent disease as DCIS after breast conservation by definition remain at a greater risk of losing the breast, rather than of dying. When considering our three objectives-preventing invasive recurrence, preserving the breast, and minimizing treatment – it appears that breast radiation therapy is the most effective in preventing breast recurrence and ultimately preserving the breast.

Intra et al [32] concluded that a sentinel lymph node biopsy should not be considered a standard procedure in the treatment of all patients with ductal carcinoma in situ of the breast, if the lesion is completely excised by radical surgery and there are free margins of resection.

Mokbel [26] wrote that three recent randomized controlled trials (RCTS) have demonstrated that adjuvant radiotherapy (RT) after local excision (LE) of localized DCIS significantly reduces the incidence of local recurrence.

Results of wide local excision alone

Several studies have evaluated the outcomes of patients treated with wide local excision only. One of the earlier of these studies compared drew similar conclusions, and axillary dissection in this group of patients is no longer recommended.

Indvall et al [33] stated the rate of ipsilateral local recurrence after DCIS and said that it varies between 5% and 30% and depends on the type of operation (mastectomy versus breast conserving operation, and whether postoperative readiotherapy has been used. Ipsilateral local recurrence can either emanate from the primary lesion or be a new primary tumor.

Tamoxifen

Tamoxifen has been demonstrated to have a major benefit in prolonging disease-free survival in patients with invasive breast cancer. A recent overview demonstrated the protective role of tamoxifen in preventing contralateral breast cancer after treatment of invasive breast cancer. Currently, there are large-scale clinical trials ongoing in the United States, the United Kingdom, and Italy to evaluate the use of tamoxifen as a chemopreventive agent. Questions concerning the possible use of tamoxifen in DCIS have naturally arisen.

Two studies are now in progress to evaluate the effectiveness of tamoxifen in patients with DCIS. The United Kingdom Coordinating Committee for Cancer Research DCIS Trial is a randomized comparison of surgery alone (local excision), surgery plus radiotherapy, surgery plus long-term tamoxifen, and surgery plus radiotherapy plus tamoxifen in patients with DCIS detected on mammography. The goals are to determine the incidence of the subsequent development of invasive breast cancer and also the incidence of subsequent DCIS in the ipsilateral and contralateral breasts. The NSABP-B24 trial is a randomized double-blind study of adjuvant tamoxifen versus placebo after lumpectomy and radiation therapy in patients with DCIS.

The aim is to study the role of tamoxifen in prevention of subsequent ipsilateral and contralateral in situ and invasive breast cancer. These studies are nearing completion. At

present, the use of tamoxifen as an adjuvant treatment for patients with DCIS should be limited to the context of a clinical trial.
The International Breast Cancer Intervention Study (IBIS-II) trial aims to evaluate the potential role of third generation aromatize inhibition in postmenopausal women with hormone-sensitive DCIS.
Future research will show relevance of gene expression profiling, proteomics, laser therapy and ductoscopy to the management of DCIS.

Recommended treatment for ductal carcinoma in situ*

*Localized carcinoma (< 4 cm)***

- Wide local excision ensure that mammographic lesion has been completely excised with clear histopathologic margins.
  Re-excise if margins are involved consider mastectomy if carcinoma >4 cm in size or if micropapillary
- Consider postoperative radiotherapy if comedo type carcinoma
- Consider tamoxifen, 20 mg a day

*Widespread carcinoma (>4 cm)***

- Mastectomy (with or without breast reconstruction) [34]
- Consider tamoxifen

* Outside trials of experimental treatments.
** Extent of carcinoma can be estimated in 80% of patients by measuring extent of malignant microcalcification on mammograms.

Areas of investigation currently being studied in clinical trials

- Natural course of screen detected ductal carcinoma in situ treated by wide excision.
- Role of tamoxifen in reducing recurrence after complete excision of localized ductal carcinoma in situ.
- Role of radiotherapy in reducing recurrence after complete excision of localized ductal carcinoma in situ.

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