Ductal carcinoma in situ

Ductal carcinoma in situ *is a pre-invasive malignancy.*

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Ductal carcinoma *in situ* (DCIS) is a proliferation of malignant epithelial cells confined within the ductolobular system of the breast with no light microscopic evidence of invasion through the basement membrane into the surrounding stroma.

It is a pre-invasive malignancy designated stage 0 breast cancer.

Range of DCIS

Figs 1 and 2 show the range of ductal carcinoma.

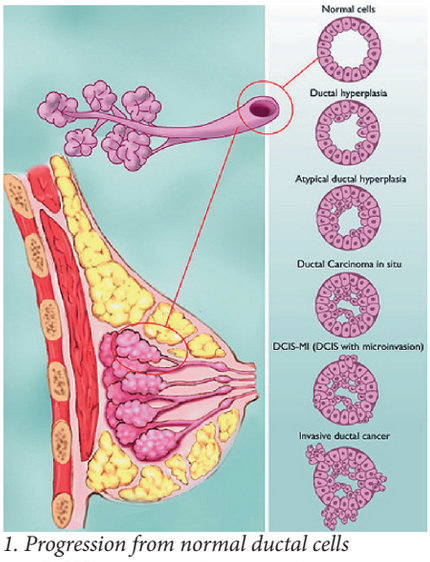

Fig. 1. Progression from normal ductal cells through DCIS to invasive ductal carcinoma.

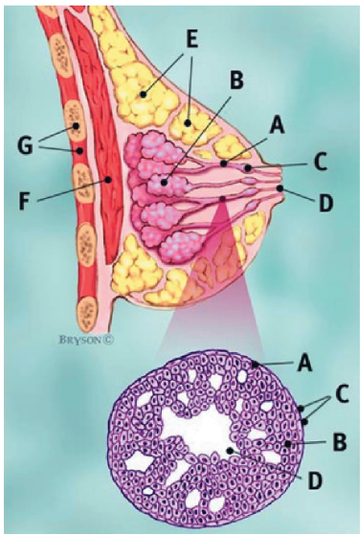

Fig. 2. Normal breast with associated DCIS. Breast profile: A – ducts; B – lobules; C – dilated section of duct to hold milk; D – nipple; E – fat; F – pectoralis major muscle; G – chest wall/rib cage. Enlargement: A – normal duct cells; B – ductal cancer cells; C – basement membrane; D – lumen (centre of duct).

Incidence of DCIS

Before the widespread use of screening mammography, only 3 - 5% of breast cancers were DCIS. Most of these cancers presented as a palpable mass, a pathological nipple discharge or Paget's disease.

Screening mammography programmes have led to a marked increase in the detection of tumours, with DCIS now accounting for 15 - 30% of all screen-detected tumours.

According to the Surveillance, Epidemiology, and End Result (SEER) programme of the National Cancer Institute the increase has been more pronounced in women aged 40 - 69 years.

What remains unknown at present is the biological significance of mammographically detected DCIS.

Presentation

The average age at presentation is late 50s, and 70% of women are postmenopausal.

Screen-detected DCIS generally has no clinical symptoms or signs. Mammographically DCIS presents as microcalcifications that may be localised or widespread, are characteristically branching, and have a variable size and density (Fig. 3). Microcalcifications are tiny specks of calcium within old cancer cells that have died off and piled up. These broken down cells, together with the calcium deposits, build up inside the ducts and manifest mammographically as a cluster of microcalcifications, a shadow or a lump. Hence, rarely, DCIS may reveal a mass on a mammogram. Symptomatic DCIS presents as a palpable breast mass (these solid-type lesions may or may not be associated with calcifications) or a pathological nipple discharge.

Paget's disease of the nipple

Paget's disease is a variant of DCIS in which the cells extend upward within the ducts to the surface epithelium of the nipple. Paget's disease appears as reddish, itching, scaling or 'eczema' of the nipple caused by cancer cells in the skin of the nipple and areola (Fig. 4).

Diagnosis

Suspicious microcalcifications can be subjected to stereotactic biopsy. In palpable lesions a percutaneous core needle biopsy can adequately be performed, preferably under ultrasound guidance for greater yield.

Nipple secretion from a pathological nipple discharge can be submitted for cytology. However, 50% of cases are associated with false negative findings and the diagnosis is then usually made after

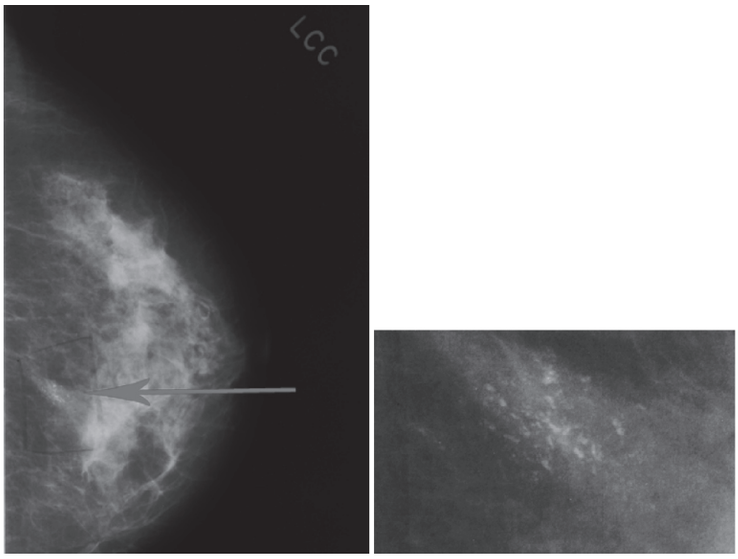

Fig. 3. Cluster of pleomorphic microcalcifications of DCIS: linear configuration on magnified view.

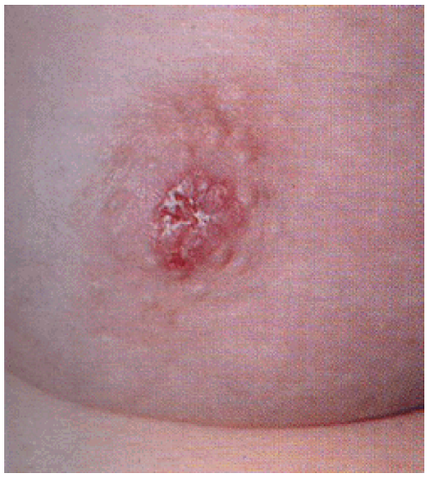

Fig. 4. Paget's disease of the nipple.

terminal duct excision. Paget's disease of the nipple can be diagnosed via cytology (nipple scrapings) or histology (wedge biopsy of the nipple).

Pathology of DCIS

DCIS is a heterogeneous group of lesions: in the past the classification was based on the architectural or growth patterns (comedo, solid, cribriform, micropapillary); nowadays it is based on factors that have proved especially useful in predicting the risk for local recurrence. These include nuclear grade and comedo-type necrosis.

Grade

This describes how much the cancer cells resemble their normal cell counterparts. The Bloom Richardson scale is widely used to determine the grade.

There are three grades of DCIS:

- low grade/grade I: the cells are slow-growing and still have many of the features of normal cells

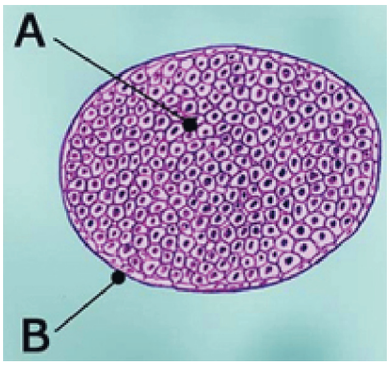

Fig. 5. Solid DCIS. A – cancer cells; B – basement membrane.

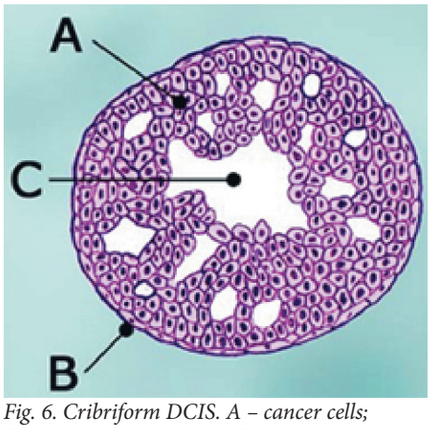

Fig. 6. Cribriform DCIS. A – cancer cells; B – basement membrane; C – lumen (centre of duct).

- moderate grade/grade II: the cells grow faster than normal cells and have some features of normal cells
- high grade/grade III: the cells are fast-growing and have none, or very few, features of normal cells.

Growth patterns

Two types of growth patterns are recognised based on the absence or presence of necrosis.

The 'non-comedo' DCIS (Figs 5 - 7) has the following growth patterns:

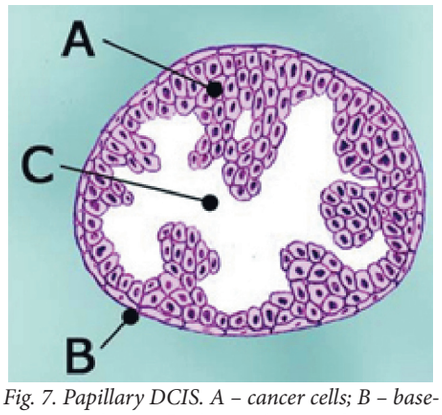

Fig. 7. Papillary DCIS. A – cancer cells; B – basement membrane; C – lumen (centre of duct).

- Solid: cancer cells completely fill the affected breast duct.
- Cribriform: there are gaps between cancer cells in the affected ducts.
- Papillary: cancer cells are arranged in a fern-like pattern within the ducts. If the cells are very small it is referred to as micropapillary. This form of DCIS is rare, but may be more extensive within the breast. It also tends to be a more aggressive subset.

Although these types of DCIS tend to grow slowly, they are nevertheless associated with an increased risk of developing invasive cancer after 5 years compared with women without DCIS. However, compared with women with high-grade DCIS, the interval to a recurrence or a new primary is longer.

The low-grade, non-comedo DCIS are more likely to be endocrine responsive (51% ER+), and less likely to over-express the Her2-neu oncogene (10%).

Comedo DCIS is associated with areas of necrosis (debris) within the cancer cells. This high-grade DCIS is a more aggressive form of the disease. It tends to grow rapidly, thus outstripping its blood supply, resulting in ischaemia and cancer cell death (Fig. 8).

These women have a higher risk of invasive cancer either at time of diagnosis of the DCIS or in the future. The risk of local recurrence (within 5 years) is also increased.

Furthermore, only 28% of high-grade comedo DCIS are oestrogen receptor-positive, and 80% over-express the Her2-neu oncogene.

Natural course

If untreated the most innocuous forms of DCIS may never cause a clinical problem.

Several studies have assessed the risk of subsequent invasive carcinoma in patients in whom the diagnosis of DCIS was missed, or in those who were left untreated after diagnosis. These studies related to low-grade DCIS. Only about 40% of untreated low-

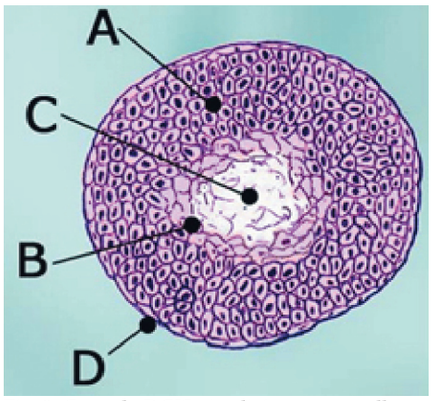

Fig. 8. Comedo DCIS. A – living cancer cells; B – dying cancer cells; C – cell debris (necrosis); D – basement membrane.

grade lesions become invasive over a time span of approximately 25 - 30 years.

On the other hand, the more aggressive forms of DCIS (higher grade; comedo-necrosis) are more likely to develop into invasive carcinomas if left untreated, and in shorter periods of time.

DCIS with microinvasion

The subtype, DCIS with microinvasion (DCIS-MI), refers to a small number of tumour cells that have invaded the ductal basement membrane. This is defined as DCIS with an area of focal invasion of 1 mm or less in diameter.

Microinvasion is more common with the comedo subtype of DCIS (53% microinvasion), multicentric DCIS and DCIS presenting with a palpable mass or large size on imaging.

Surgical management of the breast in DCIS-MI

With respect to management there is no survival benefit from mastectomy versus lumpectomy and radiation. However, where unfavourable pathological characteristics are present mastectomy is preferable. Recurrence after mastectomy with negative nodes is reported to be <1%. In the event of local recurrence alone after breast-conserving surgery (BCS) a salvage mastectomy can be performed.

Surgical evaluation of the axilla in DCIS-MI

Once the basement membrane has been violated by tumour the possibility of node metastases exist. In 'pure' DCIS the incidence of lymph node metastases is 1 - 2%. In DCIS-MI the incidence of axillary involvement ranges from 3% to 20%. Consequently surgical assessment of the axilla is recommended both for accurate staging and to determine the need for adjuvant therapy. The prognosis of DCIS-MI is intermediate between DCIS without invasion and node-negative invasive ductal carcinoma, with 5-year survival rates ranging from 97% to 100%.

Aims of treatment of DCIS

DCIS is not life threatening. Although confined to the ducts, it increases the risk of developing an invasive cancer in the future. The risk is mostly related to the grade of the DCIS.

The main goals of treating DCIS are to prevent a local recurrence, either non-invasive or invasive in the future. The incidence of a local recurrence is between 30% and 50% at 10 - 18 years. In most reported series, approximately 50% of local recurrences are invasive. In 99% of cases the invasive cancers develop in the same breast and at the original biopsy site. These local failures are usually in those patients where excision of the DCIS has been incomplete.

At the Van Nuys Breast Center in California, the chance of an invasive recurrence at 8 years is 7% and the probability of a death from breast cancer 1.4%. The incidence of subsequent invasive cancer in the contralateral breast is approximately 1%.

Surgery in DCIS

The aim of surgery is complete excision with clear margins. The definition of a clear margin is controversial, but most researchers accept a clear margin as there being no tumour at the inked margin. In practice, surgeons aim for a circumferential margin of at least 1 cm around the lesion. In most cases this can be achieved by BCS, by means of a wide local excision (WLE). Occasionally a total mastectomy is required to completely excise the tumour. Table I summarises the indications for each modality.

Role of sentinel node biopsy in DCIS

DCIS is non-invasive, therefore it follows that no axillary surgery is required. In 'pure' DCIS the incidence of lymph node metastases is 1 - 2%. The rate of axillary failure following appropriate management of DCIS is extremely low (0.1%) and does not justify the routine use of sentinel node biopsy (SNB).

SNB should be used selectively in patients with DCIS who are at a significant risk for coexistent invasive carcinoma. These include:

- patients with more extensive disease requiring mastectomy, thus increasing the risk of microinvasion
- extensive high-grade disease
- the presence of comedo necrosis
- clinically evident DCIS
- suspicion of invasive foci (DCIS-MI), as the incidence of axillary metastases ranges from 3% to 20% in these patients.

The use of immunohistochemical staining (IHC) is not recommended for evaluation of the sentinel node in DCIS. The prognostic significance of these micro-metastases seen only on IHC staining is uncertain.

Van Nuys Prognostic Index: aim and classification

Following BCS the disease is classified according to the Van Nuys Prognostic Index (VNPI), a numerical algorithm created by Silverstein in 1996 and updated in 2003. The VNPI measures prognostic factors obtained from the tumour. This stratifies the patient into one of three risk groups, assisting planning with respect to further surgery or adjuvant therapy.

The index attempts to establish:

- which women require lumpectomy alone, because of low risk of recurrence after surgery alone, and
- which women require the addition of radiotherapy after surgery, because of an intermediate to high risk of recurrence after surgery alone.

The index does not prove or disprove that a recurrence will occur. It rates four different aspects of DCIS, attributes a score to each

Table I. Indications for surgery

Breast-conserving surgery

- Localised DCIS (<4 cm extent of malignant microcalcifications on MMG)

Mastectomy (with or without immediate breast reconstruction)

- Widespread DCIS (≥4 cm extent of malignant microcalcifications on MMG, or micropapillary)
- Persistently involved margins after two attempts at re-excision
- Patient preference
- Multicentric disease

Contraindications to BCS

- Previous radiotherapy
- Connective tissue disorder
- Pregnancy
- Non-compliant patient

factor, and then places the final score into a risk category, which is the total VNPI score. The lowest possible score is 4 and the highest is 12.

The aspects of DCIS rated by the VNPI are:

- size of cancer in millimetres
- margin width
- cancer grade
- age.

The scores range from 1 (low) to 3 (high), and the categories from low risk to high risk (Table II).

Adjuvant radiotherapy

To further reduce the risk of an invasive recurrence, adjuvant radiotherapy is recommended in cases of BCT. Three large randomised trials involving more than 3 500 patients have studied the benefits of radiotherapy in women undergoing BCS for DCIS. All found a significant reduction in ipsilateral recurrence following radiation therapy. However, none of the trials showed a survival benefit.

In the NSABP B-17 trial the 12-year cumulative local recurrence rate was 15.7%. This 50% decrease of an in-breast recurrence was observed for both non-invasive and invasive local recurrences.

The EORTC 10853 trial reported a 10-year local recurrence-free incidence of 85% versus 74% in the BCS group alone. The 47% reduction was observed for both recurrent DCIS (14 - 7%) and invasive cancers (13 - 8%).

The United Kingdom, Australia, New Zealand (UK/ANZ) trial showed a significantly lower risk of ipsilateral non-invasive and invasive recurrences compared with the NSABP and EORTC trials. After a median follow-up of 53 months, the incidence was 6% with radiotherapy compared with 14% with BCS alone.

Considerable interest exists in identifying patients with DCIS who may not require radiotherapy, because of its inconvenience, expense and impact upon further therapy should a recurrence occur. To address this issue, Silverstein and colleagues[1] conducted a non-randomised study comparing DCIS treated with and without radiotherapy. They identified a subset of patients who will not benefit from adjuvant radiotherapy in reducing local recurrences at 10 years. These are patients with low-grade, <1 cm DCIS excised with a margin width greater than 1 cm.

However, to date no subgroup of patients has been reproducibly identified that does not benefit from radiotherapy.

Adjuvant endocrine therapy

The role of endocrine therapy in the management of DCIS continues to evolve. The addition of hormonal therapy in endocrine-responsive DCIS has two potential benefits. In the first place, it may be therapeutic in the prevention of local recurrence, both non-invasive and invasive. Secondly, it may prevent the development of new primary breast cancers.

The two trials that have studied the use of tamoxifen in women with DCIS have reported conflicting results.

The NSABP B-24 trial, which randomised patients with localised DCIS following BCT and radiotherapy into a placebo or tamoxifen arm, revealed a statistically significant reduction in all breast cancer events in the tamoxifen arm (8.2% v. 13.4%) after a median follow-up of 74 months.

In contrast, the UK/ANZ trial found there was no benefit from tamoxifen in preventing invasive ipsilateral or contralateral events after BCS.

Tamoxifen has been shown to reduce the incidence of DCIS in high-risk women by 50%. The benefit from tamoxifen is restricted to women with ER-positive DCIS. The dose is 20 mg/day for 5 years. Tamoxifen is contraindicated in women with an increased risk of endometrial cancer or thromboembolic events.

Raloxifene does not decrease the incidence of DCIS.

Surveillance

A new primary can occur after 25 years or longer – usually in the same area of the breast where the DCIS was excised. The new primary may be either non-invasive or invasive. Therefore patients treated with BCS should be placed under close surveillance. It is recommended that a clinical breast examination be performed every 6 months and bilateral mammography annually.

Table II. The Van Nuys Prognostic Index

	Score		
	1	**2**	**3**
Factor			
Size (mm)	≤15	16 - 40	≥41
Margin width (mm)	≥10	1 - 9	<1
Grade	I+II / no necrosis	I+II / with necrosis	III / +/- necrosis
Age	>60	40 - 60	<40
Score	4 - 6	7 - 9	10 - 12
Category	**Low risk**	**Intermediate risk**	**Highest risk**
	WLE with clear margins; low recurrence; adjuvant RT no benefit with respect to local recurrence at 10 years	WLE. Addition of RT significant decrease in local recurrence rates	Unacceptably high local recurrence rate despite the addition of adjuvant radiation; recurrence rate 50% at 5 years. Treatment: total mastectomy and immediate reconstruction

WLE: wide local excision.

Reference

1. Silverstein J. Ductal carcinoma *in situ* of the breast. *BMJ* 1998; 317 (7160): 734-739.

Recommended reading

Adamovich L, Simmons RM. Ductal carcinoma *in situ* with microinvasion. *Am J Surg* 2003; 186: 112-116.
O'Sullivan MJ, Morrow M. Ductal carcinoma *in situ* – current management. *Surg Clin N Am* 2007; 87: 333-351.
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In a nutshell

- The incidence of DCIS has increased appreciably as mammography has improved, screening programmes have increasingly been adopted, and pathologists are becoming more familiar with minimal lesions.
- DCIS is a heterogeneous group of lesions and consequently therapy needs to be individualised. The Van Nuys Prognostic Index may be helpful in planning treatment.
- There are still many unanswered questions and evolving issues, which are the focus of international debate.