Ductal carcinoma in situ

Management update

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This ninth article in our series on breast disease will focus on ductal carcinoma in situ of the breast – a proliferation of potentially malignant cells within the lumen of the ductal system. An overview of the management of ductal carcinoma in situ including pathology, clinical presentation and relevant investigations is presented, and the roles and dilemmas of surgery, radiotherapy and endocrine therapy are discussed.

The incidence of ductal carcinoma in situ (DCIS) of the breast has risen over the past 15 years. This is in part due to the introduction of screening mammography. The diagnosis and management of DCIS still pose many dilemmas (*Table 1*).

What is DCIS?

Ductal carcinoma in situ is a noninvasive abnormal proliferation of milk duct epithelial cells without light microscopic invasion of the periductal stroma. While the cells appear malignant they are still within the confines of the ductal system and therefore defined as in situ. Although in situ carcinoma has the potential of evolving into an invasive tumour (*Figure 1*) it is not clear how often, and at what rate such lesions occur.[1–4] Ductal carcinoma in situ is defined as stage 0 breast cancer and is designated TisN0M0 in the tumour, nodes, and metastasis (TNM) cancer staging classification.

The hallmark of DCIS is the proliferation of what appears to be a single cell population that may present as a single grade or a combination of high, intermediate or low grades. There are various histological patterns of DCIS and more than one of these may be present in a single case. The most common are the comedo, solid, papillary, cribriform and micro-papillary types. The biological potential for a subsequent invasive carcinoma may differ among the types of DCIS. Cells of the comedo type are cytologically more malignant, more likely to be high grade than other types of DCIS and have a higher proliferative rate.[5] The typical histological features of low grade and high grade DCIS are shown in *Figure 2, 3*.

Although in the majority of cases the diagnosis of DCIS is straightforward, DCIS may be difficult to differentiate histologically from (benign) atypical ductal hyperplasia (ADH) at one end of the spectrum, and invasive carcinoma at the other. Early stromal invasion, for example, may be missed because of sampling error or distortion of the surrounding tissue due to fibrosis and inflammation. Myoepithelial stains are used to help identify a breach in the duct lining. However, if there is any doubt, a second pathological opinion may be worthwhile. The information that is expected from a pathology report on DCIS is listed in *Table 2*.

Natural history of DCIS

Ductal carcinoma in situ is considered a precursor of invasive breast cancer. There is a 30–50% risk of untreated DCIS progressing to invasive carcinoma in the ipsilateral breast 10–20 years after initial diagnosis.[6] The cumulative risk of contralateral breast cancer is low (less than 1% per annum).[7]

When there is occult invasion or lymph vessel or node involvement, the tumour is considered to be an invasive carcinoma. Occult invasion may be present in up to 20% of cases; up to 50% when the tumour is 50 mm or more.[8]

Ductal carcinoma in situ may recur after treatment. Factors increasing the risk of local recurrence after breast conservation include:

Table 1. Dilemmas in ductal carcinoma in situ

Diagnosis – is it DCIS?
Imaging – is there correlation between imaging and the pathology?
Surgery – what to decide: mastectomy or breast conservation?
Radiotherapy – when should radiotherapy be used?
Axillary surgery – is surgery to the axilla ever necessary?
Tamoxifen – should tamoxifen be used?
Recurrence – what is the optimal treatment of a recurrence?

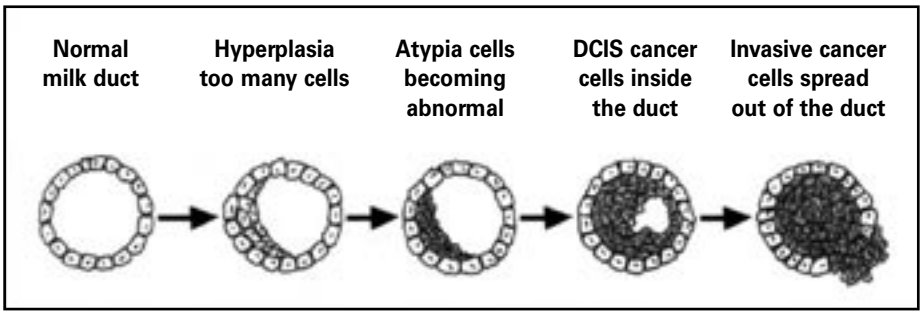

Figure 1. Progression from normal duct to DCIS (malignant cells contained within the duct) to invasive carcinoma (malignant cells invading though the wall of the duct into the parenchyma beyond)

- young age at diagnosis
- increasing tumour size
- positive margins
- high grade tumours, and
- the omission of radiotherapy.

Previous reviews from the NSW Breast Cancer Institute have examined these factors in more detail.[7,9,10] After treatment for DCIS, half the recurrences following surgery with or without radiation are invasive carcinoma, while half are DCIS.[10,11]

Clinical presentation and investigations

Before commencement of screening mammography in Australia, DCIS made up 2% of all newly diagnosed breast cancers.[12] It usually presented with a palpable mass or was associated with another abnormality such as nipple discharge or Paget disease of the nipple, with or without a mass. It now represents around 18% of all newly diagnosed breast cancers detected by BreastScreen, Australia's national screening program.[13]

Most patients with DCIS are now detected by screening mammography. It is less common for DCIS to present with a palpable mass (detected by the patient or by her doctor at clinical examination), nipple discharge or Paget disease of the nipple.[14] Uncommonly, DCIS may be an incidental finding following benign or prophylactic breast surgery.

Ductal carcinoma in situ is usually detected as an area of microcalcification on mammography. However, microcalcification is an extremely common finding in the breast and usually has a benign cause. Magnification views are usually required to fully characterise the features. Microcalcification related to DCIS is typically clustered, with a granular, heterogeneous appearance. It is classically in a 'ductal' distribution, often tracking toward the nipple. The individual pieces of calcification may be rod-shaped, or branching, taking the shape of the duct (*Figure 4a, b*). Microcalcification related to benign processes, on the other hand, tend to be scattered rather than clustered, and the individual 'specks' are more likely to be uniform in size and shape. Often microcalcification has many benign features combined with more concerning features, making its appearance 'indeterminate.' A decision must be made as to whether a biopsy should be performed or if follow up at a short interval is required. Comparison with previous mammograms is critical in such cases; often the only hint that microcalcification is related to DCIS is that the cluster is new or increasing.

Microcalcification in DCIS may be associated with a mass or architectural distortion, and the presence of these increases the level of suspicion. Age and breast density affect the diagnostic yield, with microcalcification and other features of DCIS generally being more difficult to diagnose in young women and those with dense breast tissue.[15]

Breast ultrasound may not show the microcalcification and may therefore not contribute significant additional information. However, ultrasound may be helpful if the calcifications are associated with a mass. Ultrasound showing typical malignant features such as irregular margins, heterogeneity, and posterior shadowing raises the possibility of an area of invasion.

Fine needle aspiration biopsy (FNAB) is a cytological test that has the ability to detect malignant cells, but is unable to differentiate with certainty between DCIS and invasive breast cancer. Core biopsy provides histopathology, the architecture of which may confirm a diagnosis of DCIS or invasive disease. This may allow a surgeon to perform definitive one-step surgery, including axillary surgery based on the presence of invasion. Note that the presence of DCIS alone in core samples does not rule out the possibility of invasive disease elsewhere in the breast.

The surgeon's dilemma is to determine where the tumour is located and how extensive the lesion is. While DCIS is usually detected as an area of microcalcification, it is known that not all DCIS will calcify. The size of a cluster of microcalcification on mammography may therefore underestimate the true extent of the lesion. High grade DCIS is more likely to calcify and there is better correlation between imaging and pathology size in such lesions.

There is a high correlation between the mammographic pattern of calcification and

the grade of DCIS.[16] Specifically, there is a high correlation between radiological and pathological extent for high grade lesions (84% of cases with less than 20 mm disparity), but a lesser correlation for low grade lesions. Later it was reported that the use of magnification views improved the correlation in low grade lesions.[17]

Management approach

Each patient newly diagnosed with DCIS is an individual with her own unique thoughts, experiences and needs. Treatment decisions may be influenced by social circumstances and the patient should be invited to take an active role in decision making, often along with partner or support persons.

Ductal carcinoma in situ is recognised as a condition requiring a coordinated approach by a team of health professionals. The multidisciplinary team usually includes a surgeon, radiologist, radiation oncologist, medical oncologist, pathologist, breast physician, breast care nurse, and allied health therapists. Other professionals may be required depending on the needs of the patient such as a counsellor, psychologist, a plastic and reconstructive surgeon, and a geneticist. The general practitioner plays a pivotal role in supporting and educating the patient.

While controversy remains, the treatment of DCIS broadly involves two key options:

- mastectomy (+/- breast reconstruction), or
- breast conservation surgery (BCS) with or without radiotherapy (RT).

Treatment and investigation of the axilla is not required, although it may be considered in some circumstances such as extensive high grade DCIS where the risk of invasion is higher. There is no conclusive evidence for the routine use of endocrine therapy and no evidence for the use of chemotherapy.

Table 2. Minimum requirements in a pathology report

Specimen
- Size of specimen
- Laterality
- Location of the specimen within the breast

DCIS
- Size of the area of DCIS
- Architecture (eg. solid, cribriform, papillary)
- Grade (low, intermediate, high)
- Presence of necrosis
- Presence of multifocal or multicentric disease
- Presence of microcalcifications in tumour
- Margins (distance of tumour from edge of specimen)

Table 3. Factors influencing the recommendation for mastectomy

Patient
- Breast size (small breast in relation to tumour size)
- Preference (mastectomy, or to avoid radiation therapy)
- Risk factors (including age and family history)
- Relative or absolute contraindications to radiation therapy (eg. connective tissue or genetic disorders)
- Pregnancy (use of radiotherapy to be avoided until after delivery)

Tumour
- Large area of DCIS
- Diffuse malignant appearing microcalcifications throughout entire breast
- Multifocal tumours or multicentric tumours (involving different quadrants)

Treatment factors
- Positive margins following wide local excision and re-excision neither possible nor suitable
- Residual calcifications on mammogram
- Recurrent tumour after previous breast conservation
- Radiation therapy inaccessible
- Previous ipsilateral breast irradiation

Mastectomy or breast conserving surgery?

Breast surgery

The traditional treatment for DCIS has been an ipsilateral total mastectomy. *Table 3* lists some of the factors that may influence the decision for mastectomy. The main argument for a mastectomy is that it is curative in nearly all patients, but may represent overtreatment for many women.[10,18–20] In a large review, 1.6% of the 1565 patients treated with mastectomy developed a local recurrence, of which 72% were invasive. Survival was excellent at 98–100%.[10] A meta-analysis elicited a similar local control rate of 1.4% for studies involving mastectomy alone.[9]

When mastectomy is required, the option of breast reconstruction should be discussed. Breast reconstruction may be performed as either an immediate or delayed procedure using an implant or autologous tissue. A discussion of these reconstructive options may be an integral part of a woman's pre-operative assessment. Mastectomy represents the most expedient treatment, and obviates the need for follow up imaging of the ipsilateral breast required after breast conserving techniques. It is often difficult for patients with DCIS (a noninvasive condition) to accept recommendation for mastectomy for a condition that is not invasive when paradoxically, BCS and RT is frequently

offered to treat invasive carcinoma.[21,22]

Breast conservation surgery is most frequently used in Australia to treat DCIS. The advantages of wide local excision of the tumour are the cosmetic and psychosocial advantages of breast preservation. Although recurrence in the breast is not common, the patient must be willing to accept regular mammographic and clinical follow up examinations, and the small risk of developing subsequent invasive disease.

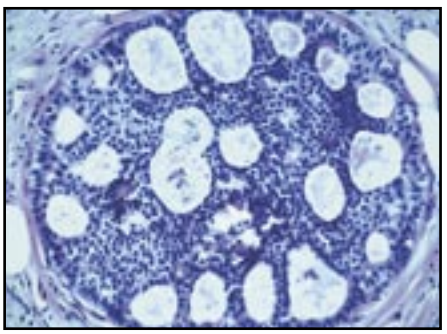

Figure 2. Typical histological features of low nuclear grade DCIS. The duct is expanded by a uniform population of cells forming a cribriform or 'sieve-like' pattern

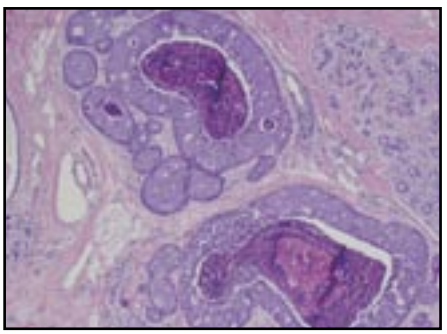

Figure 3. Typical histological features of high nuclear grade DCIS. The ducts contain an increased number of large cells that remain confined within the duct. The centres of involved ducts contain necrotic cellular debris

Local recurrence rates following conservative surgery alone without RT is in the order of 22.5%. In one study, approximately one-half of the recurrences were invasive cancer and one-half were DCIS.[10] The short term survival rates were 98–100%, but as there is a greater risk of local recurrence with time, the longer term survival rates are likely to be lower. Patients undergoing breast conserving surgery alone need to be informed that their risk of a subsequent invasive cancer may be as high as 10%.[10]

Is radiotherapy essential?

Local recurrence rates are reduced by at least 50% when RT is added to BCS.[10] This was demonstrated in three large randomised controlled trials (RCT) published in the late 1990s and early 2000s comparing BCS with or without RT,[11,23,24] and was confirmed in a meta-analysis.[10] The meta-analysis[10] demonstrated a statistically significant reduction in local recurrences from 22.5% with studies employing BCS only, to 8.9% for BCS and RT. The most apparent differences were for those patients with high grade tumours, DCIS with necrosis, tumours of the 'comedo' subtype, or DCIS with close or positive surgical margins.

The NSABP B-17 trial[11] reported a reduction in the frequency of ipsilateral breast tumours from 31% at 8 years to 13% with the addition of postoperative irradiation (p=0.0001). Mortality was 1.6% for the entire cohort. Despite only a 4 year follow up, the other two RCTs[23,24] also showed a statistically significant reduction in local recurrence. These and other studies reiterate that close to 50% of the local recurrences were invasive carcinoma and the other 50% were carcinoma in situ.

The dilemma for the radiation oncologist is the uncertainty about who may safely be treated with surgery alone, avoiding RT. There may be some patients with very small or low grade tumours for whom RT will not sufficiently alter their prognosis.

Is axillary surgery necessary?

Axillary dissection is not routinely recommended in the treatment of DCIS in view of the low incidence (0–2%) of lymph node metastases.[25–27] These metastases are presumably associated with undetected areas of micro-invasion. There are some situations, however, where an axillary

Table 4. Summary of DCIS outcomes and local recurrence treatment options

Initial surgery	Local recurrence – all	Local recurrence – invasive	Probability of breast conservation*	Breast cancer survival*	Treatment options for local recurrence**
Breast conserving surgery	22.5%	11%	80–90%	90–95%	• Total mastectomy • Re-excision + RT
Breast conserving surgery and radiotherapy	8.9%	4%	90–95%	96–98%	• Total mastectomy
Mastectomy	1.4%	0.7%	0%	98–99.5%	• Excision of chest wall mass may be possible • RT to chest wall (+/- supraclavicular fossa)

* Estimated 10 year results

** If invasive breast cancer is identified, axillary surgery is performed. Systemic therapy consisting of chemotherapy and endocrine therapy will be considered on its merits

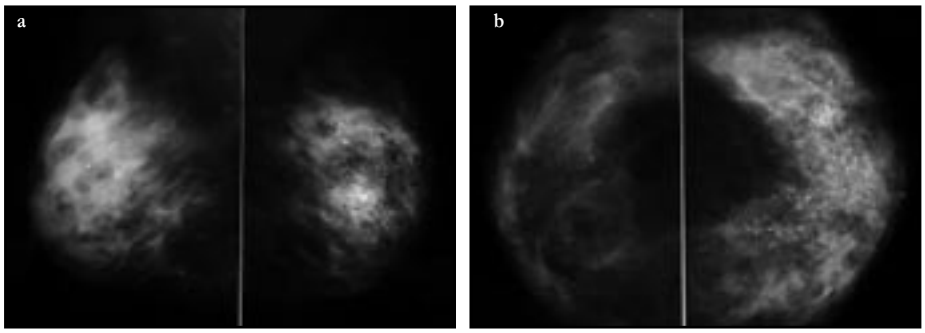

Figure 4. Mammogram illustrating the irregular, branching/casting microcalcifications in the left breast, these are typical of high grade DCIS a) Mediolateral oblique mammographic views b) Craniocaudal mammographic views

staging procedure may be recommended. These include patients with large areas of high grade DCIS (>5 cm) in whom the incidence of lymph node metastases has been reported to be as high 7%.[28] Sentinel lymph node biopsy may be appropriate for patients with extensive high grade DCIS.[29] Patients found to have a positive sentinel node are considered to have an invasive component and are best treated with a conventional axillary dissection.

Should adjuvant hormonal treatment be used?

The evidence for the use of endocrine therapy in the treatment of DCIS is unclear. The results of the two large RCTs[11,24] comparing BCS and RT with or without tamoxifen are conflicting. Tamoxifen therapy is not routinely recommended, but it may be considered for selected patients.

The NSABP B-24 trial[11] had a median follow up of 74 months and demonstrated a 5.2% absolute reduction in breast cancer events with daily tamoxifen versus placebo (8.2 vs. 13.4%, p=0.0009), and a reduction of ipsilateral invasive cancer of 2.1%. The UKCCCR[24] trial randomised 1701 patients to RT and tamoxifen after BCS. With a median follow up of 52.6 months, the ipsilateral invasive recurrence was not reduced by tamoxifen. There was no evidence of interaction between RT and tamoxifen.

What is the optimal treatment for a local recurrence?

Although local recurrences are uncommon after initial treatment for DCIS, they can be psychologically devastating for the patient, particularly if it is an invasive recurrence. The treatment of a recurrence depends on the initial treatment of DCIS, whether the recurrence is DCIS or invasive, and whether the patient has received radiotherapy to the breast. After diagnosis is confirmed histologically, a screen for distant metastatic disease is usually performed.

For a patient treated by BCS alone, management options may include re-excision followed by RT or mastectomy with or without breast reconstruction. If BCS and RT were used initially, then mastectomy is usually the only option available. If mastectomy alone was the original treatment modality, then surgical removal of a chest wall recurrence may be possible, followed by chest wall RT, but this situation is extremely rare. Treatment of the axilla and consideration of systemic therapy is also required. *Table 4* summarises DCIS treatment outcomes and management options for local recurrence.

Most recurrences can be salvaged by mastectomy. One study showed that following mastectomy, subsequent freedom from chest wall recurrence was high (92% at 5 years), and death occurred in only four of the original cohort of 272 patients (1.5%).[30]

Conclusion

Patients diagnosed with DCIS usually have an excellent outcome, with low local recurrence rates and a survival of at least 98%. Despite the increasing incidence of DCIS leading to a vastly improved knowledge of this condition, the management of this disease remains challenging, is at times controversial, and frequently presents dilemmas for the multidisciplinary team.

Regardless of the surgical and RT decisions, a patient with DCIS will require regular follow up with clinical examinations and annual mammography.

The GP plays a crucial role in supporting and educating patients with DCIS. The GP also helps the patient to participate in the multidisciplinary team, and remains the key doctor for the patient. The diagnosis of DCIS may be distressing for the patient, particularly if it is a screen detected lesion in a well woman without breast symptoms. The GP can reassure the patient that it is not invasive disease but a form of 'pre-cancer', that long term survival is high, and that in most patients DCIS does not recur. Patients should be given all options objectively. Some women prefer the added 'security' of having a mastectomy but for many women this represents overtreatment. Conservative surgery is an acceptable form of treatment that is associated with low rates of recurrence, low rates of salvage mastectomy, and low rates of invasive recurrence, and is the preferred treatment for many women.

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