Ductal carcinoma in situ of the breast

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Ductal carcinoma in situ (DCIS) is a preinvasive (also termed non-invasive) breast cancer, where proliferations of malignant ductal epithelial cells remain confined within intact breast ducts (fig 1). DCIS is a precursor lesion that has the potential to transform into an invasive cancer over a timescale that may be a few years or decades long. The development of its ability to invade and metastasise is as yet unquantifiable and is attributed to the accumulation of somatic mutations in premalignant cells. Treatment aims to prevent DCIS from progressing to invasive breast cancer.

DCIS was rarely diagnosed before the introduction of national screening programmes but is now common, accounting for 20% of screen detected cancers in the United Kingdom.1 Treatment usually comprises surgery (mastectomy or wide local excision), with or without adjuvant radiotherapy. However, it is possible that a subset of these lesions would never progress to invasive breast cancer over the lifetime of the patient if left untreated, and in this (as yet undefined) population traditional management may represent overtreatment. Deciding on appropriate personalised treatment for individual patients diagnosed with DCIS is an ongoing challenge, because the optimum management remains controversial. We review relevant randomised controlled trials, meta-analyses, preclinical, and clinical studies to provide the reader with an overview of the evidence base underpinning current management of patients with DCIS and to highlight controversies and unanswered research questions.

How does DCIS develop?
The natural course of DCIS is poorly understood. It is categorised into low grade, intermediate grade, and high grade disease according to combinations of cell morphology, architecture, and the presence of necrosis. High grade DCIS has pleomorphic, irregularly spaced, large nuclei that vary in size and have irregular nuclear contours, coarse chromatin, prominent nucleoli, and frequent mitoses. Low grade DCIS has monomorphic, evenly spaced cells with rounded centrally placed nuclei, inconspicuous nucleoli, infrequent mitoses, and rarely necrosis of individual cells. Intermediate grade DCIS lies within these extremes—the nuclei are typically larger than in low grade DCIS and show moderate pleomorphism.2 The developmental pathway of low grade and intermediate grade DCIS is thought to differ from that of high grade disease. Low grade tumours show a loss in the 16q chromosome, whereas high grade disease more often shows 17q gain.3 Atypical ductal hyperplasia is thought to be a precursor lesion of low grade DCIS and has a similar fivefold increased risk of subsequent invasive cancer. High grade DCIS has no obvious precursor lesion. Low grade DCIS, if it progresses, tends to develop into low grade invasive cancer, whereas high grade DCIS progresses to high grade invasive disease.

Risk factors for developing DCIS include a family history of breast cancer, nulliparity, older age at birth of first child, and positivity for BRCA1 and BRCA2.4,5 Since the publication of the Women’s Health Initiative and the Million Women Study,6,7 the association between invasive breast cancer and combined oestrogen and progesterone hormone replacement therapy has been well documented. However, hormone replacement therapy did not significantly increase the risk of developing DCIS in these two studies. In the Women’s Health Initiative study there were 47 cases of DCIS in the hormone replacement therapy group versus 37 cases in the control group (hazard ratio 1.18; weighted P=0.09).8 The Million Women study did not report an association with DCIS. A large surveillance study published in 2009 found that atypical ductal hyperplasia (and by implication, low grade DCIS) has become less common since women stopped using hormone replacement therapy.8 This suggests that, although hormone replacement therapy may not increase the risk of developing DCIS, it may promote the growth of pre-existing populations of oestrogen receptor positive DCIS progenitor cells.

When considering referral to a family history clinic, a case of DCIS in the family should count towards the indicators for

**SUMMARY POINTS**

Ductal carcinoma in situ (DCIS) is a preinvasive breast cancer—malignant cells are confined within an intact ductal basement membrane

Most cases (90%) are asymptomatic and detected at screening, but it can present as Paget’s disease of the nipple, nipple discharge, or a lump

Treatment aims to prevent invasive disease

Oestrogen receptor status tends to be preserved in recurrences or disease progression; this has implications for adjuvant treatment and reducing risk of recurrence

The optimum treatment is unclear, and urgent clarification is needed

Women with DCIS should have the option of entering high quality randomised controlled trials

**Fig 1 | Difference between normal, ductal carcinoma in situ (DCIS), and invasive disease**

**SOURCES AND SELECTION CRITERIA**

We searched Medline and PubMed for meta-analyses, randomised controlled trials, and original peer reviewed articles, using ductal carcinoma in situ, DCIS, preinvasive, non-invasive, treatment, radiotherapy, endocrine therapy, and psychosocial as main search terms. Only papers written in English were selected and we obtained the full text for each. We searched the Cochrane database for relevant reviews and www.Clinicaltrials.gov for current research.
Mammographic abnormality detected at screening

Patient recalled for biopsy

Case discussed at multidisciplinary team meeting and DCIS confirmed

Treatment options discussed with patient

<4 cm unilocular

Offer wire guided wide local excision

Intraoperative specimen x-ray

All microcalcifications excised

Case discussed at multidisciplinary team meeting

Margins clear

Low or intermediate grade, oestrogen receptor positive

Consider omitting radiotherapy

<4 cm or multifocal

Offer mastectomy with or without reconstruction and discuss sentinel lymph node biopsy

Intraoperative specimen x-ray

Re-excision cavity

Margins involved or <1 mm

Discuss tamoxifen if oestrogen receptor positive

Offer entry into clinical trials

>1 cm unilocular

Focus of invasive disease found at final histology

Treat as for invasive cancer

Pure DCIS

No further treatment

Fig 2 | Typical screen detected treatment pathway for ductal carcinoma in situ (DCIS)

How might DCIS present?

More than 90% of cases of DCIS are detected at screening while asymptomatic. About 6% of all symptomatic breast cancers are preinvasive. Some patients present with Paget’s disease of the nipple (an eczematous-type nipple lesion that does not resolve with topical steroid treatment), nipple discharge (which is usually from a single duct and either blood stained or clear), or a palpable mass. DCIS that presents with clinical signs is more likely to be extensive or to have an invasive component.

Men can also develop DCIS and tend to present with symptoms of blood stained nipple discharge or a retroareolar mass. The standard treatment for men is mastectomy with excision of the nipple-areola complex. DCIS accounts for about 5% of breast cancers in men, but the proportion of men who would progress to invasive cancer if DCIS was not treated is unknown.

How is DCIS diagnosed and treated?

At screening mammography, malignant looking microcalcifications are the most common abnormality. Architectural distortion, ill defined masses, nodules, or ductal asymmetry can also indicate underlying DCIS. Figure 2 shows a flow chart of a typical screen detected treatment pathway. Women with an abnormal mammogram will be recalled for an image guided biopsy, under local anaesthetic, with either a 14 gauge core biopsy gun or vacuum assisted biopsy device. If the area of abnormality is extensive, multiple cores of different areas can be taken, to try to increase the chance of detecting a coexistent invasive tumour. Core biopsy and vacuum assisted biopsy are preferable to fine needle aspiration, which cannot discriminate between in situ and invasive cancer because it provides no information on the basement membrane. A recent meta-analysis showed that, compared with 14 gauge core biopsy, use of an 11 gauge vacuum assisted biopsy device halves the risk of missing a coexisting invasive cancer (P<0.006). Other factors associated with missing associated invasive disease include having a high grade lesion (P<0.001), an imaging size greater than 20 mm (P<0.001), a breast imaging reporting and data system (BI-RADS) score of 4 or 5 (P for trend<0.005), a mass visible at mammography (v calcification only, P<0.001), and a palpable abnormality (P<0.001).

For symptomatic cases the diagnostic pathway will depend on presentation—core biopsy for a palpable lump, punch biopsy for Paget’s disease of the nipple, and smear cytology to look for malignant cells for nipple discharge. Microdochectomy (removal of just the symptomatic breast duct(s)) or total duct excision will need to be performed if the only symptom is persistent clear or bloody discharge to exclude underlying DCIS (or invasive disease).

The breast surgeon and breast care nurse will then counsel the patient on the surgical options. One option is breast conserving surgery by means of wide local excision, usually using wire localisation (a wire inserted stereotactically, under mammographic guidance; more than one wire may be needed to bracket large areas). This allows the surgeon to excise the lesion accurately. The patient will be offered mastectomy if the area of DCIS is extensive or breast size in relation to lesion size does not allow for cosmetically or surgically acceptable wide local excision, and occasionally because of patient preference. National Institute for Health and Clinical Excellence (NICE) guidance suggests that sentinel lymph node biopsy (to stage the axilla) should be performed at the time of mastectomy for lesions greater than 4 cm because of the small incidence of occult invasive disease in extensive DCIS. Axillary surgery is not indicated alongside wide local excision.

Women with extensive DCIS, if medically fit, are excellent candidates for immediate breast reconstruction. In the UK, about 35% of women with DCIS have a mastectomy and 72% have wide local excision.

After wide local excision, the specimen is x-rayed to ensure that all suspicious microcalcifications have been removed. After mastectomy, the histopathologist may request imaging of specimen slices to aid detection of the disease and its extent.

After surgery, the case will be discussed at a multidisciplinary team meeting (comprising radiologists, pathologists, oncologists and surgeons) to ensure that margins are clear histologically and radiologically. The optimum margin width is controversial, but a circumferential margin of at least 1 mm is generally accepted. If margins are close (<1 mm) or involved after wide local...
Excision, cavity re-excision or mastectomy should be offered to achieve clear margins.

What other investigative tools are useful in diagnosis and treatment?
Ductoscopy is not used routinely in the management of DCIS and is currently mainly a research tool. However, direct visualisation of the ductal system is an appealing option for a disease that is located purely within the ducts and may be especially useful for cases of nipple discharge. Instillation of chemotherapy agents directly into the ducts is also a theoretical possibility, and this feature may be exploited in the future.

There is increasing evidence that magnetic resonance imaging may have an important role in the clinical assessment of the extent of DCIS. Several ongoing trials are looking at the use of magnetic resonance imaging in the diagnosis and treatment planning of DCIS. This technique may be able to identify occult multifocal or contralateral disease in patients with DCIS, but there is still some concern that overestimation of the extent of disease may lead to wider than necessary margins or unnecessary mastectomy, in addition to identifying high numbers of contralateral lesions that turn out to be benign.

What adjuvant treatments can be used in DCIS?
No further treatment is needed after mastectomy for pure DCIS. However, after breast conserving surgery the optimum adjuvant treatment is uncertain. Large randomised controlled trials (RCTs) have looked at the use of radiotherapy and tamoxifen as adjuvant treatments for DCIS.

Radiotherapy
Four RCTs have looked at using adjuvant radiotherapy after breast conserving surgery for DCIS—EORTC 10853, NSABP B-17, UK/ANZ DCIS, and SweDCIS, with a subsequent Cochrane review. All of the trials showed a significant reduction in DCIS and invasive recurrence after radiotherapy (all used 50 Gy, standard fractionation, and no tumour bed boost dose), and all have long term follow-up (8-10 years). Radiotherapy also significantly reduced ipsilateral recurrence from 15-20% to 5-9% at five years and from 24% to 12% at 10 years of follow-up. On pooling the trial results in the Cochrane review, ipsilateral invasive recurrence was halved at 10 years across the trials (hazard ratio 0.50, 95% confidence interval 0.32 to 0.76; P=0.0001). About 50% of the recurrences over all the trials were invasive cancer, and 50% further DCIS.

The Cochrane review looked at the subgroups of age above or below 50 years, presence or absence of comedo necrosis (areas of necrotic debris within the DCIS), and size greater than or less than 10 mm; all subgroups benefited from the addition of radiotherapy, with recurrence rates approximately halving. Older (>50 years) patients had greater benefit from radiotherapy than younger ones (0.35 (>50) v 0.67 (<50)). None of these trials was prospectively designed for these subgroup analyses, so the results should be interpreted with caution. The NSABP B-17 trial recently published long term (>10 year follow-up) results, which showed that recurrence of an invasive tumour in the ipsilateral breast was associated with a slightly increased risk of death (1.75, 1.45 to 2.96; P<0.001), whereas recurrence of DCIS was not. Twenty two of the 39 deaths were attributed to breast cancer. Such an effect was not seen in the 10 year follow-up of the UK/ANZ DCIS trial, which showed no increased risk of death after wide local excision alone.

In practice, the trial results show that nine women require treatment with radiotherapy to prevent one ipsilateral recurrence (50% of recurrences are further DCIS). Clinicians can therefore advise patients that for every 100 women who opt for radiotherapy, five to 10 fewer invasive breast cancers develop. Most of the invasive cancers that do occur are detected at surveillance mammography and will probably be small, subclinical, of early stage, and cured by further treatment (mastectomy, endocrine therapy, or chemotherapy, or a combination thereof). Having a recurrence of any type will not strike most women as a trivial risk, but they will need to be carefully counselled about their risk-benefit profile, especially because patients randomised to radiotherapy in the UZ/ANZ DCIS trial had an increase in death from cardiovascular disease (P=0.008), although numbers were small.

Tamoxifen
Two large RCTs have looked at using tamoxifen in addition to radiotherapy after breast conserving surgery. Neither trial tested oestrogen receptor (ER) status at the time of diagnosis, so trial entrants were both ER positive and negative. The NSABP B-24 trial found that the addition of tamoxifen to radiotherapy decreased subsequent invasive cancer from 7% to 4% at five years. This effect was maximal in younger women (<50) and at retrospective review was shown to be of benefit only in ER positive cases. At long term review, the addition of tamoxifen to radiotherapy reduced recurrence of an invasive tumour in the ipsilateral breast (at median follow-up of 163 months) by 32% (0.68, 0.49 to 0.95; P=0.025). The UK/ANZ DCIS trial showed that tamoxifen reduced recurrent ipsilateral DCIS (0.70, 0.51 to 0.86; P=0.003) and contralateral tumours (0.44, 0.25 to 0.77; P=0.005), but it did not show a significant effect on ipsilateral invasive disease (0.95, 0.66 to 1.38; P=0.8), at a median follow-up of 12.7 years. However, the ER status of these patients was unknown. In this trial tamoxifen was more effective in low grade and intermediate grade tumours than in high grade ones; this is probably because low grade DCIS tends to be nearly 100% ER positive, with only 60% of high grade cases expressing ER. The UK/ANZ DCIS trial authors suggested that the variation in findings between the two trials may have resulted from around 34% of women in the NSABP B-24 trial being under 50 years, whereas more than 90% of women in the UK trial were over 50. Tamoxifen had no significant effects on mortality in either trial.

The IBIS-II study and the NSABP B-35 trial are investigating the use of aromatase inhibitors as adjuvant treatment in DCIS. The MAP.3 trial, which looked at the aromatase inhibitor exemestane as preventive treatment in postmenopausal women, showed that exemestane reduced the number of further breast events in women who had undergone mastectomy for DCIS, although the numbers of events were small.
What is the potential of DCIS to become invasive, and could we be overtreating it?

Pure DCIS poses no threat to life. The goal of treating DCIS is to prevent invasive cancer. The introduction of national breast screening programmes was partly based on the premise that the detection and treatment of DCIS would, after a lag phase, result in a decrease in the incidence of invasive breast cancer. However, such a decrease has not occurred, and this has led to speculation that we may be overtreating women with low risk DCIS that may never progress to invasive disease or pose a threat to life. It has been suggested that DCIS could be reclassified as a “ductal intraepithelial neoplasia,” to distance it from invasive disease. This has not been generally adopted. An investigator initiated clinical trial studying the effect of preoperative endocrine treatment in DCIS found marked morphological changes, decreased proliferation, and changes in protein expression in DCIS after neoadjuvant endocrine treatment. The authors suggested that selected cases of DCIS could be treated by endocrine therapy alone (i.e., “watchful waiting”) with no intervention at all.

This hypothesis is backed up by the previously discussed study on atypical ductal hyperplasia, which showed that this disease (and by implication, low grade DCIS) has become less common since women stopped using hormone replacement therapy. Low grade DCIS is highly oestrogen dependent and unlikely to progress to invasive disease once the oestrogen drive is removed, either postmenopausally or by the use of aromatase inhibitors. Postmenopausal women comprise the bulk of the screening population, and the recent MAP.3 trial suggests that exemestane reduces the development of DCIS in a prevention setting. It is ER positive cases of low risk DCIS that, in theory, may not need surgical treatment. However, accurate and confident definition of these “low risk” groups, if they exist, is still elusive and the existing evidence shows that overall invasive recurrence rates are as high as 10–20% after surgery alone at 15 years.

ER negative DCIS has a higher recurrence rate and is not affected by endocrine treatment, so effective local control is essential. There tends to be receptor preservation between DCIS and its subsequent recurrence. ER negative DCIS tends to recur as ER negative DCIS or ER negative invasive disease. This has implications when considering adjuvant treatment and reducing the risk of recurrence. If ER negative DCIS recurs as invasive cancer it invariably needs chemotherapy.

Genotyping might help identify high risk and low risk patients, as it does for invasive disease. Genomic Health has recently released the Oncotype DX Breast Cancer Assay for DCIS—an assay of 21 cancer related genes—which they state can estimate the likelihood of local recurrence (DCIS or invasive carcinoma) at 10 years (www.oncotypedx.com/en-US/Breast/HealthcareProfessional/DCIS.aspx). Its clinical applicability will become apparent only with time.

Which women are at risk of recurrence after treatment for DCIS?

After a diagnosis of DCIS, NICE guidance suggests that patients should be offered annual mammography for five years (or until they reach screening age) and then return to the national screening programme.

After mastectomy the risk of recurrence is low, at about 1%, although ipsilateral recurrences are mostly invasive disease. This is probably because follow-up imaging is not routinely performed on the ipsilateral side after mastectomy, so any skin flap or chest wall disease is seen only when it becomes palpable, at which point it is likely to be invasive.

The overall risk after wide local excision alone with no attention to margin status is higher, at about 25%, and recurrences are split equally between further DCIS and invasive disease. The woman’s individual risk of recurrence—most importantly invasive recurrence and subsequent risk of death—should guide any offers of adjuvant treatments after breast conserving surgery.

Key risk factors for recurrence have been identified in the main RCTs in DCIS. The most important and modifiable risk factor is involved margins at breast conserving surgery and failure to remove all suspicious microcalcifications. Younger age at diagnosis (<40 years), high grade disease, and the presence of comedo necrosis are also important.

Fig 3 | Van Nuys prognostic index

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<thead>
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<th>Score</th>
<th>Treatment</th>
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<tr>
<td>1-3</td>
<td>Wide local excision</td>
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<tr>
<td>4-6</td>
<td>Wide local excision</td>
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<tr>
<td>7-12</td>
<td>Mastectomy</td>
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TIPS FOR NON-SPECIALISTS

- Refer patients with persistent eczematous changes of the nipple to a breast clinic for exclusion of Paget’s disease of the nipple.
- Stress to the patient that a diagnosis of pure ductal carcinoma in situ (DCIS) has no direct impact on mortality.
- Medically fit women who need a mastectomy for DCIS are often excellent candidates for immediate reconstruction, which should be offered to all appropriate patients.
- Women may be confused about their optimum treatment. Explain treatment options and up to date research findings carefully, taking time to ensure that the patient understands.
- Inclusion in ongoing clinical trials should be offered to all suitable patients.

Risk factors for recurrence of ductal carcinoma in situ

- Involved or close (<1 mm) excision margins after breast conserving surgery
- High grade or poorly differentiated disease
- Comedo necrosis
- Younger age at diagnosis (<40 years)
- Oestrogen receptor negative disease
- Symptomatic presentation

1 BMJ 2012;344:e499
2 BMJ 2012;344:e288
3 BMJ 2012;344:e542
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- Improving healthcare access for people with visual impairment and blindness (BMJ 2012;344:e542)
system that brings together some of these risk factors. It was designed to achieve a less than 20% recurrence rate at 12 years (fig 3). It has not yet been independently validated, however, and its effect on a UK screening population, where most tumours are small (<2 cm), is limited. It has not been shown to be prognostic for this screen detected population, so its use is not encouraged in these patients.

Breast cancer stem cells could contribute to recurrence of DCIS. These cells can self renew, proliferate, and avoid apoptosis. Aberrant activation of cell signalling pathways involved in stem cell self renewal (such as the Notch protein) might contribute to the recurrence of DCIS by allowing the cells to survive and proliferate. These pathways are also under investigation as potential therapeutic targets.

What is the psychosocial impact of a diagnosis of DCIS?
The perceived risk of recurrence after treatment for DCIS is often higher than the actual risk. A study of 487 women with DCIS, treated with both mastectomy and breast conserving surgery, showed that 39% of women thought they had at least a moderate (25-30%) likelihood of developing invasive cancer in the next five years and 28% thought there was a moderate likelihood of DCIS spreading to other parts of their body. A recent descriptive qualitative study highlighted that women can find it especially difficult to accept the perceived paradox between having a “precancerous” condition and the extensive surgery that is sometimes needed. Women more easily accepted the need for wide local excision than for mastectomy. In the same study, some of the women did not like the term “precancerous”—they found it unhelpful and thought that it lessened the importance of the diagnosis. Women also found the need to continually justify having their treatment to themselves and others and found it difficult to explain their diagnosis. This is an area where the support, counselling, and information provided by breast care nurses is invaluable.

The potential of audit data to inform future practice
The Sloane project is a prospective UK based audit on screen detected DCIS, lobular carcinoma in situ, atypical ductal hyperplasia, and atypical lobular hyperplasia. The main aim of the project is to record the current management of non-invasive breast disease and atypical hyperplasia in the UK by collecting information on the radiological and pathological features of cases, surgical and adjuvant treatment, and recurrences. It will hopefully help to answer questions about the diagnosis, treatment, and clinical outcomes of these diseases. It is the largest audit of its kind, and currently 10,732 cases have been submitted by participating UK breast screening units. Although the addition of new cases is anticipated to end in April 2012, the collection of data on future events for cases already in the audit will hopefully continue into the foreseeable future.

What does the future hold?
There is no agreed practice in the UK or elsewhere for the use of radiotherapy or tamoxifen after breast conserving surgery for DCIS, so there is no clear standard of care. Two very different approaches could potentially be considered—evidence suggests that all women benefit from radiotherapy after breast conserving surgery, yet some experts suggest that we should be considering (at the most extreme) “watchful waiting.” Current practice seems to be somewhere in the middle, with patients being offered...
surgery, and to a variable and unstandardised extent, radiotherapy and tamoxifen. We urgently need to be able to distinguish between “low risk” women who could be safely treated with surgical excision alone, hormonal therapy alone, or possibly “watchful waiting” and “active” patients who need all available adjuvant treatment. This can be achieved only with a randomised controlled trial of active treatment versus active monitoring, stratified according to DCIS grade. Women with DCIS should therefore have the option of entering into high quality randomised controlled trials that will help to determine optimum treatment.

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