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Treatment of ductal carcinoma in situ

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Background

The introduction of screening mammography has resulted in a marked increase in the detection rates of ductal carcinoma in situ (DCIS) from 2% of newly diagnosed breast cancers before national screening, to over 20% of all screen-detected tumours.[1] DCIS is a preinvasive breast cancer; the proliferation of malignant ductal epithelial cells remain confined by an intact basement membrane, with no invasion into the surrounding stroma.[2] Around 80% of DCIS lesions currently diagnosed are impalpable, asymptomatic and detected by screening. These screening-detected cases are frequently small (<4 cm) and localised, and breast-conserving surgery is often possible. The remaining cases present symptomatically, with a palpable breast lump, nipple discharge or Paget's disease of the nipple. If these symptoms are present, the underlying disease is often more extensive and may require mastectomy.

Risk factors, natural history, pathology and receptors

Risk factors

Risk factors for the development of DCIS include a family history of breast cancer, older age at first childbirth and nulliparity.[3] Although breast epithelial proliferation is increased by the use of the oral contraceptive pill[4] and hormone replacement therapy (HRT), particularly combined oestrogen/progestogen HRT for over 5 years.[5] There is little evidence to date that either the oral contraceptive pill or HRT increases the risk of DCIS.[4] Two studies[6,7] have reported a relative risk of 1.4 for the development of DCIS following oestrogen-only HRT preparations and a relative risk of 1.7–2.3 with oestrogen- and progestogen-containing preparations.[8] In the Women's Health Initiative study there were 47 cases of DCIS in the HRT group compared with 37 cases in the control group; HR, 1.18; weighted $P = 0.09$. Other studies have shown no increased risk following HRT use.[9,10]

Natural history

Although factors that pertain to an increased risk of developing DCIS have been identified, the natural history of this heterogeneous disease remains poorly understood. It is thought that developmental pathways for low- and intermediate-grade DCIS are distinct from the development of high-grade DCIS and can be explained partly by reference to biological markers. In the sequence of progression from normal breast to DCIS, there is a variable loss of chromosomal heterozygosity dependent on nuclear grade. Low- and intermediate-grade tumours show 16q loss, whereas there is 17q gain in high-grade lesions.[11] It is likely that low-grade lesions arise from oestrogen receptor (ER)-positive atypical ductal hyperplasia (ADH) or lobular intraepithelial neoplasia and progress to low-grade ER-positive DCIS. High-grade lesions have no obvious precursor, unless they arise from usual ductal hyperplasia or ADH that expresses 17q gain. The progression of well-differentiated/low-grade DCIS

to poorly differentiated/high-grade DCIS or high-grade invasive cancer is an uncommon event.[12]

✔✔ A review of DCIS recurrences and their primary lesions from the EORTC 10853 trial[12,13] found concordant histology (similar grade) in 62% of cases, and identical marker expression (oestrogen receptor, progesterone receptor, p53 and c-erbB-2/HER-2/neu) in 63% of both invasive and non-invasive recurrences.[12] This high percentage of tumours with identical receptor profiles indicates that it is likely that residual disease after initial treatment recurs as detectable DCIS or progresses to invasive cancer.

Retrospective studies of low-grade DCIS misdiagnosed as benign conditions found that, 20 years after local excision, approximately 33% had developed an invasive cancer.[14] As not all cases of DCIS progress to invasive disease, detection by mammographic screening may lead to overtreatment of 'non-progressive DCIS', i.e. DCIS that would not progress to invasive disease if left untreated. It was hoped that breast-screening programmes would, after a lag-phase, result in a decreased incidence of invasive breast cancer, secondary to an increase in detection and treatment of DCIS. Duffy et al. studied 5 243 658 women screened in the NHSBSP and the effect a diagnosis of DCIS had on interval cancers occurring in the 36 months after the relevant screen. The average frequency of DCIS detected at screening was 1.60 per 1000 women screened. There was a significant negative association of screen-detected DCIS cases with the rate of invasive interval cancers. For every three screen-detected cases of DCIS, there was one fewer invasive interval cancer in the next 3 years. This association remained after adjustment for numbers of small screen-detected invasive cancers and for numbers of grade 3 invasive screen-detected cancers.[15] However, there remains concern that we may be overtreating DCIS and in particular 'low-risk' DCIS and that such lesions may never pose a threat to a patient's life. Suggestions for alternative management strategies for these patients include 'watchful waiting'[16] and endocrine therapy alone (no surgery).[17] However, what constitutes 'low-risk' DCIS remains undefined. Trials are currently under way to try to help define this.

The recent MAP.3 trial showed that exemestane reduces DCIS development in a prevention setting.[18] A study looking at ADH (which may be a precursor lesion of low-grade DCIS, and has an approximate fivefold increase in risk of subsequent invasive cancer), showed that ADH (and by implication, low-grade DCIS) has become less common since women have stopped using as much hormone replacement therapy (HRT).[19] The low-grade lesions that are likely being potentially overtreated are nearly always oestrogen-dependent and removing the oestrogenic drive, either following menopause, or with the use of aromatase inhibitors, may make these low-grade cases regress and reduce the rate of progression to invasive cancer.

Stem cells

Recent evidence suggests that stem cells can reconstitute various cell types within the breast after trauma. Cancers (including DCIS) arise from accumulations of mutations and mutations in stem cells disrupt their tightly controlled self-renewal and proliferation processes. Recently DCIS tissue has been separated into single cells and a subset of these cells (which are putative stem/progenitor cells) grows, in non-adherent culture conditions, to form three-dimensional (3D) branching structures (known as mammospheres). Mammosphere growth is dependent on growth simulation via the epidermal growth factor (EGF) and Notch receptor pathways.[20] The DCIS stem cell paradigm could explain the development of both multifocal DCIS and local recurrence. Stem cells could potentially survive after wide local excision with clear margins and regrow, which would also explain the 'identical' receptor expression seen in recurrent DCIS as well as early recurrences seen most often in high-grade DCIS, as there are more stem cells found in these high-grade lesions. Potentially, therefore, targeted inhibition of stem cells could reduce the rate of DCIS recurrence.

Pathology

Classification and features

DCIS has been classified into two major subtypes according to the presence or absence of comedo necrosis. DCIS is designated as comedo if atypical cells with abundant luminal necrosis fill at least one duct. In comedo DCIS cells are large with pleomorphic nuclei and abnormal mitoses. The necrotic material often calcifies and this is what is visible on mammography.

Non-comedo DCIS encompasses all other subtypes and includes the following types:

- Solid – where tumour fills extended duct spaces.
- Micropapillary – where tufts of cells project into the duct lumen perpendicular to the basement membrane.
- Papillary – where the projecting tufts are larger than in the micropapillary type and contain a fibrovascular core.
- Cribriform – where the tumour takes on a fenestrated/sieve-like appearance.

- Clinging (flat) – where there are variable columnar cell alterations along the duct margins. (There remains controversy as to whether clinging DCIS is truly in situ cancer or whether it should be considered as atypical hyperplasia rather than DCIS.)
- Rarer subtypes also exist, including neuroendocrine, encysted papillary, apocrine and signet cell.

The UK- and EU-funded breast-screening programmes classify DCIS as of low, intermediate and high nuclear grade. This definition is based on the characteristics of the lesion as seen with a high-power microscope lens (×40) and uses a comparison of tumour cell size with normal epithelial and red blood cell size:[21]

- Low-nuclear-grade DCIS has evenly spaced cells with centrally placed small nuclei and few mitoses and nucleoli that are not easily seen.
- High-nuclear-grade DCIS has pleomorphic irregularly spaced cells with large irregular nuclei (often three times the size of erythrocytes), prominent nucleoli and frequent mitoses. It is often solid with comedo necrosis and calcification.
- Intermediate-grade DCIS has features between those seen in low- and high-grade DCIS.

If a lesion contains areas of varying grade, it is awarded the highest grade present. A universally agreed classification system is yet to be established and will need to be observer-independent and clinically relevant. The majority of DCIS lesions are high grade.

Most cases of DCIS are unicentric.[22] Following extensive pathological sectioning of DCIS mastectomy specimens, only 1% show multicentric disease.[22] A **multicentric** tumour is defined as separate foci of tumour found in more than one breast quadrant, or more than 5 cm away from the initial primary. A tumour is classified as **multifocal** if there are separate tumour foci in the same quadrant and close to the original tumour although most such lesions have similar morphology and are linked.[23] This classification lacks clinical utility and some now use the term 'multisite' to encompass both multifocal and multicentric disease. The local spread of DCIS is along the branching ducts that form the glandular breast and often extend beyond the borders of a quadrant. Most DCIS is continuous along the branching ductal network. Poorly differentiated high-grade lesions are reported to be more frequently multifocal.[24] Most DCIS recurrences are at or near the site of the initial tumour,[25] but some recurrences are remote from the initial lesion yet exhibit similar genotypical and phenotypical characteristics to the primary lesion.[12]

As well as documenting pathological type and grade on the histology report, the pathologist should detail the presence or absence of microinvasion. If microinvasion is detected histologically, a thorough examination of the entire specimen should be undertaken to exclude other previously unnoticed areas of invasive cancer. Lesions that can be mistaken for microinvasion include DCIS that involves lobules, branching ducts, distortion of ducts or acini by fibrosis, crush or cautery artefacts, and DCIS involving a benign sclerosing process (e.g. radial scar).[26–30]

Lobular intraepithelial neoplasia (LIN)

The current classification combines lobular carcinoma in situ (LCIS) and atypical lobular hyperplasia (ALH) into a single group known as lobular intraepithelial neoplasia (LIN). Rather than a premalignant lesion LIN is considered a marker of increased risk. It is often an incidental finding during breast biopsy and accounts for approximately 0.5% of symptomatic and 1% of screen-detected tumours. In situ ductal and lobular tumours show different pathological and clinical features. Compared with DCIS, patients developing LIN tend to be younger and premenopausal, and have bilateral and multicentric disease of lower grade and close to 100% oestrogen-receptor expression (Table 14.1). There is an approximate eight- to ninefold increased risk of developing invasive carcinoma after a diagnosis of LCIS compared to the general population.[31] Sometimes it is difficult to distinguish histologically between LCIS and DCIS and the pathology report should state this although DCIS expresses E-cadherin whereas LCIS does not, allowing histopathologists to use E-cadherin immunohistochemistry to differentiate DCIS from LCIS.

If LIN is diagnosed coincidentally following excision of a coexisting lesion, no further surgical treatment is necessary (even if the area of lobular neoplasia is not fully excised) and the patient should undergo regular review or be considered for a prevention strategy. The current North American NCCN guidelines and the UK guidelines are that patients with LCIS or ALH on core biopsy should have surgical excision.[32,33] This is based on studies that have shown upgrade rates to invasive cancer or to DCIS as high as 50%. The logic of excision is that there is likely to be a worse lesion in the breast. There are, however, problems with the studies investigating women with LCIS on core biopsy because they have contained small numbers of women and have reported a huge variation in upgrade rates varying from 0% to 50%. More recently there has been an attempt to correlate radiology with pathology and two groups can be identified: a concordant group

Table 14.1 • Comparative clinicopathological features of ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS)

Clinicopathological feature	DCIS	LCIS
Age at diagnosis (years)	54–58	44–47
Premenopausal	30%	70%
Absence of clinical signs	90%	99%
Mammographic findings	Microcalcifications	None
Multicentric disease	30%	90%
Bilateral disease	12–20%	90%
Histological grade	65% high grade	90% low grade
Oestrogen receptor status	65% positive	95% positive
Subsequent invasive disease	30–40%	25–30%
Ipsilateral–contralateral ratio	9:1	1:1

where the histologic findings in the core biopsy adequately explain the findings on imaging and a discordant group where the histological findings on the core biopsy do not adequately explain the findings on imaging studies. The upgrade rate of core-biopsy-diagnosed LCIS and ALH in patients with concordant imaging findings is small.[34–36] A recent prospective multi-institutional study by Nakhlis enrolled 79 patients.[37] In 74 women who had LIN as the worst lesion on core biopsy with concordant imaging, 73 had no upgrade on surgical excision with only one upgrade to DCIS.[37] From a total of 335 cases from five different publications in the literature where there was concordance between histology and imaging there have been just six upgrades (1.8%). Five of these were to DCIS (1.5%) and one was a 2-mm grade I invasive cancer. There is now growing evidence that excision biopsy can be avoided in patients diagnosed with LIN on core biopsy where there is concordance with imaging. If, however, there is atypical ductal hyperplasia (ADH) or pleomorphic LCIS is diagnosed on core biopsy then excision is still required. The upgrade rate for pleomorphic LCIS is much higher than for non-pleomorphic LCIS and varies from 17% to 46% in three small series.[34–36]

The NSABP (National Surgical Adjuvant Breast and Bowel Project) P-1 prevention trial showed that tamoxifen produced a 56% reduction in the risk of developing subsequent invasive cancer in women with LCIS.[38] Further studies are ongoing with aromatase inhibitors in postmenopausal patients with LIN. Chemotherapy and radiotherapy have no place in the treatment of LIN. A problem area is pleomorphic LCIS. The current perspective is that this should be treated like DCIS rather than lobular neoplasia but the scientific basis for this is poor and not evidence-based. Further studies and clarification of the behaviour and most appropriate treatment of pleomorphic LCIS are needed urgently.

Receptors and markers

To advance our understanding of development and behaviour of DCIS, there has been interest in cell receptor expression and signalling pathways that control growth. These studies have been mainly based on immunohistochemical assessment and show that poorly differentiated high-grade comedo DCIS has lower oestrogen receptor expression, higher rates of cell proliferation[39] (as expressed by Ki67, a nuclear antigen expressed in late G_1 S, G_2 and M phases of the cell cycle but not in the quiescent G_0),[40] high rates of apoptosis,[41] and more commonly overexpress HER2 and epidermal growth factor receptor (EGFR (HER1)).[39] Low-grade lesions in contrast have higher oestrogen receptor expression, with lower rates of cell proliferation[39] and apoptosis than high-grade lesions,[41] and they rarely overexpress HER2.[39] Progesterone receptor expression correlates with oestrogen receptor expression in both low- and high-grade tumours.[39] In comparison, normal breast epithelium has low levels of expression of oestrogen receptor and progesterone receptor,[42] and a very low rate of apoptosis and HER2 expression.

The increased rate of apoptosis seen in DCIS is lost on progression to invasive cancer, but the high proliferative rate is maintained.[43] Cyclin D1, an oncogene responsible for G_1 cell cycle proliferation/progression and induction of apoptosis, is overexpressed in approximately 90% of in situ and invasive ductal cancers.[44] It also appears to be associated with a loss of differentiation (measured by $p27^{Kip1}$).[45] In ER-positive tumours, the driving force behind this increase in cell proliferation is the nuclear action of the activated oestrogen receptor, which increases growth-promoting gene transcription. In ER-negative DCIS, the driving pathway is thought to be predominantly via EGFR/HER-2/RAS/MAP kinase activation (**Fig. 14.1**).

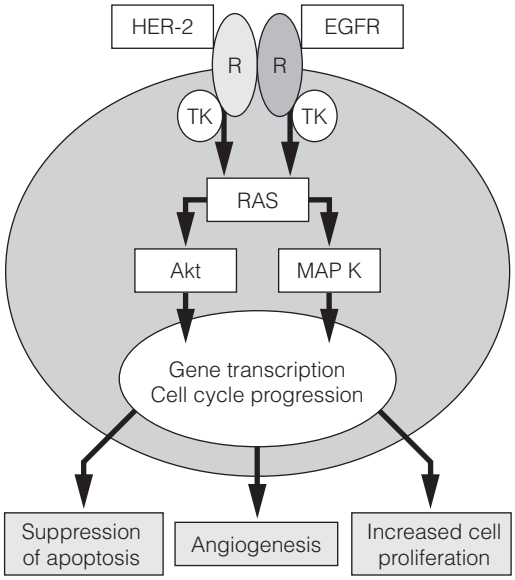

Figure 14.1 • The basic growth pathway in oestrogen receptor-negative breast tumour cells. The oestrogen receptor-positive signalling pathway is mediated via oestrogen attaching to its receptor, which then moves down its concentration gradient to the cell nucleus. The presence of oestrogen receptor in the cell nucleus subsequently increases gene transcription and expression of growth-promoting factors, leading to increased cell proliferation and tumour growth. In cells that do not express oestrogen receptors, the main signalling pathway for growth is via the epidermal growth factor (EGF)/c-erbB-2 receptor; this activates the RAS intracellular messenger, which increases cell proliferation and tumour growth via MAP kinase. RAS stimulation also leads to the suppression of the apoptosis cascade via Akt and BAD phosphorylation (an apoptotic protein). MAP K, MAP kinase; R, receptor; TK, tyrosine kinase.

This leads to a subsequent increase in transcription of both proliferative and, via Akt, anti-apoptotic genes. Activation of this pathway also induces the expression of cyclo-oxygenase-2 (COX-2), which is an inducible enzyme that converts arachidonic acid to prostaglandins. It has been found to be overexpressed in up to 80% of DCIS.[46] COX-2-positive DCIS shows increased cell proliferation, and is related to increased tumour recurrence and decreased survival in invasive cancer.[47]

In addition to alterations in cell proliferation and apoptosis, the development of neovascularisation is necessary for the growth of solid tumours. It is driven in part by angiogenic factors expressed in hypoxic areas of the tumour. Hypoxic areas of DCIS show a less well differentiated, more malignant phenotype, with increased HIF-1α (a hypoxia-induced transcription factor), decreased oestrogen receptor expression and increased expression of cytokeratin-19 (a breast stem cell marker).[28] It is felt that hypoxia-induced dedifferentiation could be a factor promoting tumour progression.[48]

Presentation, investigation and diagnosis

Presentation

Approximately 80% of DCIS is detected by mammographic screening and about 70% of mammographically detected DCIS present as microcalcifications with no associated mass lesion. Calcifications may be heterogeneous, fine, linear, branching, malignant or of indeterminate appearance. Microcalcifications with an associated mass lesion are seen in approximately 30% of DCIS diagnosed by screening.[49] Circumscribed nodules, ill-defined masses, duct asymmetry and architectural distortion are sometimes seen in association with DCIS.[50] When diagnosed clinically, DCIS is often extensive, commonly ER-negative and associated with a concurrent invasive tumour in 50% of cases.[51] It may present as a palpable mass, Paget's disease of the nipple or nipple discharge.[52]

Investigation and diagnosis

Clinical examination is important to detect possible signs of invasive disease. In addition, ultrasound can be valuable in excluding an associated mass lesion. Diagnosis is confirmed by core biopsy, as cytology gives no information on stromal invasion. Image guidance is essential to ensure accuracy of sampling. Mammographic magnification views are important to accurately delineate the extent of microcalcifications.

Stereotactic core biopsy and vacuum-assisted biopsy

In the NHS breast screening programme, the primary method of diagnosis is by stereotactic core biopsy with a 14G needle. If image-guided core biopsy is inconclusive then vacuum-assisted biopsy (VAB) using a device such as a Mammotome, which takes several contiguous biopsies of a wider calibre (11G) during a single pass, can be used. A metal clip should be inserted during the procedure to aid future localisation especially in small lesions where all microcalcification can be removed during diagnostic core biopsy. VAB is used in the UK if core biopsy is inconclusive, but in a small randomised trial both had equal diagnostic accuracy when using digital mammograms.[53] A coexisting invasive tumour is underdiagnosed in 10–20% of cases due to sampling

error.[54] Factors associated with an underestimation of the presence of associated invasive disease include high-grade lesions, imaging size >2 cm, a Breast Imaging and Reporting Data System (BI-RADS) score of 4 or 5, a visible mass at mammography (versus only calcification) and a palpable abnormality.[53] If the area of calcification is extensive (>4 cm in size), multiple areas at opposite edges should be biopsied preoperatively to confirm the extent of any DCIS and to increase the chance of detecting any associated invasive component.

Localisation-guided biopsy

If a definitive histological diagnosis cannot be made with either core biopsy or VAB, due to failure to sample the calcification adequately, or doubt exists as to whether DCIS is present histologically, then open biopsy is necessary. The excised specimen should be X-rayed intraoperatively, after careful orientation with Liga-clips or metal markers, to confirm that all microcalcification of concern has been excised. The Association of Breast Surgery guidelines[32] recommend that 90% of diagnostic biopsies for screen-detected abnormalities should weigh less than 20 g. Due to improved preoperative diagnosis, wire-guided localisation procedures are usually therapeutic rather than diagnostic. However, DCIS is often pathologically larger than mammographically estimated; this is especially true if magnification views are not used, and up to 30% of patients undergoing excision for DCIS need re-excision to clear margins adequately.[55] Accurate orientation of the specimen is essential to direct re-excision of the relevant margins and to minimise the volume of any re-excision.

Other diagnostic procedures

Ductoscopy

Ductoscopy is an appealing option for DCIS. Although there has been interest in its use in DCIS for both diagnosis and the potential for treatment with direct instillation of chemotherapy into the ducts[56] its use is not widespread and does not seem to be increasing.

Magnetic resonance imaging (MRI)

MRI can be used to image DCIS, and is currently being investigated in a number of trials. DCIS may identify occult multifocal or contralateral disease, but there are concerns about the potential of MRI to overestimate the extent of disease leading to wider than necessary excisions, unnecessary mastectomy and identifying high numbers of contralateral lesions that turn out to be benign. A meta-analysis found no convincing evidence for a role of MRI in DCIS and the current view is therefore that MRI has no routine role in assessing DCIS.[57]

Treatment: mastectomy versus breast-conserving surgery

Even though there is current debate over the potential overtreatment of some cases of DCIS, the accepted current standard management is surgical.

Mastectomy

The long-term recurrence rate following simple mastectomy for DCIS is less than 1%. Some series have reported higher rates after skin-sparing mastectomy (5%).[58] Larger studies that have included a systematic review of all data in the literature show skin-sparing and even nipple-sparing mastectomy is safe for DCIS – but it is imperative that all disease is excised (confirmed by X-ray) and that the anterior margins of the mastectomy are assessed and not involved. As current evidence points to DCIS being predominantly unicentric in origin, it is now recognised that mastectomy is overtreatment for the majority of patients.[58] In 1983 mastectomy was performed for 71% of cases of DCIS in the USA but this had dropped to 44% by 1992.[59] Mastectomy is now reserved for patients with larger areas of DCIS (arbitrarily considered as >4 cm), for multicentric disease (although again evidence suggests multisite DCIS can be treated by breast-conserving surgery – see Chapter 7) and for patients where radiotherapy is contraindicated. Women should also be offered mastectomy if the excision margins are involved following breast-conserving surgery and the patient is not deemed suitable for re-excision. Rates of re-excision versus mastectomy vary widely in different units. Women with DCIS requiring mastectomy are excellent candidates for skin-sparing mastectomy and immediate breast reconstruction.

Breast-conserving surgery

Breast-conserving surgery is the treatment of choice for localised areas of DCIS. Even large areas of DCIS can be excised but may require reshaping or an oncoplastic procedure combined with a contralateral breast reduction to achieve symmetry. Areas of DCIS usually need to be radiologically localised preoperatively, as they are predominantly impalpable. Localisation can be either wire-guided (multiple wires assist the surgeon and increase the rates of complete excision by radioactive (iodine 125) seeds) or by a ROLL technique (radioguided occult lesion localisation) using Technetium99. The use of other modalities, such as magnetic tracers, and radar-visible devices to locate the area to be removed, is also being

investigated. The lesion should be excised in one piece if possible and orientated with Liga-clips as these clips can be visualised on the specimen X-ray. Before wound closure, the specimen should undergo radiography to ensure that all suspicious microcalcifications have been removed and are clear of the radial margins. Some surgeons use a four-quadrant cavity biopsy, with or without India ink staining to assess the margins. The pathologist should assess the histological margin status and document this in the histology report. If the margins are close (<1 mm), the patient should undergo re-excision, as margin status is a key prognostic factor for local recurrence.

The recommended treatment protocol for DCIS is shown in **Fig. 14.2**.

Axillary staging

Axillary dissection is not indicated for DCIS. The incidence of macroscopic lymph node metastasis in DCIS is less than 1%, and should prompt thorough pathological examination for occult invasion. Formal axillary staging in women with DCIS should not be performed alongside breast-conserving surgery.[60] However, NICE guidelines recommend that a sentinel lymph node biopsy should be performed at the same time as mastectomy for DCIS[60] and women should be counselled as to the indications for this. The rationale for performing sentinel lymph node biopsy with mastectomy is the potential of occult invasive disease that may

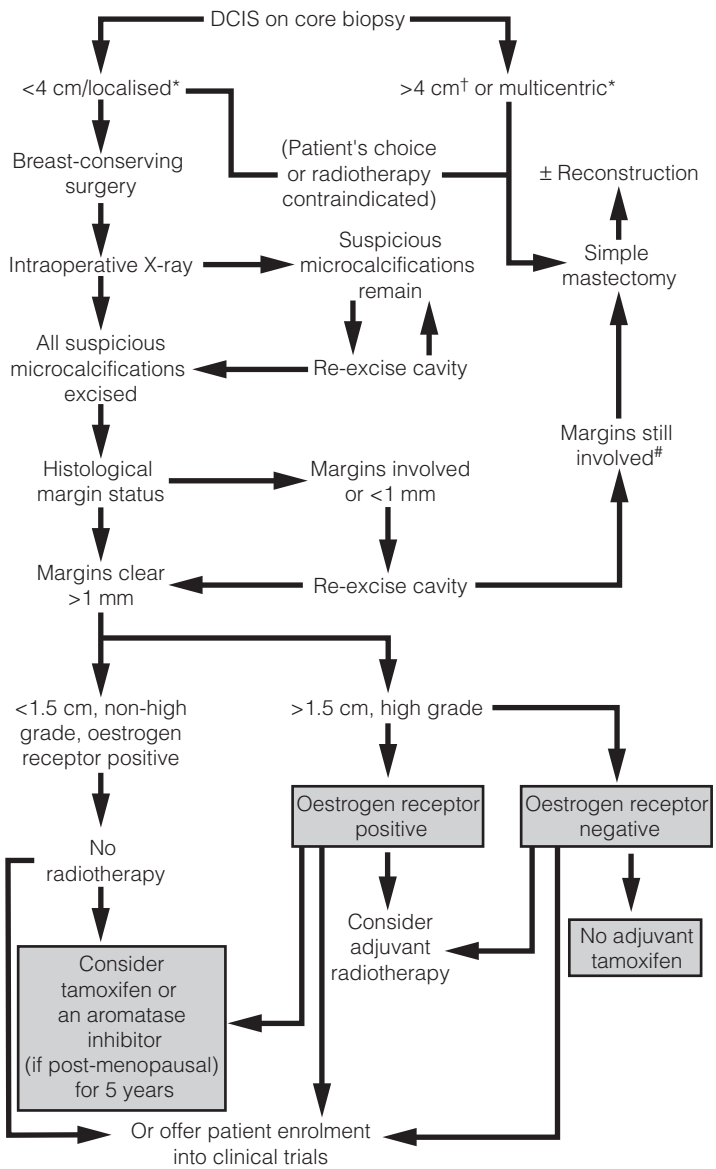

Figure 14.2 • Recommended treatment algorithm for ductal carcinoma in situ (DCIS). Shaded boxes indicate those treatments suggested by the results of trial data.[65,75] †Areas of DCIS >4 cm can be treated by breast conservation if unifocal and patient has large breast, or is suitable for an oncoplastic procedure. *Ability to achieve breast conservation with areas <4 cm and with multicentric disease will vary depending on breast size and suitability for oncoplastic procedure. #It may be possible to perform further reexcisions depending on breast size.

be identified histologically in a large area of DCIS. This would subsequently require axillary staging. A sentinel lymph node biopsy cannot easily be performed after a mastectomy. Patients found to have positive lymph nodes have occult invasive disease and should be managed accordingly. A study by Veronesi et al. of 508 patients with pure DCIS found that nine patients (1.8%) had epithelial cells found in the sentinel node (five of these nine cases were micrometastases alone). None of the cases showed further lymph node involvement at formal axillary dissection.[61] A further study, which looked retrospectively at the NSABP B-17 and B-24 data, from patients who had undergone local excision of DCIS with clear margins (no axillary surgery at initial treatment), showed that the ipsilateral nodal recurrence rate was 0.83/1000 patient-years in the B-17 trial and 0.36/1000 patient-years in the B-24 trial. Meta-analysis of the published literature showed approximately 1.8% of DCIS (almost entirely G3 or high-grade disease) had involved sentinel nodes.[62]

Recurrence: rates and predictors

No trial has specifically evaluated breast-conserving surgery versus mastectomy in DCIS. The long-term recurrence rate following simple mastectomy is known to be very low at less than 1%.[58] The majority of these recurrences are invasive disease. This reflects the fact that after mastectomy no imaging is performed routinely of the ipsilateral side and further disease is only detected when it becomes clinically apparent – at which stage it is most likely to be invasive. Recurrence rates after skin-sparing mastectomy may be higher with 3–5% rates reported especially in women under 40 years of age or with high grade DCIS.[63,64] The recurrence rate for breast-conserving surgery alone was formerly up to 25% at 8 years, with up to 50% of recurrences (i.e. 12.5% of all cases) being invasive disease.[13,52,65] The remaining 50% of recurrences are in situ tumours.[66] The rate of recurrence after breast-conserving surgery for DCIS is falling and is now less than 10% at 10 years. Reviews of clinical and pathological variables have demonstrated certain unfavourable tumour characteristics and these are outlined below.

Assessment of excision margins

A fundamental risk factor for recurrence is inadequate excision following breast-conserving surgery. This is judged as close (<1 mm) or involved margins[55] and/or failure to remove all suspicious microcalcifications.[67] Excision margin width has three times the power of tumour grade in predicting local recurrence.[68] The NSABP B-17, NSABP B-24 and EORTC clinical trials all revealed that the presence of clear margins after local excision significantly decreased tumour recurrence.[13,69–71] On multivariate analysis of the EORTC trial, non-specified, close or involved margins conferred a hazard ratio of 2.07 (95% CI 1.35–3.16, $P = 0.0008$) compared with clear margins.[71] The NSABP B-24 trial found a covariate relative risk of 1.68 (95% CI 1.20–2.34) if the margins were involved.[69] No prospective trials have looked at the optimum excision width required for in situ or invasive cancer. When considering the extent of surgical excision there has to be balance between minimising recurrence and producing an acceptable cosmetic outcome; part of the problem in defining an optimum margin is that these analyses are affected by confounding factors. The ASCO consensus statement (2016),[72] recommends a 2-mm margin, with a caveat that negative margins <2 mm are not an indication for mastectomy and clinical judgement should be used in determining need for further surgery in patients with negative margins <2 mm. This statement was based on a meta-analysis and did not look at margins between 1 and 2 mm, and classified involved margins together with 1–1.9-margins. A retrospective study by Chan et al.[55] reported that women with clear margins (judged as greater than 1 mm) had an 8.1% recurrence at a median follow-up of 47 months compared with 37.9% recurrence where excision margins were close (1 mm). There was no improvement in recurrence rates in more widely excised lesions. A more recent UK study showed no difference in local recurrence for margins of 1–2 mm compared with margins >2 mm.[73] Thus surgeons in the UK generally aim for margins of more than 1 mm. Involvement of radial or anterior margins after mastectomy requires re-excision, otherwise recurrence rates are increased.[63,64]

High-grade/comedo tumours

High grade and comedo necrosis are independent risk factors for recurrence following breast-conserving surgery for DCIS. In a review of the EORTC 10853 trial,[71] high nuclear grade was found to have a hazard ratio of 2.23 (95% CI 1.41–3.51, $P = 0.0011$) for local recurrence, with 22% of high-grade tumours and 11% of intermediate-grade tumours developing either recurrent DCIS or invasive tumour. Comedo necrosis was also shown to be important, 18% of patients with DCIS having comedo necrosis developing recurrence (hazard ratio 1.80, 95% CI 1.08–3.00, $P = 0.0183$).

Histological type and tumour architecture

The degree of tumour differentiation is predictive of both local recurrence and metastatic disease. In the EORTC trial,[13,71] poorly differentiated tumours were at significantly higher risk of developing DCIS recurrence (hazard ratio 3.58, 95% CI 1.68–7.62, $P = 0.0001$) and metastasis (hazard ratio 6.65, 95% CI 1.46–30.22, $P = 0.00083$) compared with well-differentiated tumours. In this same trial, histological type was also strongly related to DCIS recurrence, though not to invasive recurrence. Both solid/comedo DCIS (hazard ratio 4.40, 95% CI 2.28–8.48, $P = 0.0001$) and cribriform DCIS (hazard ratio 3.74, 95% CI 1.91–7.30, $P = 0.0001$) were found to be much more likely to recur than clinging or micropapillary DCIS. Within the well-differentiated group, no tumours with clinging DCIS recurred.[71] It has been suggested that this well-differentiated clinging DCIS should be reclassified separately as 'columnar alteration with prominent apical snouts and secretion',[74] with debate as to whether this subtype should be managed as atypical ductal hyperplasia or LCIS.

Age at diagnosis

A further risk factor for recurrence irrespective of tumour grade or type is young age (<40 years) at diagnosis. The EORTC 10853 trial[13,71] found that women less than 40 years at diagnosis were more likely to recur (hazard ratio 2.54, 95% CI 1.53–4.23, $P = 0.010$) than older women. The NSABP B-24 trial[69] found that the rate of ipsilateral breast tumours (in the placebo population) in women aged 49 years or less at diagnosis was 33.3 per 1000, compared with 13.0 for those aged 50 and above. In the UK/ANZ DCIS trial,[75,76] only a small proportion (9.5%) of women were less than 50 years old at diagnosis. The power of this study is thus limited, but of these younger women, 26% recurred after excision and tamoxifen compared with only 17% of women older than 50 years. Rodrigues et al.[77] studied women aged 42 years or less (mean age 38.5) or women aged 60 years or more (mean age 67.8) at diagnosis. They found that although there was no difference in tumour grade, comedo necrosis or overall histology (also found in the EORTC trial) between the groups, compared with older patients HER2 was more frequently overexpressed in the younger patient population. Approximately 65% of the younger age group were HER2-positive compared with 38% of the older age group ($P = 0.06$). No significant difference was found between oestrogen receptor, progesterone receptor, p53, Ki67, cyclin D1 or bcl-2 expression.

Tumour size and palpability

None of the major trials have found any statistical significance between recurrence and tumour size. The NSABP B-17 trial[65] found that the size of mammographically detected tumours was not significant in predicting ipsilateral recurrence. However, when researchers examined clustering of microcalcifications in women whose mammograms did not show a tumour mass, they found that clustered microcalcifications greater than 10 mm (relative risk 2.06, 95% CI 1.36–3.10) or scattered calcifications (relative risk 2.41, 95% CI 1.40–4.16) had a significantly higher ipsilateral recurrence than clustered calcifications of 10 mm or less. The problem is that there may be differences in histology between the groups, so confounding the analysis of size. The EORTC 10853 trial[71] found no difference in recurrence rates between tumours less than 10 mm in size and those 10–20 mm or greater than 20 mm in size ($P = 0.2127$). However, tumours that were clinically apparent rather than mammographically detected were more likely to recur (covariate relative risk 2.17, 95% CI 1.53–3.08).[71] The only factor of significance in a recent analysis was size, with DCIS >15 mm being more likely to recur following breast-conserving surgery than DCIS <15 mm.[73]

Predictive scoring systems for recurrence after conservation surgery

Silverstein et al.[78] developed the Van Nuys Prognostic Index, with the aim of predicting which women would be at risk of recurrence following breast-conserving surgery. This algorithm was derived from regression analysis of retrospective data pooled from patients with DCIS treated at two centres in the USA. Recurrence is clearly multifactorial but the problem with the Van Nuys index is that the data derived were not randomised and used historical controls. The predictive index included tumour size, margin width and pathological classification. The index has since been modified as the University of Southern California/Van Nuys Prognostic Index (USC/VNPI) and now includes patient age.[78] Each criterion is weighted and scored 1, 2 or 3 and the individual scores combined to give an overall score from 4 to 12. Scores of 4–6, 7–9 and 10–12 are said to be at low, moderate and high risk of 5-year recurrence, respectively. It was designed to achieve a less than 20% recurrence rate at 12 years. The data are skewed by the fact that 80% of large tumours (>4 cm) recurred, whereas in the UK many of these women would have undergone mastectomy. These

large tumours were also more likely to be high grade and incompletely excised. The value of the scoring system for a UK population, where the majority of cases of DCIS are small (<2 cm) and screen-detected (patients usually over 50 years old), may be limited. For instance, Boland et al.[68] were unable to demonstrate that size was a marker of recurrence in screen-detected DCIS in the UK.

The Memorial Sloane Kettering Cancer Center in the USA has also developed a nomogram to aid prediction of recurrence risk.[79] (This is an online tool that can be accessed at nomograms. mskcc.org.) Using 10 clinicopathological variables including age, family history and details of tumour type and oncological management it claims to predict 5- and 10-year probability of recurrence following breast-conserving surgery. It was internally validated using outcomes of 1868 patients treated with breast-conserving surgery for DCIS between 1991 and 2006. An attempt to externally validate the model was made by the MD Anderson Cancer Centre, Texas, USA using 734 patients.[80] They found a marked difference in pathology and treatment between the two cohorts, and concluded that the overall predictive accuracy of the nomogram was limited.

Markers of recurrence

To improve the detection of specific patient groups at increased risk of recurrence, biological markers that might help determine recurrence potential in DCIS are being investigated. Provenzano et al.[81] found that oestrogen receptor, progesterone receptor and bcl-2 negativity and HER2 and p21 positivity were associated with an increased risk of clinical recurrence. This was irrespective of tumour grade. Oestrogen receptor, progesterone receptor, bcl-2 and HER2 were found to be interdependent, whereas p21 was found to be independent of the above associations, and is thought to reflect the differing biological pathways of action between the markers.

There has also been interest in another member of the type 1 tyrosine kinase receptor family, HER4. DCIS and invasive tumours that show coexpression of HER2 and HER4 have a better prognosis (reduced recurrence) than HER2-positive, HER4-negative tumours.[82-84] It also appears that DCIS is likely to exhibit similar molecular phenotypes to invasive cancer, with nominally Luminal A type DCIS (ER-positive HER2-negative) showing low recurrence rates compared to other phenotypes.[85] A summary of the risk factors for DCIS recurrence is shown in Table 14.2.

The use of genomic tests may have the potential to identify patients with high and low risk of recurrence. Genomic Health provide Oncotype DX, which is a scoring system for ER-positive invasive cancer recurrence based on a 21-gene assay. They have recently shown that the use of a 12-gene DCIS assay (Oncotype DX DCIS) using data from the Eastern Cooperative Oncology Group study 5194 trial can predict that 75% of women with low- and intermediate-grade DCIS have a low risk of recurrence after treatment for DCIS (and could therefore avoid radiotherapy). The validity of this score was tested using a retrospective cohort of Ontario DCIS patients, which confirmed the ability of the score to predict recurrence, particularly in ER-positive DCIS ($P = 0.006$).[86] A more detailed recent review of predictors of recurrence is offered by Martinez-Perez et al.[87]

Table 14.2 • Risk factors for recurrence of ductal carcinoma in situ

Excision margins	Margins <1 mm after breast-conserving surgery
Tumour grade	High grade (III)
Comedo necrosis	Present
Histological type	Poorly differentiated
Patient age	Younger age at diagnosis (<40 years)
Biological markers	
Negativity	Oestrogen receptor
	Progesterone receptor
	bcl-2
	HER4
Positivity	HER2
	p21
	p53
	Ki67 (high-percentage expression)
Patient presentation	Symptomatic
Tumour size	Not significant

Poor-prognosis tumours often possess multiple bad prognostic features, i.e. they tend to be poorly differentiated high-grade, comedo tumours that are oestrogen receptor-negative and overexpress c-erbB-2.

Adjuvant therapy

Radiotherapy

Four main trials and a subsequent Cochrane review[88] have examined the value of radiotherapy following breast-conserving surgery for DCIS. The NSABP B-17,[65] EORTC 10853[13] and UK/ANZ DCIS[75,76] and SWEDCIS[89] trials each studied a radiation dose of 50 Gy in 25 fractions. All found a significant reduction in ipsilateral recurrence following radiotherapy. However none of the trials has shown any impact on mortality (Table 14.3, **Fig. 14.3**).

Table 14.3 • Summary of major radiotherapy/tamoxifen clinical trials following breast-conserving therapy for ductal carcinoma in situ

	NSABP B-17*		NSABP B-24*		EORTC 10853†		UK/ANZ DCIS‡			
	BCS alone	BCS and XRT	BCS and XRT	BCS, XRT and tamoxifen	BCS alone	BCS and XRT	BCS alone	BCS and XRT	BCS and tamoxifen	BCS, XRT and tamoxifen
Number of patients	403	411	899	899	500	502	544	267	567	316
Number of local recurrences at median follow-up:										
43 months	64	28	–	–	–	–	–	–	–	–
48 months	–	–	–	–	83	53	–	–	–	–
53 months	–	–	–	–	–	–	119	22	101	21
74 months	–	–	130	84	–	–	–	–	–	–
90 months	140	47	–	–	–	–	–	–	–	–
126 months	–	–	–	–	132	75	–	–	–	–
152 months	-	-	-	-	-	-	174	35	135	32
Local recurrence rates:										
4-year all recurrences	–	–	–	–	16%	9%	–	–	–	–
4-year invasive	–	–	–	–	8%	4%	–	–	–	–
5-year all recurrences	–	–	13%	8.2%	–	–	15%	3%	12%	3%
5-year invasive	–	–	7%	4.1%	–	–	5%	1%	5%	2%
8-year all recurrence	27%	12%	–	–	–	–	–	–	–	–
8-year invasive	13%	4%	–	–	–	–	–	–	–	–
10-year all recurrences	–	–	–	–	26%	15%	–	–	–	–
10-year invasive	–	–	–	–	13%	8%	–	–	–	–
Annual recurrence rate	_	_	_	_	_	_	3.2%	1.2%	2.2%	0.9%
Number of distant metastases	6	9	7	3	20	23	–	–	–	–
Total number of contralateral breast events	19	20	36	18	28	39	29	7	11	9
Number of contralateral invasive breast cancers	16	12	23	15	19	28	20	5	7	7

Bilateral event-free survival at:										
4 years	–	–	–	–	82%	86%	–	–	–	–
5 years	74%	84%	83%	87%	–	–	85%	97%	88%	97%
8 years	60%	75%	–	–	–	–	–	–	–	–
10 years	–	–	–	–	74%	85%	–	–	–	–

BCS, breast-conserving surgery; XRT, radiotherapy.

* Fisher ER, Dignam J, Tan-Chiu E, et al. Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) eight-year update of Protocol B-17: intraductal carcinoma. Cancer 1999;86:429–38.

† Julien J, Bijker N, Fentimen I, et al. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomized phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy group. Lancet 2000;355:528–33. Bijker N, Meijnen P, Peterse JL, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853 – a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. J Clin Oncol 2006;24(21):3381–7.

‡ UK Coordinating Committee on Cancer Research (UKCCCR). Ductal carcinoma in situ (DCIS) Working Party on behalf of DCIS trialists in the UK, Australia and New Zealand, Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia and New Zealand: randomised controlled trial. Lancet 2003;362:95–103. Cuzick J, Sestaka I, Pinder S, et al Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial Lancet Oncol 2010;12(1):21–9.

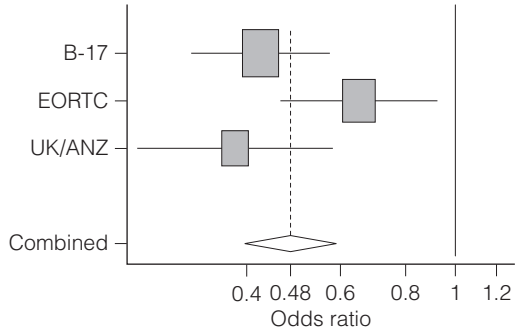

Figure 14.3 • Radiotherapy trials overview: ipsilateral ductal carcinoma in situ (DCIS) and invasive recurrences. This Forrest plot of the major randomised controlled trials of radiotherapy in DCIS (B-17,[65] EORTC[13] and UK/ANZ[75]) shows a significant reduction in ipsilateral recurrence risk following radiotherapy for all trials, with a combined odds ratio for the reduction in recurrence of DCIS and invasive disease of 0.48 for all trials.
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The reduction in recurrence was similar for both in situ and invasive disease. In the EORTC trial, radiotherapy reduced the risk of DCIS recurrence by 48% ($P=0.0011$) and invasive local recurrence by 42% ($P=0.0065$) at a median of 10.7 years follow-up.[90] The UK DCIS trial found that after a median follow-up of 12.5 years there was a reduced incidence of ipsilateral invasive disease (0·32, 0·19–0·56; $P<0.0001$) and ipsilateral DCIS (0.38, 0.22–0.63; $P<0.0001$).[76] Both groups had similar low risks of metastases and death. Twenty-year follow-up of the SWEDCIS trial has now been published and after a median follow-up of 17.5 years showed an absolute risk reduction in the XRT arm of 12% mainly in older women; younger women appeared to experience a lower absolute benefit from radiotherapy.[91] No breast cancer survival advantage following radiotherapy was found in any trial.

✔✔ Current NICE guidelines recommend that you should: 'offer adjuvant radiotherapy to patients with DCIS following adequate breast-conserving surgery and discuss with them the potential benefits and risks.'[60]

The Cochrane review concluded that 'nine women require treatment with radiotherapy to prevent one ipsilateral recurrence'.[88]

Two studies have looked at avoiding radiotherapy in 'low-risk' cases of pure DCIS. One by Wong et al.[92] was stopped in line with the trial protocol because of high recurrence rates although most recurrences were mammographically detected DCIS and the remainder were node-negative invasive cancers and thus did not impact overall survival. They concluded that it remained unclear how to identify patients who had a low recurrence risk with excision alone, and that despite margins >1 cm (or having had re-excision) the local recurrence rate was still high. The second, the Eastern Cooperative Oncology Group study 5194 (which is the study used to validate the Oncotype DX DCIS score)[93] looked at 558 cases of low- or intermediate-grade DCIS, which was 2.5 cm or less, and 103 cases of high-grade DCIS of 1 cm or smaller with 3-mm margins, none of which had XRT but some had tamoxifen. The 5-year ipsilateral overall breast-event rate for the low/intermediate-grade DCIS was 6.1% (3% for invasive disease alone). For the high-grade lesions this was increased to 15.3% (7.5% for invasive disease). They concluded that a 6% 5-year ipsilateral breast event rate for low-/intermediate-grade tumours may be acceptable to patients and physicians, but that the 15% high-grade event rate would not be. They suggested that specimens need to be rigorously evaluated to ensure they are actually 'low-risk'. This study included patients with DCIS with a median size of 1 cm. Seventy per cent of the patients were classified by the Oncotype DX assay as low risk, 14% intermediate risk and 11% high risk. Low-risk patients had a 10-year event rate of 12% and a 5% rate of developing an invasive cancer with no radiotherapy. This rate of event is higher than one currently sees in invasive cancer after breast conservation surgery and radiotherapy. A recent UK study showed that patients can be selected on the basis of grade for radiotherapy and that this does not compromise long-term outcome.[73]

✔ The National Institute for Health State-of-the-Science conference that included a multiprofessional independent panel of health professionals and public representatives who reviewed systematic literature reviews on DCIS, with presentations by investigators working in wide-ranging areas of DCIS management (2009)[94] concluded that for radiotherapy:
'Randomized clinical trials demonstrate that all subsets of patients benefit from radiotherapy in terms of decreased local recurrence. However, there may be a subgroup of women who have DCIS in which the risk of local recurrence is so low that radiotherapy may be of no benefit. In addition, there also may be a subset of women who can be monitored after biopsy in lieu of surgery or other therapies.'

Endocrine therapy

Although radiotherapy reduces tumour recurrence following breast-conserving surgery, there is still

an overall recurrence rate of between 3% and 13%[13,65,75] at 5 years and research into the use of additional adjuvant therapies for women with 'high-risk' DCIS remains important.

✔✔ The NSABP B-24 trial compared breast-conserving surgery and radiotherapy with or without adjuvant tamoxifen. The study found that tamoxifen following breast-conserving surgery and radiotherapy was of benefit in reducing recurrence. There were 43% fewer invasive breast cancer events and 31% fewer non-invasive events in the tamoxifen-treated group.[69] The main advantage was in reducing invasive recurrence in the ipsilateral breast, although there was a significantly lower cumulative incidence of all breast cancer-related events in the tamoxifen group.

In this trial, 30% of women were younger than 50 years at diagnosis and the effect of tamoxifen was largely due to a 40% reduction in this younger age group, with only a 20% reduction in the age group greater than 50 years. On this basis adjuvant tamoxifen after wide local excision for DCIS could be discussed in this younger (under 50) age group; however, current NICE guidelines indicate that tamoxifen should not be used in DCIS.[62] A retrospective review of the NSABP B-24 results showed that tamoxifen was only beneficial in ER-positive cases as one would expect. The relative risk of recurrence of any breast cancer in the ER-positive cohort was 0.41 (95% CI 0.25–0.65, $P = 0.0002$), whereas there was little benefit in the ER-negative cases (relative risk 0.80, $P = 0.51$).[95] The UK/ANZ DCIS trial found that adjuvant tamoxifen reduced overall DCIS recurrence (0.70, 0.51–0.86, $P = 0.03$) and contralateral tumours (0.44, 0.25–0.77, $P = 0.005$) but had no effect on ipsilateral invasive disease[76] (see Table 14.3). The UK/ANZ DCIS trial has not published a breakdown of tamoxifen response in relation to oestrogen receptor status, but tamoxifen was found to be more effective in low- and intermediate-grade compared with high-grade DCIS and this is likely to be a surrogate reflection of oestrogen receptor status; low-grade DCIS tends to be nearly 100% ER-positive, compared to 60% of high-grade DCIS expressing oestrogen receptor.[96] The UK/ANZ DCIS trial authors suggested that the variation in findings as to the benefit of tamoxifen in preventing ipsilateral invasive recurrence between the two trials may have been a product of the American B-24 trial having approximately 34% of women aged under 50, whereas in the UK trial >90% of participants were older than 50.[76] No significant effects were seen on mortality with the use of tamoxifen in either trial.

In randomised controlled trials, the rate of contralateral breast cancer after DCIS is 0.5% per year for 10 years. As tamoxifen can halve the risk of breast cancer in the contralateral breast, its effects in part are as a chemopreventive agent. This may possibly justify its use in some women with ER-positive disease. Approximately 60% of DCIS express HER2. ER-positive tumours that also express HER2 are considered to be more often resistant to tamoxifen but do respond to aromatase inhibitors.

✔✔ The IBIS II DCIS trial was a placebo-controlled trial that compared tamoxifen with anastrozole, after complete excision of ER-positive DCIS in 2980 women. It showed that anastrazole was as effective as tamoxifen, although the event rate was lower than anticipated.[97] The IBIS-II trialists are collecting HER2 data on the cases and aim to present results in light of HER2 positivity at a later date.

The NSABP B-35 trial compared anastrozole with tamoxifen in 3104 patients with DCIS after lumpectomy and radiation therapy.[98] This found that anastrazole provided a significant improvement in cancer-free survival mainly in women younger than 60 (all postmenopausal). There was no difference seen between anastrazole and tamoxifen at 5 years but at 10 years the estimated percentage of cancer-free patients was 89.1% (86.8–91.0%) in the tamoxifen group compared to 93.1% (91.5–94.5%) in the anastrozole group, mainly due to a decrease in contralateral invasive disease. There were no differences in overall survival. This raises the question of the potential use of aromatase inhibitors for breast cancer prevention after DCIS as well as tamoxifen. The NSABP P-1 chemoprevention trial[99] compared tamoxifen to placebo in patients at high risk of breast cancer. The study reported a 49% reduction in incidence of invasive cancer and a 50% reduction of DCIS in the tamoxifen-treated group. The reduction in contralateral breast cancer was only seen in ER-positive cases with no benefit being seen for ER-negative patients.

The MAP.3 trial looked at exemestane in a prevention setting in postmenopausal women and showed a reduction in both new cases of DCIS and further breast events in women with a prior diagnosis of DCIS, though numbers were small.[18]

Follow-up and prognosis

Following confirmation that there has been complete excision of all suspicious microcalcifications with clear margins, patients should be given the opportunity to participate in clinical trials. One such trial is investigating the role of boost radiotherapy in DCIS. Follow-up after the initial postoperative review should be by annual bilateral two-view mammography to

detect recurrence. Breast cancer-specific mortality following breast-conserving surgery for DCIS is low at less than 2% at 10 years. This figure is similar to that following mastectomy for DCIS.

Management of recurrence

Rates of local recurrence (LRR) after mastectomy for pure DCIS higher than those reported earlier have been highlighted in the UK, with a 15-year retrospective review of screen-detected lesions demonstrating a 3.1% 5-year LRR and an 8% 15-year LRR for mastectomies performed between 1988 and 1999 in the West Midlands.[100]

Emerging data from the USA highlight that LRR after skin-sparing mastectomy (SSM) is higher than previously documented and potentially as high as 5% compared to 1% after simple mastectomy.[63] A retrospective review of patients in the USA who underwent a SSM for pure DCIS with a median follow-up of 82.3 months demonstrated a local recurrence rate of 5.1% with a mean follow-up of 82.3 months and mean disease-free survival time of 51.5 months.[10] This LRR is in line with UK SSM data and similarly identified that high grade and close margins <1 mm were predictors of LRR after mastectomy for DCIS, with a 10.5% LRR in these subgroups.[10] Contralateral breast cancer rates after treatment for previous DCIS had been shown to be 6.4% (95%CI 5.9–7.1%) at 15 years, a rate of 0.4–0.5% per year.[101]

In situ recurrence

Patients with an in situ recurrence where the primary was treated initially with breast-conserving surgery alone can be offered re-excision (ensuring clear margins) followed by postoperative radiotherapy. Patients who have already received radiotherapy following their primary excision are usually advised to have completion mastectomy. A skin-sparing mastectomy with a immediate flap-based breast reconstruction gives excellent results. Implant-based reconstructions have an increased rate of complications if there has been prior radiotherapy.

Invasive recurrence

The management of invasive recurrence is dependent on the initial therapy for DCIS. If the patient did not receive radiotherapy after initial DCIS excision, then wide local excision and radiotherapy may be an option, depending on the size and location of the invasive tumour. If wide local excision is not an option, then mastectomy and axillary staging is the treatment of choice, with adjuvant therapy dictated by standard protocols for primary invasive cancers. Studies following salvage treatment for both in situ and invasive recurrences of DCIS have cause-specific survival rates in excess of 90% at 8 years.[67]

DCIS of the male breast

DCIS accounts for approximately 5% of breast cancers in men.[102] It usually presents clinically with symptoms of a retro-areola cystic-type mass or bloody nipple discharge. Clinical, rather than mammographic, detection possibly accounts for the different incidence of DCIS between men and women. The predominant histological subtypes of DCIS in men are papillary and cribriform. Standard treatment is total mastectomy with excision of the nipple–areola complex but wide excision and radiotherapy is being used more frequently.[103] Pure DCIS in men is usually of low or intermediate grade; less than 3% of cases are high grade. In a series of 114 patients, 84 with pure DCIS and 30 with DCIS and invasive cancer, there were no cases of high-grade comedo DCIS in men without an invasive tumour.[104] The percentage of men with DCIS that eventually develop an invasive cancer is not known.

The future

Ongoing DCIS trials

There is much current interest in identifying low-risk patients who can avoid treatment for DCIS. The UK LORIS trial (Low Risk DCIS) is a phase III trial comparing active monitoring to surgery in women with low- and intermediate-grade DCIS. In addition, the European LORD (Low Risk DCIS) trial and the American COMET (Comparison of Operative Treatment versus Medical Endocrine Therapy for low-risk DCIS) trial are being set up to address the same issue. The Canadian DUCHESS trial is aiming to assess whether the ONCOTYPE-DX-DCIS score changes recommendations for the use of radiotherapy following breast-conserving surgery for DCIS. The NSABP B-43 trial is comparing trastuzumab given during radiotherapy or radiotherapy alone in women with HER2-positive DCIS treated with lumpectomy. The ICICLE trial (currently in follow-up) is trying to identify genes that increase a woman's risk of developing DCIS, and also trying to identify which women with DCIS are at risk of developing an invasive recurrence if left untreated. A more novel treatment is being investigated in a phase I/II trial looking at vaccine therapy, where vaccines made from a patient's white blood cells mixed with peptides may help the body build an effective immune response to kill tumour cells. Neoadjuvant therapy with aromatase inhibitors in postmenopausal women with

ER-positive cancers is showing promise as a short-term treatment to reduce tumour extent and as long-term treatment for some patients with low- and intermediate-grade DCIS.

UK National DCIS audit (Sloane Project)

The Sloane Project is a prospective audit which is collecting data on all screen-detected DCIS, LCIS, ADH and ALH in the UK between 2003 and 2012. It has over 11 500 cases submitted by participating UK breast screening units. The aim is to correlate initital characteristics with clinical outcomes – specifically recurrence and invasive cancer development. Data from this study will hopefully be used to inform clinical management and restrict treatment to at-risk groups (www.sloaneproject.co.uk).

DCIS stem cell therapy

Breast cancers have been shown to consist of stem cells and proliferating cells.[20] The stem cells have been shown to be resistant to both chemothereapy and endocrine therapy. Stem cells evade death and subsequently re-grow leading to recurrence. Farnie et al.[20] have shown that primary culture of DCIS using a mammosphere technique demonstrated that NOTCH and the epidermal growth factor receptor/HER2 are key receptors that stem cells use to avoid death. Thus strategies to inhibit stem cell self-renewal as well as proliferating progeny will increase DCIS cure rate. HER2-amplified DCIS has an increased stem cell population and this population is targeted by lapatinib, herceptin and other anti-HER2 therapies but not by chemotherapy. In vitro lapatinib (a HER1/2 inhibitor) reduces stem cell renewal by 70% in HER2-amplified DCIS.[105]

Thus therapies that target cancer stem cells may prevent recurrence of DCIS which may well reflect stem cells that were further down the ducts and were not identified by the pathological process of assessing margins. Treatment with anti-stem cell therapy perioperatively or in combination with endocrine therapy may achieve better prevention of recurrence. Additionally, new data reflecting dual HER2 inhibition indicate complete response in up to 60% of ER-negative HER2-positive invasive cancers and suggest that such a strategy might be effective in ER-negative HER2-positive DCIS to avoid mastectomy.This strategy is being tested in the NSABP B-34 trial. This strategy is an effective anti-stem cell strategy.

Optimising treatment

Controversies regarding the optimum management of this heterogeneous preinvasive lesion still reign. Surgeons should ensure complete pathological and radiological excision of DCIS and discuss the appropriateness of adjuvant therapy (radiotherapy or endocrine) with the patient in a multidisciplinary setting in order to minimise recurrence without overtreatment.

Key points

- DCIS is a preinvasive breast lesion; the proliferation of malignant epithelial cells are confined within an intact basement membrane. The developmental pathway for low- and intermediate-grade DCIS appears different from that for high-grade DCIS.
- DCIS accounts for 20% or more of new screen-detected “cancers”.
- Small localised areas of DCIS should be treated with breast-conserving surgery with or without radiotherapy. Larger lesions are usually treated by mastectomy and sentinel node biopsy unless they can be excised using oncoplastic techniques. Axillary surgery should be avoided with breast-conserving surgery.
- We are potentially overtreating a number of ‘low-risk’ cases of DCIS that may never progress to invasive disease.
- There are current controversies in management of DCIS with respect to overtreatment and in particular the widespread use of radiotherapy in this condition.
- Up to 13% of cases recur at 5 years following breast-conserving surgery and radiotherapy, 50% of which (i.e. up to 6.5% of all cases) are invasive disease.
- The key factor for decreasing tumour recurrence is to excise the lesion to clear margins at the time of surgery.

- Bad prognostic factors include younger age at diagnosis (<40 years), poorly differentiated high-grade tumours, the presence of comedo necrosis, HER2 positivity and oestrogen receptor negativity.
- Adjuvant endocrine therapy is not indicated after mastectomy for DCIS but appears to have benefits and can be discussed with the patient in oestrogen receptor-positive lesions treated by breast-conserving surgery.
- Advances in genomics and proteomics may provide important information to select the most appropriate management for individual patients with DCIS.

Full references available at **http://expertconsult.inkling.com**

Key references

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The results of a multicentre, randomised, controlled trial of 1010 patients with DCIS treated with breast-conserving surgery, randomised to receive no further treatment or radiotherapy. The study found that radiotherapy reduced overall invasive (40% reduction, *P* = 0.04) and non-invasive (35% reduction, *P* = 0.06) ipsilateral recurrences (median follow-up 4.25 years).

65. Fisher ER, Dignam J, Tan-Chiu E, et al. Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) eight-year update of Protocol B-17: intraductal carcinoma. Cancer 1999;86:429–38. PMID: 10430251.
The 8-year update of 623 women in a randomised controlled trial of 814 women with DCIS treated with local excision who were randomised to receive radiotherapy or no additional treatment. The study found that women who received additional radiotherapy following breast-conserving surgery had a significant reduction in ipsilateral breast tumours (31% vs 13% at 8 years, *P* = 0.0001). The authors also analysed a range of clinicopathological characteristics of the patients and the tumours to assess predictors of recurrence; findings suggested that the presence of comedo necrosis was an independent risk factor for recurrence.

69. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen in the treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. Lancet 1999;353:1993–2000. PMID: 10376613.
Double-blind, randomised, controlled trial of 1804 women with completely or incompletely excised DCIS at breast-conserving surgery who were randomised to receive radiotherapy plus or minus tamoxifen. The women receiving tamoxifen had fewer breast cancer events at 5 years compared with placebo (8.2 vs 13.4, *P* = 0.0009), mainly due to a decrease in invasive cancer in the ipsilateral breast. A retrospective review of the results (reference 75) showed that this benefit was confined to ER-positive cases.

71. Bijker N, Peterse JL, Duchateau L, et al. Risk factors for recurrence and metastasis after breast conserving therapy for ductal carcinoma in situ: analysis of EORTC trial. J Clin Oncol 2001;19:2263–71. PMID: 11304780.
A review of 843 women of the 1010 randomised cases from the EORTC 10853 trial (local excision of DCIS plus or minus radiotherapy) that examined the clinicopathological characteristics of the women. The authors found that clear margins were the most important factor in reducing local recurrence (hazard ratio 2.07, *P* = 0.0008). Patients with poorly differentiated DCIS were at higher risk of metastatic disease (hazard ratio 6.57, *P* = 0.01) and other poor prognostic factors included young age (<40 years) at diagnosis (hazard ratio 2.14, *P* = 0.02) and symptomatic detection (hazard ratio 1.8, *P* = 0.008).

75. UK Coordinating Committee on Cancer Research (UKCCCR). Ductal Carcinoma In Situ (DCIS) Working Party on behalf of DCIS trialists in the UK, Australia and New Zealand. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia and New Zealand: randomised controlled trial. Lancet 2003;362:95–103.
A 2×2 factorial design, randomised controlled trial of 1701 screen-detected patients with completely excised DCIS, randomised to receive tamoxifen, radiotherapy, both treatments or none. The authors found that radiotherapy reduced the incidence of both ipsilateral invasive recurrence (hazard ratio 0.45, *P* = 0.01) and DCIS recurrence (hazard ratio 0.36, *P* = 0.0004). Tamoxifen reduced overall DCIS recurrence (hazard ratio 0.68, *P* = 0.03) but not invasive disease. The trial has not yet published results with regard to oestrogen receptor status.

97. Forbes JF, Sestak I, Howell A, et al. Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial. Lancet 2016;387(10021):866–73. PMID: 26686313.
A double-blind multicentre placebo controlled trial of 2980 women with ER-positive DCIS treated with either anastrazole or tamoxifen. There were no differences in

cancer-related outcomes between the two treatments. Anastrazole was shown to be another treatement option in postmenopausal ER-positive women after surgery for DCIS.

98. Margolese RG, Cecchini RS, Julian TB, et al. Anastrazole versus tamoxifen in postmenopausal women with DCIS undergoing lumpectomy plus radiotherapy (NSABP B-35): a randomized, double-blind, phase 3 clinical trial. Lancet 2016;387(10021):849–56. PMID: 26686957.
A phase III double blind randomised controlled trial of 3014 women assigned to tamoxifen or anastrazole. This found at 10 years an improved disease-free interval with anastrazole compared to tamoxifen, mainly in women under 60 and predominantly reducing contralateral breast cancer.