Ductal Carcinoma in Situ

Stacey A. Carter, Sarah E. Pinder, and Alastair M. Thompson

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11.1 Introduction

Ductal carcinoma in situ (DCIS) of the breast represents an intraductal lesion of the breast characterised by increased epithelial proliferation with cellular atypia not invading the basement membrane of the ductal lobular unit. Microinvasion of the local tissues (up to 1 mm) may be permitted as part of the DCIS process, but extension beyond 1 mm constitutes invasive breast cancer. DCIS reflects a spectrum of molecular changes and is a non-obligate precursor to invasive disease which may or may not have a stepwise progression from preceding DCIS; further, the time lines of, and any progression to, invasive disease are highly variable. Indeed, it is reported that some 15% of women at post-mortem have evidence of DCIS undetected during their lifetime [1]. Although the development of invasive breast cancer following DCIS may be fatal, the risk of dying of breast cancer after a diagnosis of DCIS is less than 3% after two decades [2]. This recognised heterogeneity of DCIS has prompted prospective trials to consider the need for radiotherapy and for endocrine therapy and to examine clinical, pathological and molecular predictors of recurrence and progression to invasive breast cancer to delineate appropriate management of this condition.

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11.2 Epidemiology

In general, the factors associated with invasive cancer are similar to the factors associated with intraductal proliferative lesions such as DCIS. Age remains an important risk factor for DCIS. Women 70–84 are found to have DCIS with a rate of 1.3 per 1000 screening mammograms, twice the incidence in women aged 40–49 years. However, «overdiagnosis» has been used to characterise conditions, including DCIS, which have the microscopic appearances of cancer but are not destined to cause symptoms or death during a patient's lifetime [3].

The widespread adoption of screening mammography has changed the way DCIS is detected and has contributed to the increase in new cases of DCIS. In the past, most patients presented with clinical symptoms such as a mass (91%), bloody nipple discharge (7%), both (<1%) or Paget's disease [4]. Symptomatic DCIS is more commonly of high cytonuclear grade, larger in size, ER negative and HER2 positive [4]. Indeed, symptomatic DCIS more often bears an occult invasive focus, and when this is present, there is more often nodal involvement than when occult invasive cancer is identified in screen-detected DCIS [5].

DCIS identified on screening mammography is typically asymptomatic and non-palpable, with approximately 60% of detected lesions being of intermediate or low nuclear grade compared to 55% of symptomatic DCIS in some series, [4] although in other series over half of screen-detected DCIS is of high grade. [6] The detection rate of DCIS has dramatically increased globally since the advent of breast screening. The average frequency of DCIS detected at screening in 84 units in the UK was 1·60 per 1000 women screened (median 1·50 [unit range 0·54–3·56] per 1000) [7]. Reflecting this, in the USA, the incidence of DCIS has risen from 5.8 per 100,000 in the 1970s to 32.5 in 2004 with over 60,000 women there diagnosed with DCIS annually, almost all in asymptomatic individuals [8]. In the UK in 2013, there were 7288 new cases of in situ breast carcinoma, with most women diagnosed at 60 years or older. This represents a 534% increase in incidence of in situ breast cancer (females only) since the late 1970s [9]. Indeed, DCIS now represents some 25% of all breast cancer diagnoses [10].

11.3 Natural History

Most data on the natural history of patients diagnosed with DCIS refers to retrospective reviews of missed diagnoses. They often relate to an era of lower-quality imaging, biopsy and pathology and do not include active monitoring by mammography, with almost all patients presenting symptomatically. Without treatment, it is estimated that 20–30% of DCIS overall will progress to invasive cancer [11, 12]. In keeping with this, recent evidence from the UK Breast Screening Programme has considered the effects of a diagnosis of DCIS on the incidence of subsequent invasive breast cancer [7]. For every three women with screen-detected DCIS, there was one fewer invasive interval cancer over the next 3 years, suggesting there may be benefits on a population level to detecting DCIS through breast screening [7].

11.4 Diagnosis

11.4.1 Mammogram

The majority of DCIS is detected with imaging and often appears as microcalcifications or less commonly as a mass or area of architectural distortion. The minority of DCIS is today detected by clinical symptoms (palpable abnormality, nipple discharge or nipple alterations associated with Paget's disease) or incidentally in a surgical specimen obtained for other reasons. An important factor in the management of DCIS is to determine the extent of the disease as this may influence surgical decision-making.

Different patterns of calcifications have been identified which may be suggestive of DCIS [13]. Multiple clusters of fine microcalcifications are typically seen in low-grade DCIS, while linear, continuous, often branching, coarse calcifications are seen with high-grade disease. Microcalcifications may thus be visible both at the imaging (usually mammography) and microscopic level (Figs. 11.1 and 11.2). Patients found to have an abnormal screening mammogram should undergo diagnostic bilateral mammography with magnification views to assess the extent of disease. Mammograms have

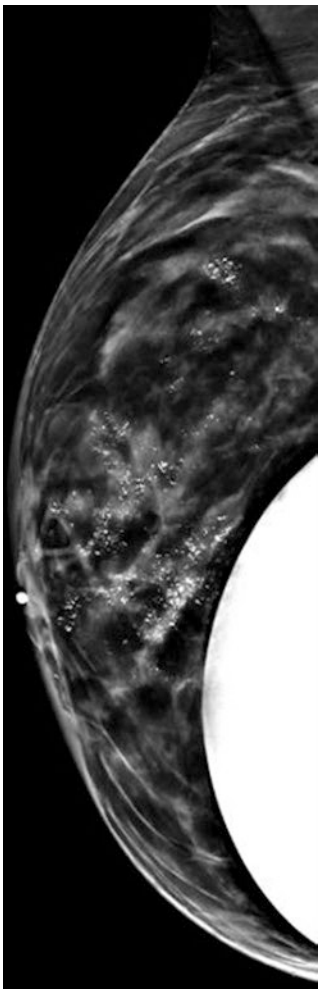

Fig. 11.1 Radiographic microcalcifications from DCIS on mammography in a patient with a prior implant

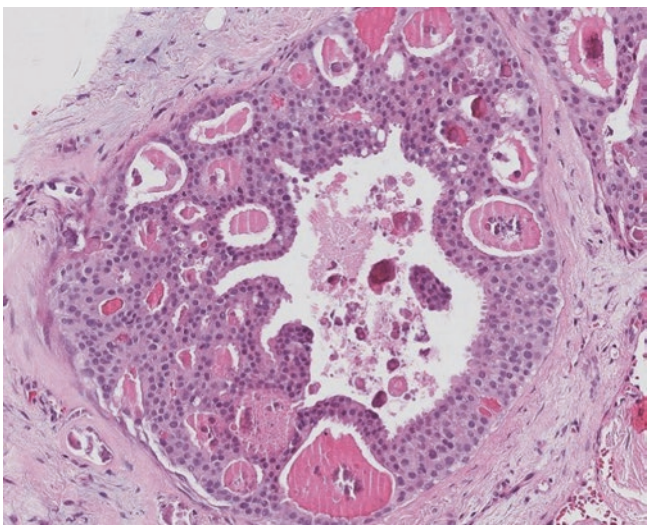

Fig. 11.2 Microcalcifications (irregular purple staining) in secretions (pink staining) in low grade DCIS

been noted to underestimate the extent of DCIS, especially with increasing tumour size, and the comparison of mammographic versus final pathology size may coincide within a centimetre in only a third of patients [14].

11.4.2 Ultrasound

Some academic centres routinely employ ultrasound on all women with an abnormal mammogram or a palpable mass. In the USA, the National Comprehensive Cancer Network (NCCN) guidelines [15] recommend that ultrasound evaluation is an optional part of the work-up for patients with early-stage breast disease. By contrast, the UK National Institute for Health and Care Excellence (NICE) guidelines [16] recommend ultrasound evaluation of the axilla as well as the breast for all patients with early invasive disease, but not per se for DCIS. Although not specifically designed to detect microcalcifications (unlike mammography), approximately 5–15% of patients with microcalcification will have a mass detectable on ultrasound.

11.4.3 MRI

A recent meta-analysis conducted to examine the effects of MRI on the surgical treatment of DCIS concluded that MRI in women with DCIS is not associated with an improvement in surgical outcomes [17]. In this analysis, there was no difference in the proportion of women with positive margins following breast conserving surgery (BCS) or in the reoperation rate for positive margins between patients having MRI and no MRI. Conversely, MRI was found to increase the odds of having mastectomy rather than an initial conservation approach. MRI use in women with DCIS does not appear to confer an oncological advantage [18] and has a lower sensitivity for DCIS compared with invasive cancer. The UK NICE guidelines caution against routine use of MRI in patients with DCIS and guides clinical teams to use this modality if there is a discrepancy regarding the extent of disease between clinical examination and other imaging modalities or if breast density precludes accurate mammographic assessment.

11.4.4 Biopsy

Any radiographically suspicious abnormality warrants biopsy. One option is fine needle aspiration (FNA) cytology. FNA offers the convenience of being a simple procedure with standard equipment (syringe and needle) for palpable lesions; however, cytological examination cannot distinguish in situ from invasive disease, and definitive preoperative diagnosis rates for screen-detected DCIS are poor (73% sensitivity compared with 94% sensitivity with core biopsy) [19]. At least

partly for this reason, FNA alone is not recommended for screen-detected abnormalities in the UK National Health Service Breast Screening Programme (NHS BSP).

Core needle biopsy provides a more accurate assessment because the tissue architecture is retained and definitive diagnosis of DCIS, i.e. compared to invasive disease, can be made (with the proviso that only a small portion of the lesion is sampled and a small invasive focus may have been missed). Additionally, core needle biopsy may provide sufficient tissue for examination of hormone receptor status, which can have important implications for treatment. A core needle biopsy can be done as a stereotactic procedure for calcifications seen on mammogram or with ultrasound guidance in patients with a lesion seen on ultrasound. An MRI-guided core biopsy can be used in situations where the lesion is occult on mammogram and ultrasound. Among women who are diagnosed with DCIS without invasive cancer on core biopsy, the estimate of upstaging to invasive cancer upon surgical excision ranges from 0% to 20% [20]. This upstaging will clearly depend on the amount of tissue provided to the pathologist and the accuracy of radiological sampling any areas of particular concern; the use of larger bore vacuum-assisted biopsy (VAB) needles accurately delineated the presence of DCIS alone in one small series [21], but in most, even with VAB, occult invasive disease will be missed on biopsy in approximately 5%–10% of women with a biopsy diagnosis of DCIS.

11.4.5 Pathology

The pathology of DCIS can be considered as a spectrum ranging between atypical ductal hyperplasia and invasive disease with features such as grade and necrosis reflecting the likely clinical behaviour as well as the presentation on mammography. There is interobserver variability when assigning a final pathologic diagnosis of ADH versus low-grade DCIS in some series (see ▶ Chap. 10) [22]. To avoid overtreatment, a more appropriate nomenclature may be to reclassify DCIS as ductal intraepithelial neoplasia (DIN) as was the idea of reclassifying lobular carcinoma in situ (LCIS) to lobular intraepithelial lesion (LIN) [23, 24]. However, this system has not achieved widespread acceptance, and cytonuclear grading is the system recommended in the USA and the UK, among others [25].

11.5 Differential Diagnosis

The pathological features of ADH and low-, intermediate- and high-grade DCIS are presented in ◘ Table 11.1. The relationship of DCIS to atypical ductal hyperplasia (ADH), lobular neoplasia and invasive disease deserves attention. Usually, diffuse-positive nuclear ER expression with contiguous reactivity throughout the entire population of atypical cells is seen in both ADH and low-grade DCIS (◘ Fig. 11.3) both of which are almost always ER positive. In addition, homogeneous absence of staining for basal cytokeratin markers such as cytokeratins 5 and 14 is also a common finding for ADH and low-grade DCIS. Thus, the distinguishing feature discriminating ADH from DCIS is that the cellular and architectural changes of low-grade DCIS occupy two or more complete membrane-bound spaces, those of ADH only one. The low-grade, solid variant of DCIS may be misinterpreted as lobular neoplasia but can almost always be distinguished definitely with E-cadherin (staining indicates ductal pathology).

◘ **Table 11.1** Features of DCIS by grade and in comparison to atypical ductal hyperplasia

Feature	Atypical ductal hyperplasia	Low grade	Intermediate grade	High grade
Pleomorphism	Monotonous	Monotonous	Intermediate	Markedly pleomorphic
Cell size	1.5 × to 2 × RBCs or normal duct epithelial nucleus	1.5 × to 2 × RBCs or normal duct epithelial nucleus	Intermediate	>2.5 RBCs or normal epithelial nucleus
Chromatin	Usually diffuse, finely dispersed	Usually diffuse, finely dispersed	Intermediate	Usually vesicular, regular chromatin distribution
Nucleoli	Only occasional	Only occasional	Intermediate	Prominent, often multiple
Mitoses	Only occasional	Only occasional	Intermediate	May be frequent
Orientation	Polarised	Polarised	Intermediate	Usually not polarised
Extent of lesion	Less than two complete membrane-bound spaces (or less than 2 mm in size)	Two complete membrane-bound spaces involved		

RBC red blood cell

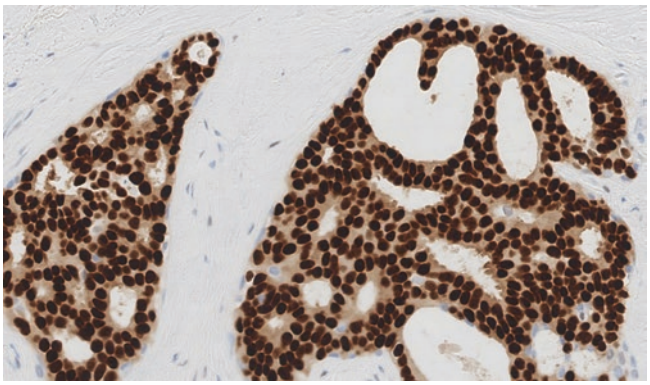

Fig. 11.3 Estrogen receptor (ER) staining of nuclei on a histological section of DCIS

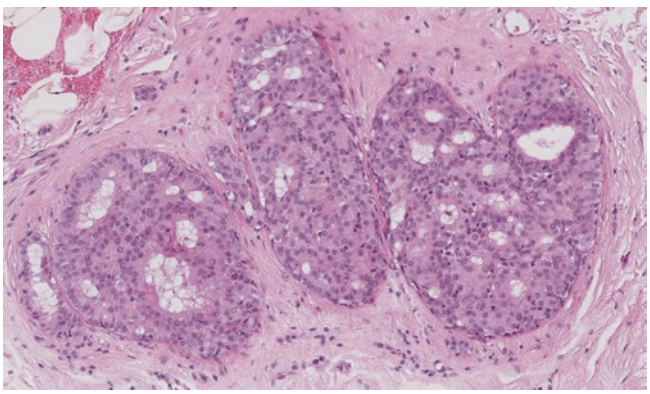

Fig. 11.4 Intermediate grade DCIS

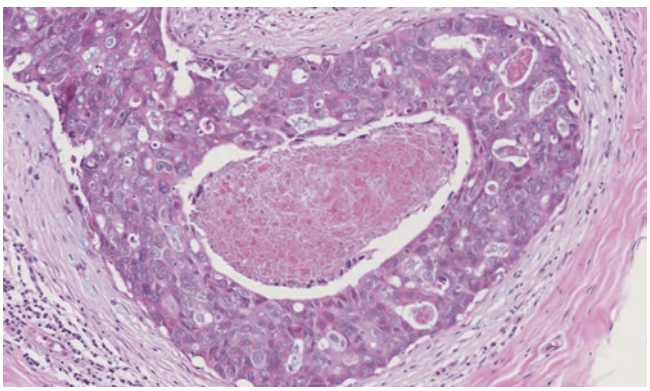

Fig. 11.5 High-grade DCIS with central necrosis

Low-grade (Fig. 11.2) and intermediate-grade (Fig. 11.4) («low risk») DCIS may have a more indolent course than high-grade DCIS (Fig. 11.5) with regard to its potential to develop invasive disease [23]. The cytomorphological appearances, the grade of the DCIS and the presence or absence of comedo necrosis (necrosis in the centre of the ducts) (Fig. 11.5) are reflected in both the mammographic appearances and the subsequent disease behaviour. In addition, the presence of ER, PR and HER2 expression on immunohistological staining of the

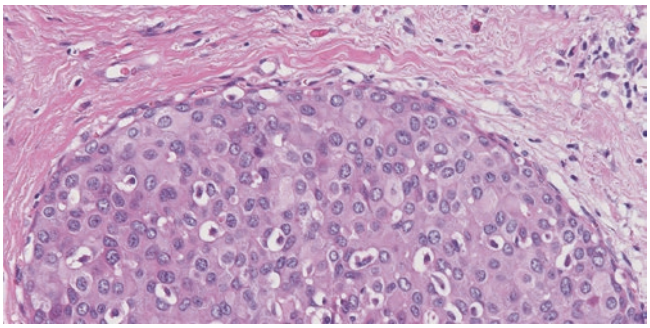

Fig. 11.6 High-grade DCIS

DCIS may have implications for the future likelihood of recurrence; however, the evidence is far from clear. While the microscopic appearances may vary, ultimately the behaviour of DCIS that is high grade (Fig. 11.6) and ER negative and/or HER2 positive may be more aggressive when compared with that of low-risk DCIS. This is considered further below in the section on recurrence.

11.5.1 Receptor Status

The oestrogen receptor (ER), progesterone receptor (PR) and HER2 protein status of DCIS is not routinely performed for DCIS in some European countries such as the UK where it is not included in national minimum datasets, although ER is considered a routine part of assessment in the US NCCN guidelines. Increasing DCIS grade correlates with a decrease in hormone receptor positivity; comedo necrosis is also more frequently seen in ER-negative tumours. The availability of ER, in particular, may determine the use of adjuvant endocrine therapy following a diagnosis of DCIS (see below), although the influence of this treatment is largely on the contralateral breast, and the relevance of the ER status of the index disease is not clear.

11.6 Treatment

Current treatment options routinely offered for DCIS include surgery (lumpectomy/wide excision/«segmental mastectomy» or mastectomy), radiation (radiation or none) and endocrine therapy. These options constitute guideline concordant care (GCC) according to the NCCN treatment recommendations [15]. Between 1991 and 2010, 23.8% of women diagnosed with DCIS in the USA underwent mastectomy, 43% lumpectomy with radiation and 26.5% lumpectomy without radiation, based on data from the Surveillance, Epidemiology, and End Points Registry [26]. Among the 97% of women with DCIS treated with guideline concordant care, neither randomised trials nor retrospective studies to date have shown a survival advantage of any treatment option over another [26].

11.6.1 Overdiagnosis and Overtreatment

Overdiagnosis (detection of a condition not causing symptoms or death if left undetected) and overtreatment (treatment without benefit) resulting from mammographic screening have been estimated to be as high as one in four patients diagnosed with breast cancer. [27] The absence of standard definitions for assessing overdiagnosis has led to uncertainty and controversy around this estimate. The national health-care expenditure resulting from false-positive mammograms as well as breast cancer overdiagnosis has been estimated in the USA to approach $4 billion annually [28], and there is general consensus that much of this burden derives from the treatment of DCIS. However, many fail to recognise that DCIS is not a single disease process (clinically, radiologically, biologically, histopathologically or genetically) and that low-grade DCIS and high-grade DCIS cannot be considered equivalent in terms of likelihood of progression to invasive disease or subsequent behaviour. Nevertheless, for those women whose DCIS may never progress even without treatment, medical intervention can only do harm. In addition, the potential for overtreatment and overdiagnosis must be balanced against the consequences of missed diagnosis and undertreatment [7]. Thus, at present, most women who receive a diagnosis of DCIS undergo surgical resection with consideration of adjuvant radiotherapy and/or endocrine therapy.

11.6.2 Surgery

With regard to surgical treatment for DCIS, the options comprise breast conserving surgery (BCS), with or without radiation, versus mastectomy (with or without breast reconstruction). There is no single approach that is best for every patient given the heterogeneity of disease, variation in extent, age, genetic carrier status, breast size (compared with the size of the DCIS) and the patient's desire for breast conservation, mastectomy and/or reconstruction. Breast conservation surgery with adjuvant radiotherapy has been accepted as a treatment option for invasive disease with equivalent survival to mastectomy; this principle in surgical management has been extended to include DCIS. Since most DCIS is identified as a non-palpable lesion, BCS usually requires the radiographic abnormality to be localised by, for example, wire localisation or iodine-125-labelled seed, for resection (Fig. 11.7). Determining the extent of disease is important, as large lesions may need to be bracketed with wires or seeds to ensure removal of the involved area. Assessment of the specimen radiograph helps confirm that the entire targeted lesion was removed.

DCIS is most commonly unifocal. Segmental, multifocal or multicentric disease is the exception; only one of 119 mastectomies was multicentric in the series examined by Holland and Hendriks [29]. However, while multifocal or multicentric lesions are traditionally considered to be a contraindication to BCS, many groups have reported success

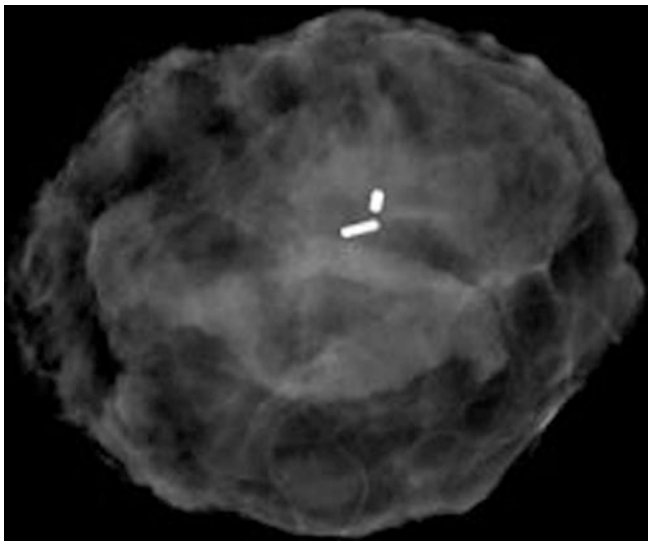

Fig. 11.7 Specimen radiography of DCIS demonstrating clip (smaller opaque marker) and I125-labelled marker (larger opaque marker); specimen orientated using sutures not visible to radiography

incorporating oncoplastic reconstruction, as for invasive disease [30]. Oncoplasty has gained momentum in recent years as it may allow for wider, negative margin resection while achieving a good cosmetic result for the patient by reshaping the breast. For larger resections, this procedure can be done with a contralateral mastopexy for symmetry. Mastectomy options include a total mastectomy, skin sparing mastectomy (SSM) or nipple sparing mastectomy (NSM). Mastectomy may be the only surgical option for a woman with a small breast and large extent of DCIS. For SSM, a circumareolar incision can be modified if the patient has a scar from a previous biopsy that needs to be incorporated with the mastectomy. For NSM, an inframammary incision provides good access, although patients with documented retroareolar DCIS are not suitable for this approach. Coring out the duct tissue behind the nipple, submitted separately for pathology, can occasionally demonstrate DCIS and necessitate a return to the operating room for excision of the nipple. For DCIS, prophylactic contralateral mastectomy does not hold a survival benefit in women that do not have a defined genetic predisposition for breast cancer [31].

In those women who undergo surgical management of DCIS, there is a risk of developing persistent pain at the surgical sites [32]. Importantly, persistent pain after lumpectomy may be as prevalent as pain after total mastectomy, leading to disability and psychological distress, which is often resistant to management. Prospective population-based data have demonstrated significant patient and surgical influences on pain, with remarkably high levels of chronic pain 4 and 9 months after breast surgery [33]. Many of these data have been collected in women with invasive cancer, not purely DCIS, and so the incidence of post-operative symptoms after resection of DCIS alone is uncertain but unlikely to be very different from that of other breast surgery.

11.6.3 Margins

The goal in margin-negative resection is to remove the targeted lesion with a margin of normal breast tissue. The optimal margin width remains unclear and an area of controversy. The margin of resection required has long been debated, with the UK NICE guidelines published in 2009 [16], which recommend a minimum 2 mm radial margin for patients undergoing BCS for DCIS, concordant with meta-analysis evidence [34]. Recently, US guidelines have changed from the traditional, wider, margins to a consensus that a 2 mm margin is sufficient for DCIS [35]. Re-excision should be considered if the margin is less than 2 mm after a discussion with the patient. The British Association of Surgical Oncology recommends that units develop local guidelines. Of note, not all of the extent of DCIS necessarily bears histological (and radiological) calcification, and imaging techniques tend to underestimate disease extent in at least a substantial proportion of patients [13, 14]. Nevertheless, even with multiple bracketed localisation techniques, disease may be present beyond that anticipated. For this reason, surgical re-excision is more frequently required than for invasive disease; a retrospective study of hospital statistics in the English NHS reports 29.5% of patients with DCIS had at least one reoperation [36]. Unfortunately, most of the evidence for optimum margin width comes from observational studies. In the literature, positive margins are well accepted to increase local recurrence. The importance of positive anatomically non-breast margins (anterior/skin and posterior/pectoral fascia) remains a point of debate. If a wide local excision incorporates full thickness breast parenchyma, the only tissue anterior to the excision cavity is subcutaneous tissue and skin, which, by definition, does not contain breast parenchyma. One poll showed the variability in margin widths for surgeons in the UK and explored the different techniques surgeons use for re-excision of a positive anterior margin (scar + skin, anterior margin + skin, anterior margin + skin + adjacent tissue, all margins including skin) [37].

Importantly, it appears that margins greater than 2 mm in women treated by breast conservation and external beam radiotherapy do not confer an advantage in terms of reduced risk of recurrence. Previously, a meta-analysis of trials for the effect of margin status on local recurrence after breast conservation and radiotherapy for DCIS [34] demonstrated that negative margins significantly reduced the risk of ipsilateral recurrence when compared with a close or unknown margin (OR 0.59 and 0.56 respectively). Where margins were specifically measured, a 2 mm margin was superior to a margin of less than 2 mm (OR 0.53) but not significantly different to a margin >5 mm [34].

11.6.4 Lymph Nodes

In the UK, NICE guidelines recommend that sentinel lymph node should be considered for patients undergoing mastectomy, as this procedure cannot be undertaken subsequently if unanticipated invasive disease is detected histologically [16]. Some also consider sentinel lymph node evaluation in patients undergoing oncoplastic reconstruction where extensive tissue mobilisation is planned. If an occult invasive malignancy is found, the tissue mobilisation can interfere with the lymphatic drainage of the breast and may result in inability to accurately stage the axilla.

When local excision is performed for DCIS, SLN biopsy is possible as a subsequent procedure if invasion is identified on final pathology. In a meta-analysis [38], Ansari and colleagues reported an overall 3.7% nodal positivity rate for patients with a definitive postoperative diagnosis of pure DCIS, although a large retrospective review in the UK identified node positivity in only 0.2% of cases of screen-detected DCIS [39]. While the routine use of sentinel lymph node biopsy in DCIS has been debated, in patients with pure DCIS, lymph node status has failed to predict inferior outcomes and hence should not change subsequent management.

11.6.5 Radiation

Unlike invasive breast cancer, radiation therapy is very rarely used following mastectomy for DCIS with a rate of less than 1% [40]. The indications appear to be close margins and large tumour size, in a large national UK survey of nearly 10,000 cases of DCIS, with no recurrences at 5 years follow-up.

In contrast, the majority of women with DCIS undergo breast conserving surgery, for whom radiotherapy is offered as adjuvant therapy in 1/3–2/3 of patients, although there is low consensus as to how best to select women for adjuvant radiotherapy. Whole breast radiotherapy following breast conserving surgery (Table 11.2) reduces the local recurrence by more than half from 28.1% to 12.9% and reduces the incidence of invasive disease from 11.0% to 5.0% at 10 years in meta-analysis [41] based on key randomised prospective trials [2, 42–44]. More recently, other retrospective cohort studies [45] or randomised trials of radiotherapy or not after surgery [46] of low-risk DCIS have suggested lower levels of recurrence than with surgery alone, but still a marked effect of radiotherapy (Table 11.2).

However, while radiotherapy halves breast recurrence, it does not appear to alter long-term breast cancer-specific survival [47]. The benefits of radiotherapy may be offset by the increased risks of lung, oesophageal and contralateral breast cancers, cardiovascular risks and, rarely, (0.1%) angiosarcoma based on historical studies of radiotherapy and DCIS [41]. While there may be no demonstrable survival advantage of breast radiotherapy, conversely there is no excess mortality from the use of radiotherapy in the setting of DCIS [41].

The survival advantages and cosmetic benefits seen for hypofractionation of radiotherapy for invasive breast cancer in large Canadian, UK and US trials may be expected to pertain to adjuvant radiotherapy for DCIS. The potential for partial breast radiotherapy (whether external beam, brachytherapy or intraoperative radiotherapy) for DCIS has not been fully explored.

Table 11.2 Recurrence of breast neoplasia with or without adjuvant radiotherapy

	Study	DCIS features	Locoregional recurrence no radiotherapy	Locoregional recurrence with radiotherapy
Wong [45]	Retrospective cohort	≤1 cm size >1 cm margin Grade I, II	15.6% at10 years	
McCormick [46]	RTOG 9804	≤2.5 cm size ≥3 mm margin Grade I, II	6.7%	0.9%
Correa [41]	Meta-analysis		18% at 5 years 28.1% at 10 years	8% at 5 years 12.9% at 10 years
Stuart [49]	Meta-analysis		24.7% at 10 years with tamoxifen	14.4% at10 years

11.6.6 Endocrine Therapy

There is evidence from one placebo-controlled trial, NSABP B-24, in the USA, that in pre- and postmenopausal patients treated for DCIS with lumpectomy and adjuvant radiotherapy, the addition of tamoxifen reduces the risk of ipsilateral local recurrence by 30% and of contralateral breast cancer by 50% [48]. The absolute risk at 5 years of any (invasive or non-invasive) breast cancer event was small (tamoxifen arm 8% and placebo arm 13%). Survival was not influenced by treatment. Another complex trial design examined the use of tamoxifen versus no adjuvant therapy following complete local excision of DCIS in the absence or presence of radiotherapy [42]. In the absence of radiotherapy, tamoxifen was, again, associated with a 30% overall reduction in breast events through reduction in DCIS recurrence as well as contralateral DCIS and invasive disease events. Tamoxifen was, however, ineffective in preventing ipsilateral invasive recurrence, and in the presence of radiotherapy, tamoxifen also appeared ineffective. Survival was not improved by the addition of radiotherapy or tamoxifen on top of surgery alone in this trial, with breast cancer accounting for only 20% of all deaths (2% breast deaths and 11% overall deaths) [42]. Overall, meta-analysis including these trials suggests a modest additional benefit of tamoxifen over a combination of breast conservation and breast radiotherapy for local recurrence with a reduction from 14.1% to 9.7% [49].

Recently, anastrozole, an aromatase inhibitor (AI), has been compared to tamoxifen in postmenopausal women with DCIS. In NSABP B-35 which enrolled 3104 postmenopausal women who had undergone lumpectomy with confirmed clear margins and subsequent adjuvant radiation for DCIS, anastrozole treatment was associated with a small but statistically significant improvement in breast cancer-free interval compared to tamoxifen (HR 0.73 [95% CI 0.56–0.96], $p = 0.023$), although disease-free survival was the same at 120 months (HR 0.89 [95% CI 0.75–1.07], $p = 0.21$) [50]. Among women <60 in this study ($n = 1447$), anastrozole was associated with significant improvements in breast cancer-free interval and disease-free survival compared to tamoxifen, with hazard ratios (HR) of 0.53 (95%CI 0.35–0.80) and 0.69 (95% CI 0.51–0.93), respectively. However, the International Breast Intervention Study (IBIS) II trial, which enrolled 2980 postmenopausal women with DCIS who had undergone lumpectomy to achieve clear margins +/− radiation, failed to demonstrate an improvement with the AI compared with tamoxifen/placebo (HR 0.89 [95% CI 0.64–1.23], $p = 0.49$) [51].

The reduction in contralateral disease and potentially of local recurrence of DCIS with endocrine therapy needs to be weighed against the relatively common side effects of tamoxifen (hot flashes, DVT and endometrial cancer) or aromatase inhibition (hot flashes, arthralgia). The quality of life impacts of symptoms secondary to endocrine therapy and the other diseases associated with these agents give pause for thought. As a result of the side effects, adherence to endocrine therapy is poor; only 70% of women in the IBIS II trial were still taking their endocrine agent at 5 years [51]. Data from a Canadian cohort [52] suggest that as few as 26% of women will take tamoxifen as adjuvant therapy which, if extended to the wider community, would diminish the value of adjuvant endocrine therapy for DCIS. However, for one woman to benefit, 15 women with breast cancer need to be treated with endocrine therapy [53].

Overall, by meta-analysis of 10-year event rates in 9404 women with DCIS, the event rate was 14.4% following breast conserving therapy + radiotherapy but nearly twice that at 24.7% after breast conserving therapy + tamoxifen [49].

11.6.7 Neoadjuvant-Targeted Therapy

Neoadjuvant therapy has become standard of care for downstaging both the primary and nodal disease for selected patients with invasive breast cancer, but there is little evidence for its use in DCIS. Although the issue of nodal disease is not relevant for DCIS, theoretically reducing the size of DCIS could allow the option of conservation rather than

mastectomy as for invasive breast cancer. For DCIS, targeting the oestrogen receptor or HER2 receptor preoperatively may have theoretical appeal. The CALGB 40903 trial whereby 6 months of neoadjuvant letrozole has tested the potential benefits of this AI to downstage DCIS in selected postmenopausal women. However, given the time frames for DCIS to recur or develop invasive disease, this currently experimental approach will take some time to report outcomes.

11.7 Recurrence

11.7.1 Clinical Factors

Symptomatic presentation of DCIS is associated with higher local recurrence rates [2, 43], with a relative risk on meta-analysis of 1.35 (95% CIs 1.12–1.62) [54]. The risk of recurrence of DCIS decreases with age, independent of other clinical and pathological factors; young women have a higher overall risk and particularly a higher subsequent invasive recurrence rate [55], although the cut-off varies within individual studies. Given the predominance of DCIS in a screen-detected population (usually >50 years historically), it is largely from retrospective data sets that a higher-risk age cut-off of 35 is apparent [47]. While family history may be associated with a higher risk of local recurrence, socioeconomic status and ethnicity do not appear to be associated (unlike for several forms of invasive breast cancer) [47].

11.7.2 Pathology Factors

Extent (size) of DCIS has been associated with an increased risk of DCIS recurrence in both the randomised controlled trial (RCT) and cohort study setting. Tumour size greater than 2 cm compared to <0.9 cm was associated with increased risk of local recurrence (HR 2.67, 1.66–4.30) in the UK/Australia and New Zealand 2 × 2 design RCT of tamoxifen and radiotherapy [44]. Similarly, extent >1.5 cm was shown to be a risk for local recurrence in a large case series (2037) of women treated at a single cancer centre [56].

The presence of DCIS at the resection margin in breast conservation specimens increases the risk of local recurrence, whether or not radiotherapy is administered. In a meta-analysis of 4660 women treated with breast conservation and radiotherapy from 22 trials [34], there was a two thirds reduction in risk of local recurrence for negative compared with positive margin involvement (OR 0.36, 0.27–0.47). While no tumour on ink is acceptable at least in some countries for invasive breast cancer margins, a margin of 2 mm between the DCIS and resection appears to be superior to 1 mm or no tumour (DCIS) on ink in reducing the odds of recurrence (OR 0.53, 0.26–0.96) [34], although margins up to 10 mm do not confer additional benefits.

Grade of DCIS is difficult to assess consistently between even experienced pathologists; the UK NHS BSP pathology EQA scheme showed moderate reproducibility in DCIS when assessed on slides from a single block [57], but data in the «real-life» setting are less consistent. The issue is complicated further with different systems to grade DCIS, albeit that DCIS grade is not typically variable within an individual lesion [58]. The solid histological subtype of DCIS appears to carry an increased risk of local recurrence over papillary and micropapillary subtypes [35]. Indeed, comedo necrosis is often a feature associated with high-grade DCIS, and at least in some older clinical trials, the presence of comedo necrosis has been associated with increased risk of DCIS recurrence (HR 2.21, 1.52–3.20) [2].

Multifocality (using a definition of 5 mm separating two foci of DCIS) has been associated with local recurrence, independent of other pathology features both in the clinical trial setting (HR 2.62) [59] and cohort series (HR 1.97, 1.27–3.02) [60]; the risk, however, appears to be abrogated in part by use of radiotherapy [41] such that breast conservation can still be considered appropriate for such patients.

11.8 Prognostic Scores

Following the subtyping of invasive disease, it now appears that similar molecular subtyping may be achievable and clinically meaningful for DCIS. Progression from DCIS to invasive disease seems to be related to the intrinsic subtype of the DCIS, reflecting distinct evolutionary pathways. A small proportion of preinvasive expression profiles appear to resemble those of invasive breast cancer with the DCIS microenvironment potentially also involved. This raises the possibility that such subtype-specific molecular markers could predict risk of progression [61].

In practical terms, integrating clinical and pathological factors is desirable to predict which DCIS may or may not recur or which patients may develop invasive disease. However, in the breast-screening era, such a prognostic scoring system has not been achieved, and thus consideration has been given to molecular markers including oestrogen receptor (ER) progesterone receptor (PR), HER2 and markers of proliferation. Based on retrospective series, ER-negative DCIS has a higher rate of recurrence (12.2%) than ER-positive DCIS (3.7%) at 5 years [62]. HER2-positive DCIS is associated with an increased risk of recurrence of the DCIS even when corrected for use of radiotherapy [63, 64]. The NSABP B-43 trial examining the effect of two doses of adjuvant trastuzumab concomitant with radiotherapy for HER2+ DCIS is of interest in this regard (clearly trastuzumab as therapy for DCIS is not considered a standard of care). High proliferation as assessed by Ki67 expression has been linked to an increased risk of local recurrence even adjusting for radiotherapy [64]. All these trials suffer somewhat from short length of follow-up, given that DCIS progression to invasive disease is recognised to take more than 40 years in some cases [65].

Following on from the invasive breast cancer revolution in molecular phenotyping, integrating molecular markers and multigene expression scoring have become possible even from formalin-fixed paraffin-embedded clinical material. From the

biomarker point of view, it has been proposed that expression of p16, cox2 and Ki67 (with a cut off of 10%) is associated with a higher (19.6% vs 4.1%) risk of subsequent recurrence as invasive disease in a retrospective cohort of some 1162 women treated by lumpectomy alone [66]. However, more recent interest has focused on the Oncotype DCIS score (Genomic Health, CA, USA) derived from the invasive breast cancer scoring system of examining proliferation markers, ER and HER2. The Oncotype DCIS 12 gene score, like the invasive breast cancer score from which it was derived, generates a low risk (<39), intermediate risk (39–54), or high risk (>55) score on a scale of 0–100. It has been applied to two data sets of patients treated with breast conservation alone, the ECOG E5194 trial [67] and an Ontario cohort [68], respectively, totalling 898 patients. Within these data sets, the DCIS gene score has been reported to be an independent predictor of local recurrence going beyond conventional predictive factors such as age, size, subtype and multifocality. However, while clear margins were required for the data analyses, the historical nature of the data sets and the relatively high local recurrence rates have hindered widespread adoption.

For 689 women treated with breast conservation and radiotherapy (median follow-up of 9.2 years), the Oncotype DCIS score was significantly associated with risk of local recurrence (HR 2.42) although there was no interaction between the DCIS score and radiotherapy [68]. Age < 50 years, tumour size >1 cm and multifocality were independent risk factors for local recurrence. Use of a DCIS risk score, which could help quantify the risk of recurrence, may contribute to individual patient decision making in the future.

Given that the recurrence rate is only 0.9% 7 years after radiotherapy for low-risk patients with DCIS based on grade and size [46], the true value of any genomic test may be to distinguish which patients will benefit from radiotherapy or even which patients benefit from any intervention at all.

11.9 Survival

Death from breast cancer after a diagnosis of DCIS is rare: 1.1% at 10 years and 3.3% at 20 years in one large US population-based study. Young-age women (with a diagnosis of DCIS before the age of 35) and black women had a worse prognosis [47]. ER negativity, high grade, comedo necrosis and larger tumour size were associated with increased risk of death from breast cancer [47]. Surgery is associated with improved survival for intermediate and high-grade DCIS, but not for low-grade DCIS [69]. However, mastectomy versus breast conservation was not associated with a significant difference in survival [47]. Despite the reduction in local recurrence, there is data indicating that use of radiotherapy is not associated with a survival advantage [47], at least with the current duration of follow-up available from most studies. However, many still consider the prevention of invasive disease after treatment for DCIS a key issue as the minority of women who do develop invasive disease have relatively poor survival from the invasive breast cancer [2, 43].

11.10 Future Perspectives

Along with tailoring future treatment and selection of those patients that may benefit from less intervention (active surveillance rather than surgery, omitting radiotherapy and/or avoiding endocrine therapy), other options may emerge. For example, the concept of vaccine trials against HER2 for DCIS is attractive [70] and may further change the outlook for women with this diagnosis.

11.11 Conclusions

DCIS is currently a catch-all diagnosis for a form of non-invasive breast neoplasia with particular histological features but which represents a wide spectrum of conditions with potential for overdiagnosis and overtreatment in some. Despite concerns about overdiagnosis and overtreatment, surgery remains the mainstay of treatment with adjuvant radiotherapy reducing by half local recurrence of DCIS or the development of invasive disease for breast conservation patients and endocrine therapy also protective. The tailoring of treatment on an individual patient basis is less certain than for invasive breast cancer, but prognostic and predictive biomarkers may improve therapy selection for women in the future.

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