NATIONAL BREAST CANCER CENTRE
Incorporating the
Ovarian Cancer Program

The clinical management of ductal carcinoma in situ, lobular carcinoma in situ and atypical hyperplasia of the breast

Royal Australasian College of Surgeons

RCPA
The Royal College of Pathologists of Australasia

The Royal Australian and New Zealand College of Radiologists

The Cancer Council Australia

Breast Cancer Network Australia

The clinical management of ductal carcinoma in situ, lobular carcinoma in situ and atypical hyperplasia of the breast

First Edition

Prepared by the
National Breast Cancer Centre
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This document provides recommendations regarding appropriate practice, to be followed subject to the clinician's judgement and the patient's preference in each individual case.

The information contained in this document is designed to assist decision making and is based on the best evidence available at the time of production.

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FOREWORD

Evidence-based reports and recommendations regarding clinical practice serve as a reference for experienced practitioners and as a resource for clinical trainees. Such recommendations should take into account what is feasible in current practice and recognise that results obtained in controlled clinical trials may not always be realised in routine practice.

The recommendations contained in this document address the management of the following conditions: ductal carcinoma in situ (DCIS), atypical ductal hyperplasia (ADH), lobular carcinoma in situ (LCIS) and atypical lobular hyperplasia (ALH). They bring together the conclusions of two separate working groups established by the National Breast Cancer Centre – the DCIS Working Group and the LCIS and AH* Working Group – supported by the National Breast Cancer Centre's Secretariat.

Currently about 1200 women are diagnosed with DCIS each year in Australia.[1] DCIS is not an invasive cancer; some would say that it is not a cancer at all. Nevertheless, its close association with invasive breast cancer has serious implications for women who develop DCIS. There is a need to achieve consensus among health professionals about the nature of this disease and its management.

The increasing frequency of diagnosis of DCIS associated with mammographic screening programs underlines the need for reliable information about this condition for clinicians and consumers. Among clinicians, there will be many who are already familiar with the evidence and the principles presented here; for others, the presentation of relevant evidence may provide a clearer understanding of the management of this peculiarly difficult condition.

LCIS and the atypical hyperplasias – ADH and ALH – are also associated with an increased risk of invasive breast cancer. It therefore seemed

* atypical hyperplasia

appropriate that these conditions should be considered together with DCIS in relation to the management and subsequent risk of invasive breast cancer. The National Breast Cancer Centre's DCIS, LCIS and AH Working Groups and the Early Detection and Diagnosis Expert Advisory Group have paid particular attention to the emotional and psychological needs of women diagnosed with DCIS, ADH, LCIS or ALH. In particular, the confusion caused by the term 'carcinoma' (albeit *in situ*) in relation to DCIS and LCIS, and the uncertainty of outcome after treatment can contribute to a psychological morbidity which is comparable to that experienced by women with invasive breast cancer. The provision of appropriate support for women diagnosed with DCIS, ADH, LCIS or ALH is therefore an important component of management, and is addressed in this document.

Some of the clinical studies identified in this document are not yet mature, and revising the evidence and recommendations as new data emerge is an important future objective. Health professionals who are involved in the management of the breast conditions addressed here also have a responsibility to consider new information when it becomes available. Relevant research published up to the end of 2000 has been considered for inclusion here and, where appropriate, evidence published up to early 2003 has also been included. It is intended that the document will be updated in 2005, resources permitting.

Dr Colin Furnival
Chair
DCIS Working Group

LIST OF ABBREVIATIONS

ADH	atypical ductal hyperplasia
AH	atypical hyperplasia (ductal and/or lobular)
ALH	atypical lobular hyperplasia
CEA	carcinoembryonic antigen
CLE	complete local excision
DCIS	ductal carcinoma in situ
EFS	event-free survival
EORTC	European Organisation for Research and Treatment of Cancer
ER	oestrogen receptor
FNAB	fine needle aspiration biopsy
GP	general practitioner
Gy	Gray (unit of radiation dosage)
HR	hazard ratio
HRT	hormone replacement therapy
IBIS	International Breast Cancer Intervention Study
IBT	ipsilateral breast tumour
IBTR	ipsilateral breast tumour recurrence
LCIS	lobular carcinoma in situ
NHMRC	National Health and Medical Research Council
NSABP	National Surgical Adjuvant Breast and Bowel Project
RFS	recurrence-free survival
VNPI	Van Nuys Prognostic Index

IMPORTANT NOTICE

This document provides recommendations regarding appropriate practice, to be followed subject to the clinician's judgement and the woman's preference in each individual case. The information contained in this document is designed to assist decision making and is based on the best evidence available at the time of production.

Research evidence was reviewed up until late 2000. Where appropriate, evidence published up to early 2003 has also been included. Data about many aspects of carcinoma in situ are continually emerging, and additional information about management is likely to be forthcoming from future clinical trials.

Resources permitting, it is envisaged that the document will be updated in 2005.

INTRODUCTION

This document is aimed at health professionals involved in the care of women with ductal carcinoma in situ (DCIS), atypical ductal hyperplasia (ADH), lobular carcinoma in situ (LCIS) and atypical lobular hyperplasia (ALH). Its overall purpose is to inform the reader about current best practice in the diagnosis and management of these conditions. Several evidence-based recommendations have been made with the intention that these will:

- assist the treatment decision-making process
- inform all involved in the care of women with DCIS, ADH, LCIS and ALH of the current evidence regarding the diagnosis and management of these conditions in Australia
- enhance quality assurance and audit processes relating to these conditions.

Recommendations and key points are made regarding diagnosis, histopathology, prognosis, principles of treatment, management options and women's information and support needs.

Development of the recommendations

Ductal carcinoma in situ

This document was developed by the DCIS Working Group, a multidisciplinary group convened by the National Breast Cancer Centre. This group consisted of representatives from surgery, radiation oncology, diagnostic radiology, medical oncology, pathology and consumer groups.

The working group defined the aim and scope of this document. Members with expertise in a particular area were requested to write each section using the most robust evidence available. A systematic review of the prognosis and management of women with DCIS was commissioned.[2]

Each chapter and section was reviewed and the significance of the evidence was considered and discussed by the whole working group. Agreement was sought on the levels of evidence attributed to each recommendation using the National Health and Medical Research Council (NHMRC) recommended levels of evidence.[3]

The evidence that has been considered here has come from a number of different sources. Each recommendation is based on a review of the available evidence by each author. Evaluation of treatment strategies is restricted by the lack of completed, published, randomised controlled trials. For example, there are no randomised trials of treatment versus non-treatment of DCIS, and it is highly unlikely that this type of evidence will ever be available. While there are a growing number of trials investigating the role of adjuvant therapy in the management of women with DCIS, at present there is limited Level I and Level II evidence relating to *in situ* disease. However, new data about the management of women with DCIS are emerging from ongoing clinical trials.

Atypical ductal hyperplasia, lobular carcinoma in situ and atypical lobular hyperplasia

The information about the management of ADH, LCIS and ALH was developed with multidisciplinary input from the National Breast Cancer Centre's LCIS and AH Working Group, and is largely based on Level III and Level IV evidence.

Levels of evidence

The NHMRC evidence rating system[3] used in the review of scientific literature in this document is as follows:

Level I	Evidence obtained from a systematic review of all relevant randomised controlled trials
Level II	Evidence obtained from at least one properly designed randomised controlled trial

Level III-1 Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)

Level III-2 Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group

Level III-3 Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group

Level IV Evidence obtained from case series, either post-test or pre-test and post-test

Level I evidence represents the 'gold standard'. However, Level I and Level II evidence is not available for all areas of practice.

In this document, Level III-1, Level III-2 and Level III-3 are all referred to as Level III evidence.

If published, peer-reviewed evidence was not available at the time of preparation, expert consensus was used to provide guidance for clinical practice. It should be noted that, as further evidence emerges, opinions may change.

Key points have been highlighted to draw the reader's attention to other issues of importance.

Consultation and feedback

Since acceptability of the recommendations by relevant stakeholders is a critical first step towards their implementation, consultation is an integral part of the development process. Prior to completion, the document was

sent to a number of experts in the field and to the following professional colleges and organisations for comment:

- Royal Australasian College of Surgeons
- Royal College of Pathologists of Australasia
- Australasian Society of Breast Physicians
- Royal Australian College of General Practitioners
- The Royal Australian and New Zealand College of Radiologists
- The Royal Australian and New Zealand College of Radiologists (Faculty of Radiation Oncologists)
- Australian Institute of Radiography
- Breast Cancer Network Australia
- Cancer Screening Section, Primary Prevention and Early Detection Branch, Department of Health and Ageing.
- The Cancer Council Australia

Comments received were considered by the working groups, and the document was refined accordingly.

Endorsement

The following professional colleges and organisations have officially endorsed these recommendations:

- Royal Australasian College of Surgeons
- The Royal Australian and New Zealand College of Radiologists
- The Royal Australian and New Zealand College of Radiologists (Faculty of Radiation Oncologists)
- The Royal College of Pathologists of Australasia
- The Cancer Council Australia
- Breast Cancer Network Australia

Dissemination and implementation

The National Breast Cancer Centre will be responsible for disseminating, implementing, evaluating and updating this document.

An initial print run will be disseminated to relevant professional groups free of charge. Copies will also be made available to allied health organisations, State and Territory health authorities, breast cancer treatment centres, consumer and patient groups, professional colleges and associations, public policy makers, health economists and professional journals.

The document will be included on the National Breast Cancer Centre's website and its availability will be advertised through the National Breast Cancer Centre's newsletters.

Lastly, the recommendations will be promoted through presentations at relevant professional meetings, conferences and submissions to professional journals.

Local considerations

The recommendations have been framed in a manner that is flexible and mindful of variations in local conditions and resource considerations. In particular, some of the psychosocial recommendations may currently be difficult to implement due to a shortage of psychiatrists or clinical psychologists. Strategies to provide adequate supportive care services are being trialled through organisations such as the National Breast Cancer Centre, the Commonwealth Department of Health and Ageing and the Cancer Strategies Group.

Disclaimer

Readers should be mindful that recommendations may not be appropriate for use in all circumstances. A limitation of recommendations regarding clinical practice is that they may appear to simplify clinical decision making.[4] Decisions to adopt any particular recommendation must be made by the practitioner in the light of: available resources; local services, policies and protocols; the particular patient's circumstances and wishes; available personnel and equipment; clinical experience of the practitioner; and knowledge of more recent research findings.

Consumer information

Consumer information based on these recommendations will be available in early 2004. Clinicians are encouraged to promote the use of consumer guides and to discuss the information with the woman as required. Consumer guides will be available in printed format and on the National Breast Cancer Centre's website at www.nbcc.org.au

SUMMARY OF RECOMMENDATIONS

The following table provides a summary of the recommendations presented in this document. The recommendations should be considered in the care and management of women with DCIS. Readers should refer to the appropriate sections to understand the context of this evidence.

Recommendation	Level of evidence	Section	Reference
DIAGNOSIS OF DCIS			
Image-guided core biopsy is the recommended diagnostic method for DCIS.	IV	1.2	5
PSYCHOSOCIAL SUPPORT			
Women should be offered appropriate support and information about their diagnosis and treatment to enhance their emotional wellbeing and physical recovery.	I	1.4	6–8
SURGERY			
It is essential to ensure that clear margins are obtained when DCIS is excised. If the margins are involved, further excision is required.	II	1.5	9,10
Axillary dissection should not be performed in the management of DCIS unless invasion is suspected.	III		1,11–17

Recommendation	Level of evidence	Section	Reference
ADJUVANT RADIOTHERAPY			
The addition of radiotherapy after complete local excision reduces the risk of subsequent invasive breast cancer and recurrence of DCIS for all pathological subgroups of patients.	II	1.6	2,18–21
For women with good prognostic features, the overall clinical benefit of adjuvant radiotherapy may be small. In these circumstances, the woman may choose to omit radiotherapy.	II		9,10
Women with high-grade DCIS with necrosis, close margins and larger lesions have a relatively high risk of recurrence with conservative surgery alone, and adjuvant radiotherapy is therefore recommended.	II		18,22,23
RISK OF RECURRENCE			
The risk of recurrence of DCIS or subsequent invasive breast cancer following complete local excision, with or without radiotherapy, will vary depending on identified predictive factors, such as nuclear grade, size, presence or absence of necrosis, margin width and other prognostic factors. All these factors should be considered when discussing the risk of recurrence and management options with the woman.	II	1.9	19

CHAPTER 1 DUCTAL CARCINOMA IN SITU

1.1 NATURAL HISTORY

Ductal carcinoma in situ (DCIS) is an abnormal proliferation of cells in the mammary ducts. While cells display abnormal cytological features similar to those of invasive breast cancer, unlike invasive breast cancer, DCIS is confined within the duct system. If left untreated, DCIS may increase the risk of developing invasive breast cancer later in life.[24] An understanding of the natural history of DCIS is still evolving. However, it is believed to be a unicentric process, most commonly confined to a single segment of the breast, and therefore usually amenable to complete surgical excision without the need for mastectomy.[25,26]

The prevailing view of the development of DCIS is that there is a spectrum of epithelial proliferative lesions in the breast, with duct epithelial hyperplasia without atypia at one end and high-grade DCIS at the other. Within this spectrum, there are intermediate lesions, such as atypical ductal hyperplasia (ADH), and low- and intermediate-grade DCIS. However, this classification system is based upon morphological features and is being challenged by recent genetic studies.

Molecular genetic techniques, such as comparative genomic hybridisation, have been employed to characterise the genetic changes in DCIS. These have shown that low-grade DCIS is associated with loss of genetic material of *16q, 17p* and *22q,* and with gains of *17q, 6q* and *20q*.[27,28] Similar genetic alterations have been identified in low-grade invasive breast cancer, supporting the view that DCIS is a precursor lesion to invasive disease.[29] By contrast, high-grade DCIS shows more genetic changes than low-grade DCIS: these occur at different sites to low-grade DCIS and are similar to changes seen in high-grade invasive breast cancer.[30] Interestingly, ADH – which shares common morphological

features with low-grade DCIS – also shares similar genetic changes, supporting the view that the distinction between ADH and low-grade DCIS may be artificial.[31]

As more studies into the genetic basis of DCIS become available, it is likely that future classification systems for DCIS will reflect both morphological features and genetic alterations linked to clinical outcomes, such as the association with invasive breast cancer.

Occurrence

Before the widespread availability of mammography, diagnosis of DCIS was uncommon, comprising only 2% of all breast malignancies.[32]

During the period 1993–1998, the number of women recorded with a diagnosis of DCIS in Australia increased by over 80%.[24] This was mainly due to two factors: increased numbers of women receiving mammographic screening, and improved data collection.[24]

Almost 1200 women were diagnosed with DCIS in Australia in 1998. Approximately 58% were diagnosed by the BreastScreen Australia Program and the remainder through other mammography services.[24] DCIS is usually not detected as a palpable lesion.

The ratio of DCIS to invasive breast cancer, as detected by BreastScreen Australia, is 1:4.[33] Like invasive breast cancer, DCIS is an extremely rare condition in men.[34]

Age incidence of detected ductal carcinoma in situ

The incidence of DCIS peaks at an earlier age than invasive breast cancer. During the period 1993–1998, more than half of the women diagnosed with DCIS were 50–59 years of age, with the mean age of diagnosis around 59 years.[24]

Relation to invasive breast cancer

Although women do not die from DCIS, it is known that some women who have DCIS will subsequently develop invasive breast cancer.[35] In rare cases, a woman may die from metastatic disease after treatment for DCIS when no evidence of invasive breast cancer was found. This emphasises the importance of effective treatment for DCIS to minimise the risk of subsequent invasive breast cancer.

While there is no direct evidence that DCIS is a stage of progression from normal epithelial cells to invasive breast cancer, it is widely assumed that this is the case.[36] The high prevalence of *in situ* disease in and around invasive breast cancers supports this hypothesis: approximately two-thirds of invasive breast cancers are associated with *in situ* disease.[36,37] Molecular genetic studies of DCIS indicate changes similar to those seen in invasive breast cancer, giving further support to the theory that DCIS and invasive breast cancer are related diseases.[38-40]

The clinical significance of DCIS lies in the proportion of women diagnosed with DCIS who will eventually develop invasive breast cancer. Historical studies of small numbers of women treated by **biopsy alone** indicate that 14–28% of women diagnosed with DCIS are diagnosed subsequently with invasive breast cancer (**Level IV**).[41-43] These studies had an average follow-up period of 15–21.6 years. However, the applicability of these findings is limited by the fact that the women with DCIS were treated by biopsy alone. At present, it is not possible to identify which cases of DCIS will be associated with a subsequent diagnosis of invasive breast cancer.

Recent studies show a high frequency of invasive breast cancer after surgical excision of DCIS. In a study of mammographically detected DCIS, invasive breast cancer occurred in 13% of women within eight years of complete local excision (CLE) of intermediate-to-high-grade DCIS.[22] Cohort and case-control studies have investigated the risk of women

subsequently developing invasive breast cancer after treatment for DCIS with CLE, CLE plus radiotherapy, or mastectomy. The standardised incidence ratio for a subsequent invasive breast cancer after DCIS has been found to range from 4.5 to 11.7.[44,45] After breast-conserving treatment, the majority of subsequent invasive breast cancers were in the ipsilateral breast.

Although there are no reliable predictors for which women with DCIS will subsequently develop invasive breast cancer, the risk may be greater when the DCIS lesion displays biologically aggressive features, such as central necrosis or high nuclear grade.[46] In some cases, an invasive breast cancer may never occur. It has been suggested that this may be because not all lesions have the same potential to undergo further malignant transformation.[37]

Key points

- The clinical significance of DCIS lies in the proportion of women diagnosed with DCIS who eventually develop invasive breast cancer.
- Estimates indicate that women who have had DCIS are 4–12 times more likely to develop subsequent invasive breast cancer than population norms.[44,45]

1.2 DIAGNOSTIC PATHWAYS

Presentation

Most cases of DCIS are detected by mammography. In a small proportion of women, DCIS is clinically palpable or detected by biopsy as an incidental finding.

Investigations

A recommended pathway for the diagnosis of DCIS is shown in Figure 1.

Clinical examination

DCIS is not usually detectable by clinical examination. Nevertheless, both breasts should be examined to assess clinical features, exclude any other clinical abnormality, and plan initial surgery in conjunction with imaging findings. Ideally, clinical examination should be done in a facility with access to a multidisciplinary team.

Mammography

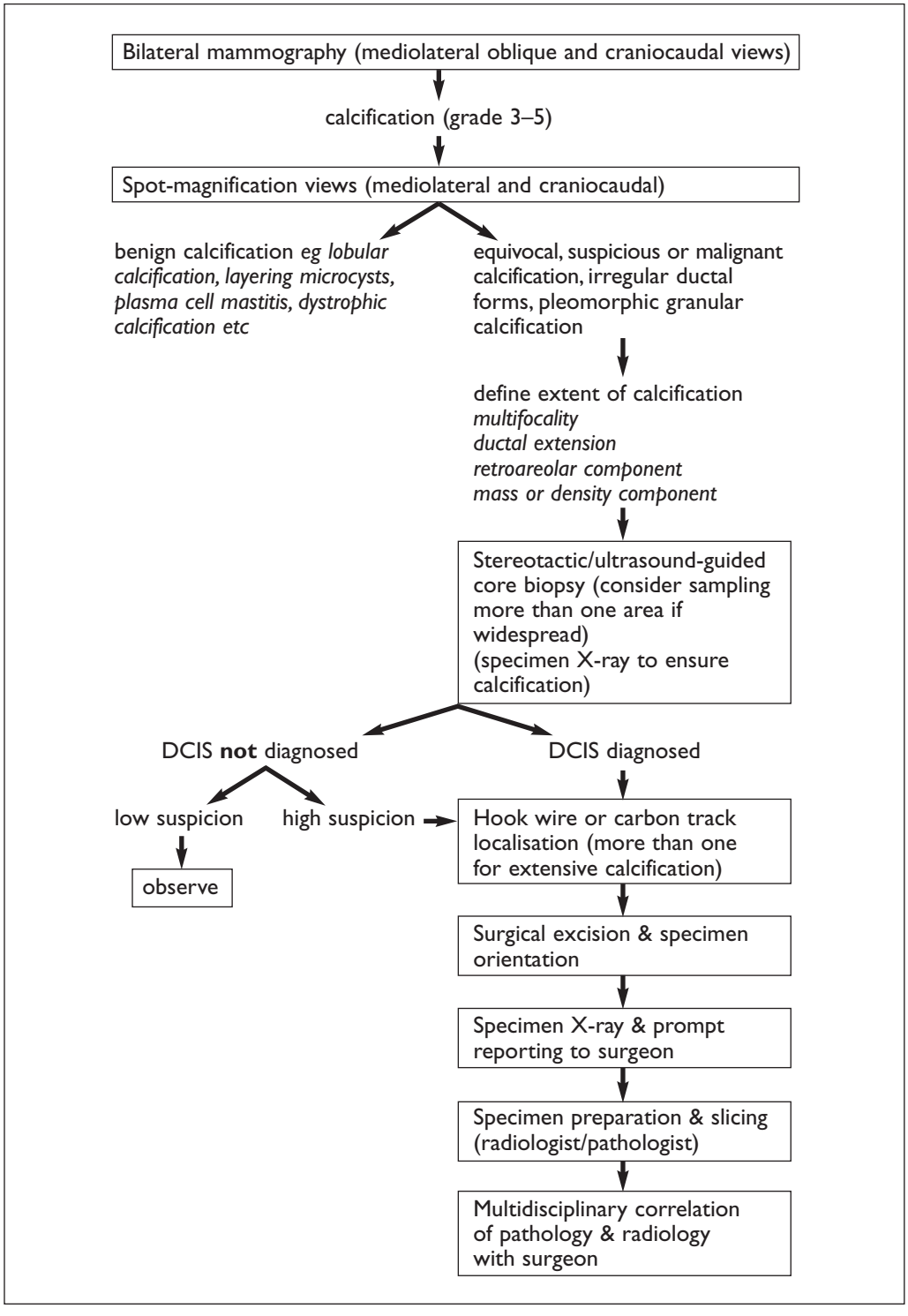
DCIS is most commonly detected as mammographic microcalcification. However, microcalcification is a common finding with numerous benign causes. Within the BreastScreen Australia Program and the National Breast Cancer Centre's *Breast imaging: a guide for practice*,[47] lesions are classified as:

1. no significant abnormality
2. benign findings
3. indeterminate/equivocal findings
4. suspicious findings of malignancy
5. malignant findings.

Calcification graded 3–5 after radiological assessment requires biopsy for pathological evaluation.

High-grade DCIS usually displays linear branching or coarse granular calcification; low-grade DCIS often shows fine granular calcification similar to benign lobular calcification (**Level IV**).[48] In about 10% of mammographically detected DCIS, a mass, density or architectural distortion without calcification is the presenting feature (**Level IV**).[49]

Figure 1 Recommended diagnostic pathway for ductal carcinoma in situ



Mammographic assessment with magnification views defines the extent of calcification, although this often underestimates the full extent of the disease (**Level IV**).[48,49] Widespread calcification may indicate multi-focality or extension along the mammary ducts towards the nipple. In this circumstance, spot compression magnification views of the tissue behind the nipple are indicated. A mammographic density or mass indicates an increased probability of invasion. Although DCIS is seldom bilateral, the contralateral breast should always be assessed.

Ultrasound

In DCIS, diffuse tissue changes are sometimes seen without a focal mass. An ultrasound mass lesion is uncommon with DCIS and, as with a mammogram, usually suggests an invasive component. Calcification is echogenic and can sometimes be detected with high-resolution ultrasound, usually in high-grade lesions. The use of ultrasound should be considered in cases where extensive, high-grade, malignant type microcalcification is present, to facilitate the detection of an invasive component. Stromal changes can be detected with ultrasound in some cases of DCIS.[50] In both scenarios, ultrasound can be used to guide core biopsy.[50]

Key points

- DCIS is most commonly detected as mammographic microcalcification.
- DCIS is not usually detectable by clinical examination. Nevertheless, both breasts should be examined to assess clinical features, exclude any other clinical abnormality and plan initial surgery in conjunction with the imaging findings.

Biopsy

Most DCIS detected by mammography is amenable to image-guided biopsy. All sampling methods have a small false-negative rate and a smaller

false-positive rate. Stereotaxis is usually necessary, as most cases have no ultrasound or clinical findings. Image-guided core biopsy is the recommended diagnostic sampling method for DCIS detected by mammography (**Level IV**).[5]

- **Ultrasound-guided core biopsy**
  When sonographic findings, such as echogenic calcification or a mass lesion, have been identified, ultrasound-guided core biopsy is a useful diagnostic method.

- **Stereotactic core biopsy**
  Stereotactic core biopsy enables histological assessment of the abnormal area, establishes a provisional diagnosis and facilitates planning of the surgical procedure. It can determine whether invasive breast cancer is present. If no invasion is seen on biopsy, CLE is necessary to establish whether invasion is present. Wherever possible, the shortest distance from skin entry point to lesion should be used, to optimise the accuracy of the procedure and to facilitate good cosmesis.

A specimen radiograph should be performed to demonstrate calcification in the core specimens and confirm that a representative sample has been obtained.

Dedicated prone stereotactic tables are expensive and not yet widely available. However, 'add-on', upright stereotactic devices that can be used with a conventional mammographic machine are less expensive and have been demonstrated to increase the positive sampling rate over fine needle biopsy sampling.[51] Core biopsy with an 'add-on' stereotactic device is technically more demanding, but reliable samples can be obtained.[51]

In experienced hands, stereotactic core biopsy has a sensitivity of more than 95% (**Level IV**).[52] Due to the small volume of tissue sampled by core biopsy, low-grade DCIS may be mistaken for ADH, as they have similar

features. A core biopsy that shows ADH should be followed by surgical excision; about 50% of these will prove to be DCIS (**Level IV**)[53,54] (see Section 1.3, page 23 and Section 2.4, page 67, 68).

New technologies, such as vacuum-assisted core biopsy devices, can reduce the already low rate of inadequate sampling associated with conventional core biopsy by producing larger and more representative samples, and can enable differentiation between ADH and DCIS (**Level IV**).[53] Large core biopsy techniques are also being evaluated in Australia.

Occasionally, core biopsy may cause a haematoma, particularly if the woman has a bleeding tendency. This may delay definitive surgery, as the haematoma may obscure the extent of microcalcification.

- **Fine needle aspiration biopsy**
  When a prompt and reliable cytological service is available, stereotactic or ultrasound-guided fine needle aspiration biopsy (FNAB) has the advantage of being quick, sensitive and economical (**Level IV**).[55] FNAB should be used in association with other diagnostic modalities. Used alone, FNAB does not discriminate between *in situ* and invasive disease and should not be used for treatment planning. While FNAB may demonstrate malignant cells, DCIS is more reliably diagnosed by core biopsy or surgical excision.

- **Surgical biopsy**
  Diagnostic excision biopsy is necessary if image-guided techniques are not available, or if a definitive diagnosis has not been obtained using the previous methods. It has the advantage of more extensive sampling and a higher chance of detecting any invasive component. When the lesion is malignant, the additional procedural costs of surgical biopsy are offset if CLE is achieved. Localisation is invariably required for surgical biopsy of DCIS (see Section 1.5, page 31).

Recommendation	Level of evidence	Reference
Image-guided core biopsy is the recommended diagnostic method for DCIS.	IV	5

The radiologist's report

The National Breast Cancer Centre's *Breast imaging: a guide for practice*[47] recommends that a standardised report, such as the sample below, be used for breast imaging.

Radiologist's Report **1. Patient identification details:** **2. Reason for examination:** **3. Number of significant imaging lesions:**			
	Lesion #1	**Lesion #2**	**Lesion #3**
4. Location:			
Side			
Site			
Distance from nipple (U/S)			
5. Size (mm):			
6. Mammography characteristics:			
Not performed			
No abnormality			
Abnormality			
7. Ultrasound characteristics:			
Not performed			
No abnormality			
Abnormality			
8. Correlation with clinical findings:			
Yes/No/No clinical findings			
9. Combined imaging diagnosis:			
10. Classification:			
1. No significant abnormality			
2. Benign findings			
3. Indeterminate/equivocal findings			
4. Suspicious findings of malignancy			
5. Malignant findings			
11. Recommendation for further investigation:			

1.3 HISTOPATHOLOGY

In the clinical management of DCIS, the histopathologist has a role in:

- establishing the pre-operative diagnosis from a core biopsy
- establishing the final diagnosis from a surgical excision specimen
- correlating pathology with mammographic features and ensuring that the radiologically diagnosed affected area is evaluated fully
- measuring the size of DCIS and the distance to the nearest surgical margin
- defining the histopathology features that are prognostic and predictive factors.

The pathology data affecting clinical outcomes for women with DCIS essentially all constitute Level III evidence. This is due to the absence of published detailed pathology data and long-term follow-up in randomised clinical trials. It is hoped that ongoing multicentre randomised controlled trials will provide more substantial evidence of pathological factors that may be used as entry criteria in future randomised clinical trials.

Histopathological classification

The purpose of histological classification following surgical excision is to define the prognostic and predictive characteristics of DCIS.

Traditionally, DCIS has been classified as having either a comedo pattern of ducts distended by large, pleomorphic cells and showing central necrosis, or being of the smaller cell, non-comedo type. More recently, the importance of nuclear grade and the presence or absence of central necrosis have been emphasised over architectural pattern. However, it is possible that all three have relevance as prognostic characteristics.

The Australian Cancer Network guide, *The Pathology Reporting of Breast Cancer*[56] recommends that six characteristics should be recorded for each case of pure DCIS: size, margins, nuclear grade, necrosis, architecture and

calcification. In the histopathology report of DCIS, the following features are important components.

Specimen: type, dimensions and location

The pathology report is often the most accessible source of data. It is therefore essential that the information provided by the surgeon be transcribed onto the report. For clinical, research and medico-legal purposes, the following information should be given as accurately as possible: whether the specimen is a needle core, incisional/excisional biopsy, CLE or re-excision its dimensions in millimetres and its location.[56] It is essential to record details of the breast and quadrant from which the specimen was removed, and the orientation of the specimen marked by the surgeon (see Section 1.5, page 33). In the case of multiple biopsies, effort should be made to relate these precisely to each other and (ideally) to the nipple. The presence of a previous core biopsy track should be noted.

Size

The pathologist should record the maximum diameter of the entire lesion, which may encompass separate foci. The measurement should be taken from the pathology slides, with reference to the gross specimen and the specimen X-ray.

Nuclear grade

As with other nuclear grading systems, high-grade DCIS nuclei (grade 3) are large, show variation in shape, have multiple and/or enlarged nucleoli and increased mitotic figures. Low-grade nuclei (grade 1) are small, round and uniform. The intermediate-grade (grade 2) classification is used for nuclei that fall between high- and low-grade. Australian pathologists have

agreed to follow the criteria for nuclear grading described by Elston and Ellis.[57]

Architectural pattern

This is a descriptive analysis of the visual pattern. High-grade lesions are usually comedo or solid. Low-grade lesions are cribriform, micropapillary, solid or combinations of these. Pure micropapillary patterns may indicate extensive disease within the breast.[58]

Central necrosis

It is important to record whether central necrosis is present in the ducts with DCIS and to distinguish this from the tiny, punctate, non-central apoptosis seen in cribriform and micropapillary lesions, as the latter appears to indicate a less aggressive lesion.[59] As some classifications for clinical care use the percentage of ducts with DCIS that show central necrosis as part of a prognostic index, this percentage should be assessed accurately.[59,60]

Calcification

The presence or absence of calcification in association with DCIS should be reported. If present, the location of each focus and the pathology in that duct should be reported. Correlation with mammography films is essential. Occasionally, calcification may be non-haemato-oxyphillic (Wedderlite) and only demonstrable with polarised light. Finer secretory calcification, and calcification in benign ducts, arteries and stroma should also be reported.

Assessment of distance from the affected duct to the nearest margin of surgical excision

This assessment is particularly important in predicting the likelihood of future local recurrence. It is essential that excision specimen margins are inked and correctly orientated, that the distance to the nearest duct with DCIS is measured carefully and the position of that margin identified. However, as ducts involved in DCIS may pass out of the plane of the section examined, the pathologist cannot be certain of the completeness of the excision. Other complicating factors include the distortion of fatty breast tissue following excision, fixation and processing.

Paget's disease of the nipple

Pagetoid invasion of the nipple and areola by individual or small groups of neoplastic cells is usually associated with a subareolar area of DCIS. Occasionally, the DCIS may be more distant. Associated occult subareolar or more distant invasive breast cancer should be considered.

Hormone receptors

Although hormone receptors can be assessed by immunohistochemistry, there is currently no evidence to recommend routine testing. This should be kept under review, as it is possible that current tamoxifen trials may show significantly different outcomes for women with DCIS who have positive or negative oestrogen receptor (ER) or progesterone receptor (PR) status. If this is the case, research may be needed to determine whether the discrimination between positive and negative hormone receptor status is the same as that currently used for invasive breast cancer. Hormone receptor status can be determined retrospectively using sections from paraffin blocks.

Data collected for research

Data from molecular/genetic studies, hormone receptor immunohistochemistry or other factors should be linked to the original pathology report for possible future use.

Possible diagnostic problems

1. Associated invasive breast cancer. Where larger areas of DCIS have one or more small foci of invasive breast cancer, the components of invasive breast cancer and DCIS should be assessed and reported separately. In other cases, DCIS may have artefactual appearances that mimic invasion.

2. Associated ADH. If ADH is present, this should be described, as it has been shown to increase the risk of subsequent contralateral or bilateral invasive breast cancer.[61]

3. In some cases, it may be difficult to distinguish between DCIS and ADH. The distinction may be aided by following the criteria of Page and Rogers[62] and Page and Anderson.[63] Although Australian pathologists have agreed to follow these criteria, there are currently no Australian data about the reproducibility of the classification of difficult lesions between pathologists.

Summary of essential data that should be stated clearly on the pathology report

Specimen	1. Type	Biopsy: core, incisional, excisional Excision: complete local excision, re-excision
	2. Dimensions	in millimetres
	3. Location	which breast, which quadrant, other localising features
DCIS	1. Size	maximum extent of DCIS in millimetres
	2. Margins	distance from DCIS to nearest surgical margin in millimetres, specifying the margin involved
	3. Nuclear grade	high (3), intermediate (2), low (1)
	4. Necrosis	present, absent, % of DCIS ducts with central necrosis
	5. Architectural pattern	dominant pattern and other patterns, eg solid, cribriform, micropapillary, apocrine
	6. Calcification	present/absent; type: coarse necrotic, fine/secretory in benign ducts (in some cases more detail of size and extent may be needed to allow histo-radiological correlation)
	7. Hormone receptor status (if performed)	oestrogen receptor, progesterone receptor
	8. Tissue sent for research studies: if so, institution where these will be done.	genetic/molecular studies: yes/no, type, immunohistochemistry markers or other markers: yes/no, type

For clarity and completeness a synoptic format of pathology report is recommended.

1.4 PRINCIPLES OF TREATMENT

The purpose of treating DCIS is to eradicate or diminish the risk of subsequent invasive breast cancer. Published data reveal that women diagnosed and treated for DCIS are 4–12 times more likely to develop subsequent invasive breast cancer than women in the general population.[44,45]

It is assumed that if DCIS is left untreated, the risk of invasive breast cancer may be even greater. Given the risk of invasive breast cancer following DCIS and the difficulty in determining which women with DCIS will eventually develop invasive breast cancer, it is recommended that DCIS be treated.

Multidisciplinary care

There is evidence that survival of patients with breast and other cancers is better if they are treated by a specialist who treats a significant number of similar patients, and who has access to the full range of treatment options in a multidisciplinary setting (**Level III**).[64,65] While there are no data regarding the management of women with DCIS in a multidisciplinary setting, it seems likely that benefits would be similar to those for women with invasive breast cancer. It is therefore recommended that, where possible, women with DCIS be managed in a multidisciplinary setting.

In all circumstances, it is important to establish effective lines of communication between relevant specialists and the referring general practitioner (GP).[64,66,67]

The multidisciplinary team addressing treatment issues for women with DCIS should include the following disciplines:

- diagnostic radiology
- pathology
- surgery

- radiation oncology
- supportive care.

The team should also include the woman's GP.

Key point

- Where possible, women with DCIS should be managed in a multidisciplinary setting.

Good communication practices

As with other forms of breast disease, effective communication between a woman with DCIS and her treating clinician is likely to enhance the woman's understanding of the nature of the disease, her treatment options and potential outcomes. Evidence suggests that good communication and the provision of information at the initial and subsequent consultations can reduce psychological morbidity following treatment,[7,8] improve psychological adjustment,[6] increase treatment compliance and enhance satisfaction with care.[68] (For further details see *Psychosocial clinical practice guidelines: providing information, support and counselling for women with breast cancer*).[68]

The woman should be informed at the first and subsequent consultations that:

- DCIS is not invasive breast cancer*
- DCIS does not spread to other parts of the body
- DCIS is associated with an increased risk of subsequent invasive breast cancer, but this may be reduced with appropriate treatment
- not all women with DCIS will ultimately develop invasive breast cancer; at present we are unable to predict which women with DCIS will or will not subsequently develop invasive breast cancer.

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* It is recognised that rare cases of metastatic disease have been recorded after treatment of DCIS. In such cases, it is presumed that associated invasive breast cancer was present but undetected.

The woman should be informed that, for these reasons, DCIS is treated somewhat differently from invasive breast cancer. In particular:

- lymph node dissection is generally not required (see Section 1.5, page 37)
- the absolute benefit of radiotherapy after CLE varies for each patient, based on various histological criteria (see Section 1.6, page 39)
- chemotherapy is not used in the treatment of DCIS (see Section 1.7, page 47)
- the role of tamoxifen and other hormone treatments is uncertain (see Section 1.7, page 47–49).

A treatment plan should be formulated, in consultation with the woman, when the detailed histopathology results are available. The surgeon should discuss the pathology report with the woman. The discussion should address the size or extent of DCIS, its type and grade, the adequacy of surgical margins and the risk of recurrence after various treatment options. Consultation with the radiation oncologist should also occur so the woman can discuss the relative advantages and disadvantages of radiation therapy. Access to accurate and reliable information about treatment options is of major importance to women with breast cancer.[69,70]

Adequate time is a prerequisite for effective communication about the disease and treatment options. A hasty summary of a recommended treatment plan is no substitute for a dialogue in which all treatment options are presented and discussed before a final decision is reached.

The woman's preference is an important factor in reaching a final decision, and she may require time to consider all the treatment options discussed. She should be reassured that taking a week or two to decide on treatment will not make any difference to the outcome, but she should be advised that it would be unwise to take months to reach a decision[71] (see Chapter 3, page 76).

Some women may ask why it is necessary to excise a small focus of DCIS. This question should be discussed in the context of current evidence. Active treatment should be recommended because of the associated increased risk of subsequent invasive breast cancer.[2]

The option of 'no further treatment' post-surgery should be discussed in the context of current evidence and may be considered following excision of small, well-circumscribed lesions with clear margins. Some women may find this an attractive option. However, the risk of local recurrence and subsequent invasive breast cancer must be explained clearly.

If the woman has any difficulty reaching a decision, it may be appropriate to suggest a second opinion from another specialist.

Recommendation	Level of evidence	Reference
Women should be offered appropriate support and information about their diagnosis and treatment to enhance their emotional wellbeing and physical recovery.	I	6–8

Post-treatment support

The woman should be offered continuing support after treatment. The surgeon should discuss any concerns and anxieties the woman may have and enquire about common symptoms of post-treatment morbidity. Continuing support is an integral part of post-operative care and follow-up.

There are limited data about the proportion of women diagnosed with DCIS who experience psychological morbidity after treatment. One study from the United States found that 15% of women with DCIS had potentially clinically significant depression.[72] In Australia, for women with

early invasive breast cancer, rates of depression have been found to range from 10% to 27% at two to six months after diagnosis.[73] Similarly, the prevalence of anxiety has been found to range from 12% to 23%.[74,75] Similar rates of anxiety and depression could occur amongst women with DCIS. It is therefore necessary to enquire specifically about symptoms that indicate psychological morbidity; without enquiry, such symptoms may not be detected. Most women with anxiety or depression will benefit from appropriate treatment.

There are a range of referral options for clinicians who are concerned about the emotional wellbeing of a woman with breast disease and/or her family members, including: counsellors, clinical psychologists and/or psychiatrists.[68] Referral should be arranged in consultation with the woman and her GP (see Chapter 3, page 76).

Clinical trials

Clinical trials are essential in establishing evidence to improve the management of breast diseases. Where available, clinicians should encourage women to participate in a clinical trial for which they are eligible.

Key points

- Women should be informed that DCIS is not invasive breast cancer.
- Women should be informed that DCIS does not spread to other parts of the body.
- Women should be informed that DCIS is associated with an increased risk of subsequent invasive breast cancer; however, this risk will be reduced with appropriate treatment.
- Not all women with DCIS will ultimately develop invasive breast cancer; at present we are unable to predict which women with DCIS will or will not subsequently develop invasive breast cancer.
- There is a need for further clinical trials to explore the effectiveness of treatments for DCIS. Women should be offered the opportunity to participate in clinical trials where available.

1.5 SURGERY

The aim of surgical treatment for DCIS is to ensure complete excision of the detected lesion with the best possible cosmetic result.

When a diagnosis has not been established firmly by core biopsy, excision serves the purpose of a diagnostic biopsy. However, it is always advantageous for the surgeon to have a pre-operative diagnosis, as this facilitates informed discussion with the woman, and planning of the therapeutic procedure.

Key point

- The aim of surgical treatment for DCIS is to ensure complete excision of the detected lesion with the best possible cosmetic result.

Diagnostic excision biopsy/complete local excision

In many cases, the diagnostic excision biopsy will also be the definitive surgical treatment if the lesion is completely excised. CLE is indicated when the size of the lesion in relation to the size of the breast allows for good cosmetic results. In other situations, mastectomy may be indicated (see page 36). If a woman is considering mastectomy, she should be informed that body image is better preserved with CLE.[74,76,77]

Irrespective of whether the procedure is of diagnostic or therapeutic intent, the following principles for the management of impalpable lesions should be observed.

Pre-operative localisation is essential for a mammographically detected impalpable lesion. Hook wire localisation is the most common method, but carbon particle injection is also used. When performing localisation, good communication between the surgeon and the radiologist or clinician performing the localisation is essential, with recognition of the following requirements:

- the wire (or carbon track) should be placed along the shortest possible distance from skin to lesion[78]
- the hook (or end of carbon track) should be placed through or into the lesion and no further than 1cm from the lesion[79]
- the length of wire (or carbon track) into the breast (depth of lesion) should be recorded
- two-view mammography (usually a true lateral and cranio-caudal) should be taken with the wire (or carbon track) in place
- in appropriate cases, more than one wire (or carbon track) should be used to define the extent of calcification.

The surgical procedure can be performed under:

- local anaesthesia, with or without intravenous sedation
- general anaesthesia.

In planning the surgical approach, the best possible cosmetic incision should be selected. Where a core biopsy has been performed, consideration should be given to including the core track and skin entry point if it does not alter the cosmetic effect of the excision.[80-82] This fact should be taken into account when considering a stereotactic core biopsy. It may be important to discuss this technique with the radiologist in the multidisciplinary team, in order to avoid dissection of core biopsy tracks that pass for a considerable distance through the breast to the lesion of concern. The appropriateness of the skin incision should be considered in case a re-excision is required. The incision should always be planned so that it can be included within a mastectomy incision if this proves necessary.

In all cases, the biopsy/CLE incision should be as close as possible to the site of the lesion. The incision need not include the site of guidewire entry. However, if there is a carbon track it is usual to remove it. Two-view mammography facilitates planning of the incision by demonstrating to the surgeon the approximate position of the lesion within the breast, and the direction of the wire, so that pursuit of the wire from the skin entry site is unnecessary. This approach also minimises dissection through normal breast tissue, reduces the volume of excised tissue and enhances the cosmetic result.

In performing CLE, the surgeon should consider the evidence about the grade of DCIS and the margins required to ensure complete excision of the lesion. A study by Faverly *et al.* demonstrated that DCIS can be surgically removed in 90% of cases if a 10mm margin of normal breast tissue is obtained (**Level III**).[26] An exception to this may occur when excising low-grade DCIS, as the extent of DCIS may be much greater than

the apparent extent of calcification seen on mammography. In such cases, a wider excision may be necessary.

Use of diathermy should be minimised, as it may make assessment of the histological margins difficult.

If a radiotherapy boost dose to the bed of excision of DCIS is planned, it may be helpful to mark the perimeter of the cavity of the excised DCIS with metal clips. This may assist the radiation oncologist with planning and subsequent treatment (see Section 1.6, page 45).[83]

Key points

- Pre-operative localisation is essential for a mammographically detected impalpable lesion.
- Excision of impalpable DCIS lesions requires close collaboration between the surgeon, radiologist and pathologist.

Specimen handling

The surgeon should observe the following principles when excising **impalpable** lesions:

- specimens should not be incised by the surgeon, as this can impair histopathological assessment
- specimen orientation should be marked[84,85] in at least two planes using a method agreed by the multidisciplinary team; sutures and/or metal clips can be placed on the appropriate edges
- pathology request forms should include details of the position of the lesion within the breast, breast side, features and extent of radiological findings and position of orientation markers
- specimen radiography is mandatory to confirm excision of the mammographically detected lesion

- minimal compression of the specimen should be applied to avoid disturbance of tissue
- the multidisciplinary team should agree on techniques for specimen handling and radiography
- serial slicing of the specimen and X-ray of the individual slices facilitate identification of calcifications by the histopathologist;[86] the specimen radiograph of the whole and/or sliced specimen should accompany the specimen to the pathologist
- frozen section should not be performed on mammographically detected impalpable lesions (**Level IV**);[87] the surgeon should explain to the patient that it is prudent to await the results of paraffin sections
- if the pathology report does not identify calcification, or fails to confirm a lesion that correlates with the mammographic lesion, it may be helpful to ask the histopathologist to have the paraffin blocks X-rayed.

Key points

- The localisation biopsy specimen should be carefully orientated and assessed using specimen radiography.
- Frozen section should not be performed on mammographically detected impalpable lesions.

Margins and definitive treatment

The surgeon should take note of salient features of the pathology report, particularly:

- the extent of the margin of excision
- which margin/s, if any, is/are close to the DCIS (see Section 1.3, page 22).

These factors determine whether further surgery is indicated and what advice should be given regarding adjuvant radiotherapy.

If any surgical margin is involved (apart from the posterior margin, where the resection extends to the pectoral fascia), the risk of local recurrence increases (**Level III**)[88-91] and further surgery should be recommended. Whether the surgery considered is a re-excision of the involved margin, or a mastectomy, depends on the extent of the re-excision required relative to the breast size. The final cosmetic result should be taken into account. If the posterior margin is the close margin, and an excision has already been performed back to (and including) the pectoral fascia, no additional re-excision may be possible.

The surgeon should be aware of the varying evidence regarding margins of excision.[26,60,92-94] Some case reports state optimal margins of 10mm. However, randomised clinical trials have assessed adjuvant radiotherapy after excision in selected patients with 'clear margins' (ie no DCIS at the section edge) and have demonstrated acceptable local control with surgery and radiotherapy (**Level II**).[18,23]

In summary, there is no reliable definition of an adequate margin, but the surgeon should ensure that the DCIS has been completely excised. It may be beneficial for the surgeon to discuss the pathology report with the reporting pathologist to gain insight into the adequacy of the excision.

The pathology report should be discussed with the woman, and the risks and benefits of additional treatment outlined (see Section 1.4, page 27).

Recommendation	Level of evidence	Reference
It is essential to ensure that clear margins are obtained when DCIS is excised. If the margins are involved, further excision is required.	II	9,10

Mastectomy

In selected cases, mastectomy may be the most appropriate treatment for DCIS. There is evidence to indicate that DCIS treated by mastectomy is associated with an approximate overall local recurrence rate of 1–2%,[2,20,21] which is the lowest local recurrence rate using any method of treatment. This evidence comes from studies of clinically detected DCIS in which lesions were generally large and included a high proportion of high-grade tumours.

Mastectomy may be considered in the following circumstances:

- widespread contiguous or multi-focal DCIS, where adequate excision cannot be achieved with a cosmetically acceptable wide excision
- widespread microcalcification (on pre-operative mammogram) in the presence of proven DCIS, even if some of the calcification is considered benign
- recurrence of DCIS (following initial treatment) when either of the above indications is present
- when mastectomy is the woman's choice
- when other relevant risk factors for breast cancer, such as a family history of the disease and age at diagnosis, are considered and suggest that mastectomy may be appropriate.

A total mastectomy, including nipple excision, is the optimal procedure in such cases. There is a risk of local recurrence after subcutaneous mastectomy because of preservation of the nipple and the possibility that some breast tissue remains. While some studies have recorded local recurrence rates as high as 50% after subcutaneous mastectomy, these involved small numbers of patients.[95,96] The risk of local recurrence may be reduced by coring out the central ducts from behind the nipple.

Breast reconstruction

Many women who have had a mastectomy are able to have breast reconstruction. The decision to choose breast reconstruction is a personal one. Women should be given the opportunity to consider the procedure so they can balance the advantages and disadvantages of reconstruction after mastectomy.[97-100]

Opinions vary as to whether breast reconstruction should be performed at the time of mastectomy or some time later. In some cases reconstruction can be planned before mastectomy and carried out at the same time. Women requiring mastectomy for DCIS are perhaps most suitable for immediate reconstruction, as they require neither axillary dissection nor post-operative radiotherapy. Issues surrounding immediate versus delayed reconstruction should be discussed with the woman.

Axillary dissection

There is no place for axillary dissection in the management of localised DCIS, because the risk of positive nodes is negligible (**Level III**).[1,11-17] Axillary dissection should therefore be discouraged to avoid the resultant morbidity, which includes the possibility of lymphoedema.

In published series of DCIS of varying sizes and presentations, the incidence of nodal involvement is about 1–2%, but this is usually associated with widespread high-grade DCIS where invasion may be present.[11] Level I axillary dissection may therefore be considered as a sampling procedure only in exceptional circumstances, for example, large (> 5cm) or widespread high-grade DCIS in which the presence of invasion may be overlooked or undetected. The role of sentinel node biopsy in this situation is the subject of further clinical investigation.[101]

Recommendation	Level of evidence	Reference
Axillary dissection should not be performed in the management of DCIS unless invasion is suspected.	III	1,11–17

Paget's disease of the nipple

Paget's disease is almost invariably associated with underlying DCIS in the central ducts. If this is localised and surgical margins are clear, excision of the nipple and central ducts may provide adequate surgical management, and radiotherapy should be considered.[102] If underlying DCIS is extensive, mastectomy should be recommended (see Section 1.6, page 46).

Other surgical procedures

Some new, 'minimally invasive' techniques have been developed for excision biopsy of small foci of microcalcification. These stereotactic large-core biopsy procedures[103-106] offer women complete removal of small focal lesions under local anaesthesia, with localisation and excision performed while the breast is maintained in compression on a prone mammographic table. Currently, these procedures are recommended for diagnostic purposes only. Until data from clinical trials become available, it should not be assumed that these techniques are reliable for the treatment of DCIS.

Management of recurrent ductal carcinoma in situ after treatment

The management of recurrent DCIS after initial treatment depends on:

- extent of the original focus
- previous management
- nature and extent of recurrence
- woman's choice.

There is only limited evidence on which to base recommendations for the treatment of recurrent DCIS. If CLE was the initial treatment, and the recurrence is focal and amenable to wide excision, re-excision can be considered with preservation of the breast. In such cases, radiotherapy should be considered if it was not part of the initial treatment. If the recurrence is widespread, multi-focal, or if the woman has previously had radiotherapy to the affected breast, mastectomy should be recommended.

1.6 RADIOTHERAPY

The use of radiotherapy following conservative surgery in the treatment of DCIS has been examined in randomised controlled trials. These have demonstrated lower recurrence rates for women with DCIS treated by breast-conserving surgery and adjuvant radiotherapy compared with conservative surgery alone (**Level II**).[18,22,23] These studies had insufficient statistical power to detect small differences in survival.[18,22]

Evidence for the benefit of radiotherapy after complete local excision for ductal carcinoma in situ

The National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol 6 trial was established to investigate the role of radiotherapy after lumpectomy for invasive breast cancer. However, pathology review revealed that some participants in this study had DCIS alone. In 76 patients, where pathological review led to re-classification to DCIS, local recurrence following lumpectomy alone was 23%, compared with 7% for lumpectomy and radiotherapy at a mean follow-up of 83 months.[107]

This observation generated a small number of randomised controlled trials designed to measure the effect of adjuvant radiotherapy after breast-conserving surgery for DCIS. Two of these trials, NSABP B-17

and a trial by the European Organisation for Research and Treatment of Cancer (EORTC), have been published.[18,22] Both trials randomised patients with localised DCIS to either excision alone or excision plus radiotherapy.

The eight-year follow-up data from NSABP B-17 showed a statistically significant improvement in local control for patients treated by surgical excision and radiotherapy when compared with breast-conserving surgery alone.[22] All patient and pathological subgroups benefited. The largest benefit was to patients with high-grade lesions with necrosis.[22] At a mean follow-up period of 90 months, there appeared to be a greater reduction in the risk of invasive recurrence than in the risk of recurrent DCIS in those patients receiving post-operative radiotherapy (Table 1).

Some aspects of the design and reporting of NSABP B-17 are controversial. Issues include what is perceived by some to be a small treatment benefit, the fact that histological sub-types were not considered, that the rigorous mammographic and pathological evaluations currently available were not available during the study period, and that the definition of tumour-free margins used by the investigators varied between institutions.[108,109] These limitations should be taken into account when interpreting the results of the trial.

Table 1 Results of NSABP B-17 (mean 90-month follow-up)[22]

Treatment	Patient numbers	EFS* ipsilateral	Non-invasive IBTR	Invasive IBTR
Conservative surgery	405	62%	13.4%	13.4%
Conservative surgery & radiotherapy	413	75%	8.2%	3.9%
p value		p = 0.00003	p = 0.007	p < 0.0001

EFS event-free survival
IBTR ipsilateral breast tumour recurrence

* EFS was calculated actuarially, taking into consideration variations in follow-up between patients. Since the non-invasive and invasive ipsilateral breast tumour (IBT) rates were calculated as crude percentages, the non-invasive and invasive IBT and EFS rates for each of the treatment groups do not necessarily add up to 100%.

The EORTC reported a trial of 1002 patients randomised between breast-conserving surgery alone, versus breast-conserving surgery and adjuvant radiotherapy (EORTC 10853).[18] The results, outlined in Table 2, were similar to those from NSABP B-17, with a statistically significant improvement in local control for those patients treated with post-operative radiotherapy. In contrast to NSABP B-17, the EORTC study did not indicate the same magnitude of reduction of recurrence of invasive breast cancers following radiotherapy.

Table 2 Results of EORTC 10853 (median 4.25-year follow-up)[18]

Treatment	Patient numbers	4-yr RFS	All local recurrence	Non-invasive IBTR*	Invasive IBTR*
Conservative surgery	500	84%	16.6%	8.8%	8.0%
Conservative surgery & radiotherapy	502	91%	10.6%	5.8%	4.8%
p value		p = 0.005	p = 0.005	p = 0.06	p = 0.04

RFS recurrence-free survival
IBTR ipsilateral breast tumour recurrence

* 1 patient with recurrence of DCIS had a second local recurrence that was invasive

EORTC 10853 found that the risk of an invasive recurrence was not related to the histologic grade of the original DCIS. However, for those patients who developed recurrence, distant metastases were much more likely if the original DCIS was poorly differentiated (hazard ratio (HR) 6.57, p = 0.01). This did not translate into a statistically significant difference in survival.[9] However, the study did not have sufficient statistical power to exclude a small survival difference.

EORTC 10853 also found a significant increase in the incidence of contralateral breast cancer in the group that had post-operative radiotherapy compared with the group that had surgery alone (4.2% vs 1.8%; p = 0.01 at 4.25 years median follow-up). The authors suggest that the relatively short follow-up period makes it unlikely that this observation reflects

any carcinogenic effect of the irradiation, as the typical latency for radiation-induced second malignancies is usually greater than eight years. Neither NSABP B-17, nor any of the six reported randomised studies of breast irradiation after breast-conserving surgery in invasive breast cancer, showed any similar increase in contralateral breast cancer in the irradiated group. The reason for this increase in contralateral cancer therefore remains undetermined.

Three meta-analyses of prospective and retrospective DCIS trials were published before the EORTC 10853 results in 2000. These meta-analyses showed a local recurrence rate of 17–23% for women with DCIS treated by conservative surgery alone, and 8–9% for women treated by conservative surgery with radiotherapy (**Level III**).[2,20,21] An assessment of risk of recurrence based on prognostic factors and treatment is summarised in Section 1.9, page 50.

Selecting cases where omitting radiotherapy may be considered

In NSABP B-17, local control was better with the addition of radiotherapy for all subgroups, irrespective of the presence or absence of mammographic calcification, method of detection, tumour size, histological grade, pathological classification, presence or absence of central necrosis and margin status.[10,19,22] In the group of women with low-risk DCIS, radiotherapy reduced the relative risk of second ipsilateral breast tumours by 7% at eight years follow-up.[19]

EORTC 10853 reported a pathologic subgroup analysis with respect to risk of recurrence of DCIS and invasive breast cancer. One pathologist reviewed slides from 889 patients (88% of the entire study population) and the pathological criteria were correlated with recurrence and treatment delivered. All pathological and clinical subgroups treated with surgery alone had a risk of recurrence of more than 10% when radiotherapy was omitted, with the exception of patients exhibiting clinging or micropapillary

architecture (only eight patients studied, recurrence 8%).[9] Patients rated 1 on the Van Nuys Prognostic Index (VPNI) (patients predicted by Silverstein *et al.* to have a negligible risk of recurrence with surgery alone) had a risk of recurrence of 15% with omission of radiotherapy, and a risk of recurrence of 4% with inclusion of post-operative radiotherapy.[9] Univariate analysis of these factors is shown in Appendix B. (See Section 1.9, page 53, for more information on the VNPI.)

In addition to these randomised studies, large reviews of non-randomised retrospective data[2,10] demonstrated a low ipsilateral breast tumour recurrence rate in some cases (see Section 1.9, page 55 for discussion of how risk can be assessed based on pathological features).

Results from a retrospective study suggest that the proximity of surgical margins may be a predictor for the utility of radiotherapy.[110] Although radiotherapy reduced local recurrence when the resection margins were close, (eg 1mm), there was no benefit from radiotherapy when the resection margins were 10mm or more. These findings require replication. Such large margins may be associated with significant cosmetic defects, particularly for larger areas of DCIS. Other reports from the same centre indicate that the benefits of radiotherapy may also relate to histological grade and tumour size (**Level III**).[60] Women with high-grade DCIS with central necrosis have high rates of recurrence with conservative surgery alone, and radiotherapy should not be omitted in these instances.[60]

Recurrence of DCIS and the occurrence of invasive cancer appear to decrease with the addition of radiotherapy, even for women with 'low-risk' lesions. This information should be included in discussions with the woman about her pathology report. The decision of whether to treat with radiotherapy should be discussed by the woman and her radiation oncologist, and should take into consideration the woman's overall health, life-expectancy and estimated risk of recurrence based upon individual risk factors and the informed input of the woman.

Appendices B and C provide local recurrence data based on various pathological criteria that may provide useful background when deciding whether to treat with radiotherapy.

Key points

- Radiotherapy following CLE reduces the risk of subsequent invasive breast cancer and *in situ* recurrences for all women with DCIS, regardless of the grade of DCIS or pathological subgroup.[19]
- Irrespective of treatment, the risk of recurrence is relatively low for women whose DCIS has good prognostic pathological features, such as clear surgical margins, low-grade lesions without necrosis, and small extent (<10mm). Although radiotherapy offers a statistically significant benefit over conservation alone, for these women, the absolute benefit may only be small. In such cases, the small gain in local control should be weighed against the inconvenience and morbidity of radiotherapy in discussion with the woman.
- Women with high-grade DCIS with necrosis, close margins and larger lesions have a relatively high risk of recurrence with conservative surgery alone, and adjuvant radiotherapy is therefore recommended.

Survival following treatment

A collaborative study involving 10 centres from Europe and North America has examined 268 patients treated by conservative surgery and radiotherapy. This study has the longest follow-up of any trials on this topic to date, and has been updated several times. At 15 years, disease-specific survival was 96% (**Level III**).[111] Similar long-term survival data for mastectomy or conservative surgery alone have not been reported. Randomised studies with shorter follow-up periods have not identified a survival difference between conservative surgery alone,

and conservative surgery followed by radiotherapy. However, it should be noted that these randomised trials had insufficient statistical power to detect small differences in survival.

Radiotherapy after mastectomy

Women with DCIS treated with total mastectomy alone have recurrence rates of less than 1%.[2,20,21] There is no evidence to support the routine use of radiotherapy after mastectomy for DCIS.[20]

Contraindications for radiotherapy

Contraindications to radiotherapy include: pregnancy, previous radiotherapy in the planned treatment area, and some collagen disorders, such as scleroderma and lupus, which may increase the risk of long-term toxicity.

Radiation technique

Standard fractionation radiotherapy (45–50.4 Gray (Gy), 5 days per week at 1.8–2.0 Gy/fraction) is currently recommended. This is the dose used in the randomised controlled trials mentioned previously.[18,22] The treatment volume is the entire ipsilateral breast. As neither of the randomised studies investigated the use of a boost, there are insufficient data to make a recommendation about the inclusion or omission of a boost to the surgical site.[18]

The rationale for using a boost is that the surgical site is the area at greatest risk of recurrence, and a higher dose of radiotherapy can be given to a small area of the breast without compromising the cosmetic result. Placement of clips in the surgical site can assist in planning treatment (**Level IV**),[83] particularly when the scar does not immediately overlie the tumour site.

Radiotherapy and management of Paget's disease of the nipple

Very few data are available concerning the long-term outcome of treatment for Paget's disease of the nipple. Traditionally, mastectomy has been the recommended treatment. Treatment of Paget's disease of the nipple with underlying invasive breast cancer should be as described in the NHMRC *Clinical practice guidelines for the management of early breast cancer.*[71] In the absence of an underlying breast mass or area of microcalcification, local excision of the nipple/areola complex with clear surgical margins followed by breast radiotherapy provides a lower risk of recurrence compared with excision alone (**Level IV**).[112] Treatment of Paget's disease with radiotherapy alone has been reported to result in local recurrence rates as high as 28% (**Level IV**).[112-116] Radiotherapy is not recommended as the sole treatment for Paget's disease of the nipple outside a clinical trial.

Recommendations	Level of evidence	Reference
The addition of radiotherapy after complete local excision reduces the risk of subsequent invasive breast cancer and recurrence of DCIS for all pathological subgroups of patients.	II	2,18–21
For women with good prognostic features, the overall clinical benefit of adjuvant radiotherapy may be small. In these circumstances, the woman may choose to omit radiotherapy.	II	9,10

Recommendations	Level of evidence	Reference
Women with high-grade DCIS with necrosis, close margins and larger lesions have a relatively high risk of recurrence with conservative surgery alone, and adjuvant radiotherapy is therefore recommended.	II	18,22,23

1.7 SYSTEMIC THERAPY

Chemotherapy has never been investigated or used in the treatment of women with DCIS. In relation to adjuvant hormone treatment, only tamoxifen has been submitted to randomised clinical trials to determine its effectiveness in the treatment of DCIS.

Role of tamoxifen

Results are available from only one of the two large randomised trials of tamoxifen in the treatment of DCIS. In NSABP B-24, 1804 women with DCIS treated by lumpectomy and radiotherapy were randomly assigned to receive adjuvant tamoxifen or placebo for five years. Findings from this trial, with a median follow-up of five years, are summarised in Table 3.[117]

Table 3 Results of NSABP B-24 (5-year follow-up)[117]

		All breast cancer			Ipsilateral breast cancer		
		Total	Non-invasive	Invasive	Total	Non-invasive	Invasive
Placebo (n = 899)	No. of events	130	60	70	87	47	40
	Cumulative incidence (%)	13.4	6.2	7.2	–	5.1	4.2
Tamoxifen (n = 899)	No. of events	84	43	41	63	40	23
	Cumulative incidence (%)	8.2	4.2	4.1	–	3.9	2.1
p value		0.0009	0.08	0.004	0.04	0.43	0.03

In the tamoxifen group, there were fewer invasive breast cancer events and fewer non-invasive breast cancer events than in the placebo group. The rate of non-invasive ipsilateral breast tumours was not significantly lower in the tamoxifen group than in the placebo group. Reduction in local recurrence was significant only for invasive ipsilateral breast cancer (2.1% vs 4.2%). Recent evidence from this trial showed that the benefit was greater in women with ER-positive DCIS.[118] However, it should be noted that these data were based on small numbers and a short follow-up period.

In the tamoxifen-treated group, endometrial cancer (7 cases, 0.8%) was more common than in the placebo group. Deep venous thrombosis was recorded in 1% of the tamoxifen group but there were no deaths from pulmonary embolism.

In conclusion, the limited available data suggest that tamoxifen may reduce the risk of subsequent local invasive breast cancer in women who have had breast-conserving treatment for DCIS (**Level II**).[117] The absolute risk reduction is small and the associated side-effects must be considered before advocating this treatment. The risk-to-benefit ratio is not currently known and should be discussed with each woman.

In Australia, tamoxifen is approved under the Pharmaceutical Benefits Schedule for women with hormone-dependent breast cancer.

Key points

- Chemotherapy is not recommended in the treatment of women with DCIS.
- The limited available data suggest that tamoxifen may reduce the risk of subsequent local invasive breast cancer in women who have had breast-conserving treatment for DCIS.
- Further research is required to determine the role of adjuvant tamoxifen in the treatment of women with DCIS.

1.8 SUMMARY OF DATA COMPARING TREATMENT OPTIONS AND RISK OF RECURRENCE

Table 4 summarises the risk of invasive and non-invasive breast cancer recurrence, as presented in the three preceding sections. The table includes published data from the three randomised controlled trials for treatments for DCIS.

Table 4 **Summary of randomised trials comparing CLE, CLE with radiotherapy and CLE with radiotherapy plus tamoxifen**

Trial	Follow-up	CLE		CLE + radiotherapy		CLE + radiotherapy + tamoxifen	
		Non invasive (%)	Invasive (%)	Non-invasive (%)	Invasive (%)	Non-invasive (%)	Invasive (%)
NSABP B-17[22] n = 818	8 yrs	13.4	13.4	8.2	3.9	–	–
EORTC 10853[18] n = 1002	4.25 yrs	8.8	8	5.8	4.8	–	–
NSABP B-24[117] n = 1804	5 yrs	–	–	5.1	4.2	3.9	2.1

NSABP National Surgical Adjuvant Breast and Bowel Project
EORTC European Organisation for Research and Treatment of Cancer
CLE complete local excision

1.9 PREDICTORS OF LOCAL RECURRENCE AFTER COMPLETE LOCAL EXCISION

Features that may predict 'recurrence' of DCIS, or subsequent development of invasive breast cancer after initial surgical treatment, have been sought to identify those women who should have additional therapy (more extensive surgery and/or radiotherapy). Approximately half the 'recurrences' are actually reappearances of DCIS, and half are invasive breast cancer.[59]

This section limits discussion to predictors of ipsilateral local recurrence of DCIS and/or invasive breast cancer. Whenever the term 'local recurrence' is used, this refers to recurrence of either DCIS and/or invasive breast cancer within the ipsilateral breast.

When considering treatment options, it is useful to be aware of those pathological and patient characteristics that may predict a greater likelihood of recurrence and may therefore indicate that further treatment (more extensive surgery and/or radiotherapy) is needed. This is because the advantages and disadvantages of treatment need to be weighed up against the risk of recurrence.

Comprehensive reviews (Level I)

Two recent overviews examined recurrence risk for conservative surgery alone and conservative surgery plus radiotherapy, using retrospective data and the results of randomised trials.[2,21] The main factors associated with recurrence were high-grade lesions, presence of central necrosis, lesion size and adequacy of surgical margin. Findings from one of these overviews are summarised in Appendix C, which provides information about risk of recurrence based on the treatment chosen and the pathological features. These overviews should be interpreted with caution, as most of the studies included were single-arm or single-institution studies and therefore prone to selection biases. In addition, surgical techniques and pathological assessments may have varied considerably between studies and over time. Insufficient data were available to show whether recurrences were more likely in the immediate vicinity of the primary lesion.

Appendices B and C summarise local recurrence of DCIS according to clinical, histological and pathological characteristics and treatment.

Prospective randomised studies (Level II)

National Surgical Adjuvant Breast and Bowel Project

NSABP B-17 was a randomised controlled study of CLE versus CLE and radiotherapy. This study was randomised according to treatment type, but was not stratified for pathological factors because the pathological analysis was not intended as an endpoint of the study. However, the assessment may give some indication of those women at a potentially higher risk of recurrence.

In a detailed examination of data obtained from NSABP B-17,[19] the presence of moderate or marked comedo necrosis was an independent predictor of local recurrence on multivariate analysis. Moderate-to-marked comedo necrosis, the presence of a lymphoid infiltrate, multifocality and solid type were identified as univariate factors associated with prediction for a greater risk of local recurrence. In this study, it was found that factors of borderline statistical significance included involved or unknown margin status and nuclear grade. Factors found not to have a significant impact were extent of cancerisation, appearance of the stroma and tumour size (**Level II**).[19] As discussed in Section 1.6, page 40, there were some methodological limitations to this study and these should be taken into account when interpreting the results.

European Organisation for Research and Treatment of Cancer

The EORTC conducted a similar trial (10853), where patients with DCIS were randomised to CLE with or without radiotherapy.[9] An assessment of clinical and pathologic predictive factors for local recurrence was undertaken. On multivariate analysis, the factors that impacted most on local recurrence were: young age (≤ 40 years, HR 2.14; p = 0.02); symptomatic detection of DCIS (HR 1.80; p = 0.008); growth pattern

(solid and cribriform; HR 2.67 and 2.69, respectively; p = 0.012); involved margins (HR 2.07; p = 0.0008) and treatment by local excision without radiation (HR 1.74; p = 0.009). Univariate recurrence rates according to prognostic categories from the EORTC study are presented in Appendix B.

Prognostic index

The VNPI, reported by Silverstein *et al.*[60] is an alternative method for determining prognosis in which DCIS is separated into three categories based on grade, adequacy of surgical margin and size of lesion (**Level III**). Table 5 summarises this prognostic model, which was developed from a retrospective review of 333 patients treated at one institution and is based on recurrence rates and factors that impacted on local recurrence. In the VNPI, the tumour is allocated a score out of three for each prognostic category. The total score ranges from 3 (low risk of recurrence) to 9 (higher risk of recurrence).

DCIS with a VNPI of 8–9 had a high risk of local recurrence after CLE with or without adjuvant radiotherapy. Mastectomy was recommended for this group. DCIS with an intermediate VNPI score of 5–7 showed a statistically significant improvement in local control with the addition of adjuvant radiotherapy after wide excision. DCIS with a VNPI score of 3–4 had a low recurrence risk in this study, with no evidence of benefit from adjuvant radiotherapy after excision.

The prognostic significance of the VNPI has not been reproduced in further studies, including NSABP B-17 and EORTC 10853, and should be used with caution.[9,19]

Table 5 Van Nuys Prognostic Index Scoring System*

Predictor	Score		
	1	2	3
Tumour size (mm)	≤ 15	16–40	> 41
Margin width (mm)	≥ 10	1–9	< 1
Pathological classification	Low- or intermediate-grade *(nuclear grades 1 and 2)*, without necrosis	Low- or intermediate-grade *(nuclear grades 1 and 2)*, with necrosis	High-grade *(nuclear grade 3)* with or without necrosis

* Scores (1–3) for each of the predictors are summed to yield a VNPI score ranging from 3 to 9. Suggest mastectomy for VNPI 8–9; recommend breast conservation and radiotherapy for VNPI 5–8, and consider omitting radiotherapy for VNPI < 5.

Other possible risk factors for recurrence (Level III)

A number of biological variables have been examined as indicators of prognosis. Overexpression of the *HER2/neu* (*c-erb-2*) oncogene,[119-125] mutations in the *p53* tumour suppressor gene,[126,127] aneuploidy[128] and ER-negativity[129] have all been shown in single studies to influence the risk of local recurrence. However, none of these indicators is used routinely in clinical practice for DCIS due to limited data.

Apart from histopathological characteristics, the only factors shown to be associated with the likelihood of 'recurrence' are age,[130,131] family history of breast cancer[134] and absence of mammographic microcalcification.[130] 'Recurrence' may be more frequent in pre-menopausal women or women younger than 45 years than in post-menopausal or older women,[130,131] and more likely in those with a family history of breast cancer than in those without.[17]

Summary of risk factors for recurrence

A number of studies have examined the impact of pathological features, such as grade, size and margins, on recurrence of DCIS or subsequent invasive breast cancer, but no consistent results have been reported. Therefore, all that can be achieved with the available data is to estimate the risk of recurrence with CLE with and without radiotherapy. The data enable classification of 'risk categories' as high, intermediate and low, based on the features described earlier. High-risk features include: high DCIS grade, large size of lesion, close or involved surgical margins, presence of necrosis, presence of clinical symptoms, solid type and lymphocytic infiltrate. Some of these factors may also be linked. For example, larger lesions are more difficult to remove with an acceptable cosmetic result and, as a consequence, may have narrower surgical margins compared with smaller lesions. However, the limited available data do not categorically identify individual women with DCIS who will or will not experience a recurrence of DCIS or subsequent invasive breast cancer.

Recommendation	Level of evidence	Reference
The risk of recurrence of DCIS or subsequent invasive breast cancer following complete local excision, with or without radiotherapy, will vary depending on identified predictive factors, such as nuclear grade, size, presence or absence of necrosis, margin width and other prognostic factors. All these factors should be considered when discussing the risk of recurrence and management options with the woman.	II	19

1.10 FOLLOW-UP

As outlined in earlier sections, the probability of local recurrence of DCIS varies according to type, grade and treatment. However, unlike invasive ductal cancer, where 70% of all recurrent disease is detected by the woman herself, almost all recurrence of DCIS will be detected by mammography.[132,133] When invasive ductal cancer occurs following treatment of DCIS, a high proportion of these tumours can also be detected at an early stage by routine mammography.[132]

Overall, about 50% of 'recurrences' of DCIS are likely to be invasive breast cancer.[22] In such cases, management should follow the recommendations in the NHMRC *Clinical practice guidelines for the management of early breast cancer.*[71]

Frequency of follow-up

There is no evidence defining the optimum follow-up protocol for women with DCIS. The consensus recommendation is that annual review should include clinical examination and mammography. Until further evidence is available, follow-up should continue indefinitely.

Mammography

Regular mammography is important in the follow-up of women with DCIS. It is helpful if the clinician indicates the site, diagnosis and type of treatment on the mammography request.

If there is doubt about the margins at excision, early follow-up imaging of the breast with magnification views may be helpful. This may be performed successfully after a few weeks. However, at that time, density related to surgery may obscure fine calcification. If so, the examination should be repeated after a few months.

Mammographic assessment of the treated breast should begin 6–12 months after treatment. In cases where microcalcification is identified, magnification views should be used for assessment.

Thereafter, annual bilateral mammography is recommended with magnification views when indicated. Dystrophic microcalcification may develop at the cavity margins and may simulate recurrence. Although an experienced mammographer can usually distinguish malignant from dystrophic calcification, biopsy (core or excision) is required occasionally.

Clinical examination

Clinical examination is of limited value in the detection of recurrent DCIS. However, women who have had DCIS are at higher risk of subsequent invasive breast cancer. It is therefore recommended that an annual clinical examination is arranged at the same time as the mammographic examination. The option of an interim six-month clinical review should be considered if this is the woman's preference, or if there are any unusual concerns about the risk of recurrence.

Who should provide follow-up?

As with treatment planning, follow-up is ideally conducted in a multidisciplinary setting. The treating surgeon should have an active role in follow-up. When radiation treatment has been given, the radiation oncologist should also be involved.

Interpretation of a post-treatment mammogram also requires specialist expertise. It is recommended that this be performed by a diagnostic radiologist with special training in mammography.

It is essential that good communication be maintained between the specialist and the referring GP, who must be fully informed of any concerns or plans for further investigation arising from a follow-up consultation.[71,134]

Goals of follow-up

Information and support

Although follow-up visits may cause anxiety, they provide an opportunity for discussion and for the woman to obtain information. Follow-up provides clinicians with the opportunity to assess the need for psychological or emotional support (as described in Chapter 3, page 76), and to address any concerns the woman may have about her health.

Detection of local recurrence

Recurrence of DCIS usually presents in the same way as the original disease, (eg microcalcification). However, since a high proportion of 'recurrence' is invasive breast cancer, any density, mass or architectural distortion should be treated with suspicion. Full assessment – including FNAB and core sampling – is indicated when a suspicious mammographic or sonographic lesion is detected.

Detection of distant metastases

Although the woman should be reassured that distant metastases do not occur when DCIS is present as a sole pathological finding, both the clinician and the woman should be aware of the possibility of undetected focal invasion, particularly in the case of high-grade lesions. In this context, it is possible that metastases have developed in conjunction with invasive breast cancer. Any symptoms suggesting such an occurrence should be investigated.

Use of other therapies

Doctors should be aware of any complementary or alternative therapies being used by the woman. Discussion of the use of these therapies should

be encouraged in an open and accepting manner.[71] Most alternative or complementary therapies have not been tested in randomised clinical trials and their efficacy has not been proved. These therapies may involve some interference with conventional therapies, and may cause harm.[71]

Among post-menopausal women, long-term use of oestrogen plus progestin combination hormone replacement therapy (HRT) is associated with increased risk of developing breast cancer.[135,136] There is no evidence about the effect of exogenous oestrogens in women with DCIS and their risk of subsequent invasive breast cancer. Women with DCIS who are considering HRT and/or hormonal contraceptive preparations should be informed of all associated risks and benefits.

Key points

- Women diagnosed with DCIS should be encouraged to attend regular long-term follow-up, including annual clinical examination and mammography.
- Follow-up of women affords opportunities for clinicians to detect recurrence at an early stage and to offer information and support to healthy women.

CHAPTER 2 ATYPICAL DUCTAL HYPERPLASIA, LOBULAR CARCINOMA IN SITU AND ATYPICAL LOBULAR HYPERPLASIA

2.1 INTRODUCTION

Atypical ductal hyperplasia (ADH) is a term used to describe a proliferation of ductal epithelial cells in which some, but not all, features of DCIS are present.[61]

Lobular carcinoma in situ (LCIS) is a non-invasive multicentric proliferation of atypical epithelial cells in the lobules and terminal ducts of the breast. A diagnosis of atypical lobular hyperplasia (ALH), is made when cells similar to those seen in LCIS only partially occlude the duct lumen and slightly distend the lobule.[137]

ADH, LCIS and ALH are uncommon as sole pathology findings in breast excision specimens and are often incidental findings in biopsies for other pathology. In most cases, women diagnosed with these lesions do not develop invasive breast cancer.[61] The importance of finding any of these lesions in an excision biopsy is that they are associated with an increased risk of subsequent invasive breast cancer when compared with unaffected women.[61,138,139] The risk of subsequent invasive breast cancer is higher for women diagnosed with LCIS than for those diagnosed with ALH or ADH. The risk is similar for women with ALH and ADH. However, when both lesions are present, the risk is doubled and is the same as that associated with LCIS. When ADH is diagnosed by core needle biopsy, undetected, concurrent DCIS or invasive breast cancer may be present.[140-142] When DCIS or invasive breast cancer is diagnosed, one or all of these changes may be found in the tumour or adjacent breast tissue. The significance of this finding is unknown.

As yet, there are no definitive criteria for the diagnosis of ADH. It can therefore be difficult to distinguish ADH from either ductal hyperplasia without atypia or DCIS (usually low-grade). This distinction can be particularly difficult on core biopsies, where a limited sample size compounds the problem. It may also be difficult to distinguish ALH and LCIS from each other and from ADH and DCIS. However, new immunohistochemical markers are helping to distinguish ALH and LCIS from other epithelial proliferations.

ADH, LCIS and ALH are usually mammographically and clinically occult. Studies about prevalence, natural history and treatment have been based on small numbers and therefore provide limited evidence to help guide clinical care.

2.2 NATURAL HISTORY

The natural history and biological significance of ADH, LCIS and ALH are unclear. The importance of a diagnosis of ADH, LCIS or ALH lies in the increased risk of concurrent or subsequent invasive breast cancer relative to women in the general population.[61]

Atypical ductal hyperplasia

In a study of 150 women with ADH, the average age at biopsy was 46 years (**Level III**).[61] Women with ADH are at higher risk of subsequent invasive breast cancer. Two studies of women diagnosed with ADH as a sole pathology finding in an excision biopsy for other pathology (with follow-up of 17 and 21 years, respectively) found that most women did not develop invasive breast cancer during the follow-up period (**Level IV**).[138,139]

The true size of the increased risk of invasive breast cancer in women

with ADH is unknown. Clinical follow-up studies have shown that the relative risk of subsequent invasive breast cancer in women diagnosed with ADH as the sole pathology following excision biopsy is four times higher than for the reference population (**Level IV**).[61,138] The absolute risk of women with ADH developing invasive breast cancer is 8–10% in the 10–15 years following diagnosis.[143] The risk of invasive breast cancer appears to be greatest in the first 10 years after diagnosis of ADH.[144] (See Appendix D for an explanation of absolute and relative risk.)

The risk of invasive breast cancer associated with ADH increases when other associated risk factors are present. Table 6 compares the relative risk of invasive breast cancer in women with a diagnosis of ADH as the only factor for increased risk with that in women with a diagnosis of ADH and other risk factors. The relative risk increases when ADH occurs in women with a family history of breast cancer in a first-degree relative to 10 times that of women with a cancer risk close to that of the general population and no such family history.[61]

Table 6 Relative risk of breast cancer in women with a diagnosis of atypical ductal hyperplasia

	Relative risk of breast cancer
Women with ADH compared with women in the general population (17-year follow-up)[61,138]	4
Women with ADH and ALH compared with women with a cancer risk close to that of the general population (8-year follow-up)[145]	8
Women with ADH and a family history of breast cancer in a first-degree relative compared with women with a cancer risk close to that of the general population and no such family history (17-year follow-up)[61]	10

The above table is drawn from cohort studies.

The risk of invasive breast cancer associated with a diagnosis of ADH appears to be bilateral, with a slight bias for development of cancer in the ipsilateral breast (**Level IV**).[61]

Lobular carcinoma in situ

The average age of women diagnosed at biopsy with LCIS is 44–46 years.[146] Most women with LCIS do not subsequently develop invasive breast cancer during the 15 years after diagnosis (**Level IV**).[146] The true size of the risk of developing invasive breast cancer is unknown. During the first 15 years following biopsy, women diagnosed with LCIS have seven to nine times the risk of a subsequent invasive breast cancer, compared with biopsied women without LCIS (**Level IV**) (Table 7).[146-149] Studies using different populations and designs have calculated a range of estimates of relative risk of subsequent invasive breast cancer up to about a 10-fold higher risk in women with LCIS compared with women without LCIS.[139,147] The absolute risk of developing invasive breast cancer within 15 years of a diagnosis of LCIS is 17%; this applies to both breasts (**Level IV**).[146]

Table 7 Relative risk of breast cancer in women with a diagnosis of lobular carcinoma in situ

	Relative risk of breast cancer
Women with LCIS compared with women in the general population (15-year follow-up)[146–149]	7–9

In some studies with small sample sizes, the incidence of invasive breast cancer in a woman with LCIS was as common in the contralateral breast as in the ipsilateral breast, and could also be bilateral (**Level IV**).[45,146,149]

Atypical lobular hyperplasia

In a study of 126 women with ALH, the average age at biopsy was 46 years **(Level III)**.[61] The relative risk of invasive breast cancer for women with ALH has been estimated at three to four times that of the general population after a minimum follow-up period of 15 years (**Level IV**).[61,138,145] In addition, an increased risk of breast cancer (intermediate between that associated with ALH alone and the risk associated with LCIS) has been described in cases of ALH with ductal involvement.[143] The absolute risk of developing invasive breast cancer following a diagnosis of ALH at 15 years is 10%.[146]

Table 8 compares the relative risk of breast cancer in women with a diagnosis of ALH as the only factor for increased risk, with that in women with a diagnosis of ALH and other risk factors. The relative risk increases when ALH occurs in women with a family history of breast cancer in a first-degree relative to eight times that of women with a cancer risk close to that of the general population and no such family history.[61]

Table 8 Relative risk of breast cancer in women with a diagnosis of atypical lobular hyperplasia

	Relative risk of breast cancer
Women with ALH compared with women with a cancer risk close to that of the general population (15–17-year follow-up)[61,138,145]	3–4
Women with ALH with ductal involvement compared with women in the general population (15-year follow-up)[145]	3.5
Women with ALH and ADH compared with women with a cancer risk close to that of the general population (15-year follow-up)[145]	8

	Relative risk of breast cancer
Women with ALH and a family history of breast cancer in a first-degree relative, compared with women with a cancer risk close to that of the general population and no such family history (17-year follow-up)[61]	8

The above table is drawn from cohort studies.

The risk of breast cancer associated with a diagnosis of ALH appears to be greater in the ipsilateral breast (68%) compared with the contralateral breast (24%) (**Level III**).[145]

2.3 DETECTION AND PREVALENCE

ADH, LCIS and ALH are usually clinically occult and only sometimes associated with indeterminate microcalcification or other mammographic findings.[137,150-153] While it is difficult to estimate the prevalence of these lesions in the general population, they are uncommonly diagnosed as a sole pathology finding. There are two means of determining the prevalence of ADH, LCIS and ALH: through studies that measure the frequency of these lesions found at biopsy for other pathology, and through studies of autopsy specimens. As a result, the prevalence of these lesions has been studied only in highly selected groups of women and the true prevalence is unknown.

Atypical ductal hyperplasia

The prevalence of ADH on core biopsy following mammographic screening is estimated at 5–7% (**Level IV**).[154,155] Based on data from international studies, the prevalence of ADH as a sole pathology finding in women referred to excision biopsy from mammographic screening is estimated at 1–2% (**Level IV**).[141,150,155,156] The prevalence of ADH in random autopsy specimens is 1% (**Level IV**).[157]

Lobular carcinoma in situ

The prevalence of LCIS on core biopsy is estimated at 0.4–3.8% in women with otherwise benign biopsies (**Level IV**).[142,146,148,153,158-160] In studies correlating a core biopsy diagnosis of LCIS with excision biopsy diagnosis, LCIS was reported as the sole pathology finding in 0.2–0.4% of cases.[142,158,159] The prevalence of LCIS in random autopsy specimens is 0–3%.[37,157,161]

Atypical lobular hyperplasia

The prevalence of ALH in women referred to core-needle biopsy from mammographic screening is estimated at 0.7–1.6% (**Level IV**).[61,153,160] Few published studies have examined excision biopsy results for lesions diagnosed as ALH at core biopsy, and existing studies involve small numbers. In one study, six core biopsies diagnosed as ALH were correlated with excision biopsy diagnosis. ALH occurred as the sole pathology finding in one excision biopsy, and benign fibrocystic changes with adjacent residual ALH were found in another four.[153] The prevalence of ALH in random forensic autopsy specimens is 0.4% (**Level IV**).[157]

Table 9 summarises the prevalence data for ADH, LCIS and ALH.

Table 9 Prevalence of atypical ductal hyperplasia, lobular carcinoma in situ and atypical lobular hyperplasia

	Core biopsy	Excision biopsy	Autopsy specimen
ADH	5–7%[154,155]	1–2%[141,150,155,156]	1%[157]
LCIS	0.4–3.8%[142,146,148,153,158-160]	0.2–0.4%[142,158,159]	0–3%[37,157,161]
ALH	0.7–1.6%[61,153,160]	Limited evidence	0.4%[157]

2.4 DIAGNOSIS AND HISTOPATHOLOGY

A review of the international literature shows that the reproducibility of histopathologic diagnosis of atypical hyperplasia is poor, with diagnosis ranging from hyperplasia to carcinoma in situ and even invasive breast cancer. No national Australian data are available about the reproducibility of histopathologic diagnosis of ADH, LCIS and ALH. However, pathologists in Australia have been trained in the diagnosis of these lesions, and the opinion of an experienced pathologist should be sought when a diagnosis is in doubt.

Atypical ductal hyperplasia

The criteria of Page *et al*.[61] are accepted in Australia for diagnosis of ADH. Criteria include cytologic (nuclear) features and histologic patterns, along with some indication of size or extent. In ADH, uniform cytologic (nuclear) appearance and even placement of cells similar to DCIS are present in some parts of the duct, while other areas of the duct are not involved. The areas of ADH are usually less than 3mm in overall size, but larger lesions can occur occasionally.[58] As the criteria are both qualitative and quantitative, it can be difficult to distinguish ADH from proliferative changes without atypia, and from low-grade DCIS.

The large tissue volume obtained with directional, vacuum-assisted large core-needle biopsy using 11-gauge needles improves the diagnosis of ADH by core biopsy. However, it does not entirely eliminate the risk of missing areas of DCIS and invasive breast cancer.[162,163]

Lobular carcinoma in situ and atypical lobular hyperplasia

LCIS and ALH have similar histologic characteristics and may be part of the same continuum of abnormality, differing only in the extent to which abnormal cells involve the duct lumen. The two lesions can be

distinguished using the criteria developed by Page *et al.*,[146] which are the accepted diagnostic standard in Australia and include cytologic (nuclear) features, histologic patterns and indications of size and extent.[56] According to these criteria, LCIS is diagnosed when all of the following occur:

- cellular proliferation is characterised by round, cuboidal or polygonal cells that are regularly arranged and evenly spaced
- cell nuclei are predominantly round, monotonous and hyperchromatic
- proliferation involves, distends and distorts at least half the acini in the terminal duct-lobular unit and fills involved lobular spaces, resulting in the absence of central lumina.

ALH is diagnosed when a lesion fails to meet at least one of the diagnostic criteria for LCIS in over 50% of acini within a lobular unit.[58] ALH may co-exist with DCIS, and DCIS must be treated appropriately (see Section 1.5, page 30).[137]

Core biopsy and excision biopsy in the diagnosis of atypical ductal hyperplasia, lobular carcinoma in situ and atypical lobular hyperplasia

Atypical ductal hyperplasia

Among women who have had a core biopsy diagnosis of ADH, further tissue in the form of excision biopsy is required for pathologic evaluation of the area of concern. This further evaluation is necessary because of the association with DCIS or invasive breast cancer (**Level IV**).[141,154,156,163-167]

Studies correlating the results of core and excision biopsies revealed DCIS and invasive breast cancer in 33–87% of subsequent excision biopsies reported as ADH in the core biopsy.[153,156,164]

Lobular carcinoma in situ and atypical lobular hyperplasia

There is no strong scientific evidence about whether to perform excision biopsy when LCIS or ALH is found on core biopsy. Typically, surgical excision biopsy is performed in order to exclude the presence of a more significant lesion, such as invasive breast cancer or DCIS. LCIS within a fibroadenoma is a rare circumstance of localised LCIS, which may require follow-up without excision biopsy.[153]

Preliminary published reports suggest that excision biopsy may not be required in certain circumstances, particularly for large core biopsies obtained with a vacuum-assisted unit.[153,160] However, in these studies, patient numbers were small and more studies are required to validate their findings before recommendations can be made to change current practice.

2.5 MANAGEMENT AND FOLLOW-UP

Diagnosis and initial management of women with ADH, LCIS or ALH should involve a multidisciplinary team including a surgeon, pathologist and radiologist. Supportive care services should also be available.

Limited evidence is available to determine the most appropriate management of women with ADH, LCIS or ALH. In the absence of data, current clinical opinion is that surveillance appears to be the best management option for women who have been diagnosed with ADH, LCIS or ALH as the only abnormality.[168] Surveillance currently includes annual clinical examination and annual bilateral mammography for at least 15 years following diagnosis. The aim of follow-up is to detect DCIS and invasive breast cancer at early stages of development.[148,149]

There is no established role for CLE or mastectomy in the treatment of ADH, LCIS or ALH.

Hormonal therapies

Among post-menopausal women, the long-term use of oestrogen plus progestin combination HRT is associated with an increased risk of developing invasive breast cancer.[135,136] There is no evidence concerning the effect of exogenous oestrogens in women with ADH, LCIS or ALH and their risk of subsequent invasive breast cancer. Women with ADH, LCIS or ALH who are considering HRT and/or hormonal contraceptive preparations should be informed about all the associated risks and benefits.

Tamoxifen has been shown to lower the overall rate of invasive breast cancer due to its effect on ER-positive tumours. The Breast Cancer Prevention Trial (P-1), initiated by the NSABP in 1992, found that the use of tamoxifen reduced the risk of invasive breast cancer by 56% in women with a history of LCIS, and by 87% in women with atypical hyperplasia of the breast.[169,170]

Initial results from the International Breast Cancer Intervention Study (IBIS) were released in September 2002. In this study, women at increased risk of breast cancer, including those with LCIS and atypical hyperplasia, were randomised to receive either tamoxifen or placebo for five years. Results to date indicate a reduced incidence of breast cancer in women taking tamoxifen compared with those taking placebo (relative risk reduction: 32%).[171]

Both NSABP P-1 and IBIS demonstrated a significant increase in thromboembolic events and endometrial cancer in the tamoxifen group. Therefore, the overall risk-to-benefit ratio of tamoxifen as a preventive strategy remains unclear.[171] Since neither study differentiated between women with ADH and ALH, it is unclear whether the reported effects are equal for both conditions. There is currently insufficient evidence to recommend the use of tamoxifen for the prevention of invasive breast cancer following a diagnosis of ADH, LCIS or ALH.

Key points

- Among women who have had a core biopsy diagnosis of ADH, further tissue, in the form of excision biopsy, is required for pathologic evaluation of the area of concern, because of the association with DCIS or invasive breast cancer.
- There is no strong scientific evidence about whether to perform excision biopsy on women with LCIS or ALH found on core biopsy. Typically, surgical excision biopsy is performed in order to exclude the presence of a more significant lesion, such as invasive breast cancer or DCIS.
- Current clinical opinion is that surveillance appears to be the best management option for women who have been diagnosed with ADH, LCIS or ALH as the only abnormality.[168] Surveillance currently includes annual clinical examination and annual bilateral mammography for at least 15 years following the diagnosis.
- There is no established role for CLE or mastectomy in the management of ADH, LCIS or ALH.
- There is currently insufficient evidence to recommend the use of tamoxifen for the prevention of invasive breast cancer following a diagnosis of ADH, LCIS or ALH.

CHAPTER 3 PSYCHOSOCIAL SUPPORT

3.1 INFORMATION AND SUPPORT NEEDS OF WOMEN WITH DUCTAL CARCINOMA IN SITU

Recent studies indicate that women are confused about the nature of DCIS, its relationship with invasive breast cancer, and the reasons for mastectomy in non-invasive disease.[72,172] Psychosocial support and the provision of clear information for women diagnosed with DCIS is required to help women understand the disease, their prognosis, and management (**Level IV**).[172]

Confusion surrounding a diagnosis of DCIS[173] is influenced in part by the medical terminology used – many women think 'carcinoma' means 'invasive cancer' – and also by the fact that the treatments discussed (eg CLE plus radiotherapy or mastectomy) are commonly associated with invasive breast cancer. The limited available information about the natural history of the disease and the relative risks of different treatments[173] also complicates treatment decision making for women.

As a first principle, women diagnosed with DCIS should be given the same level of information and support as women diagnosed with early breast cancer. Information should be provided in a form and manner appropriate to each woman's circumstances, personality, expectations, fears, beliefs, values and cultural background. Information should also be available for the woman's family at her request.[71]

Another important principle is that women who are not fluent in English should be offered the assistance of qualified interpreters so they are not reliant on family or friends. Interpreters are available free of charge in both the public and private sectors. However, they must be booked in advance of any consultation.

Women should also be encouraged to have another person, such as a friend or family member, present at their consultation, if they wish. Some women find that this helps them understand and remember the nature of their diagnosis and the treatment options available.

Clinicians may want to consider using the checklist in Appendix E as an aid for identifying issues that should be covered when talking to women diagnosed with DCIS.

Little is known about the psychological consequences of being diagnosed with DCIS. However, studies involving cancer ptients have identified a number of factors that may increase the risk of an adverse psychosocial outcome. These include: living alone,[174,175] fatigue,[176,177] lack of social support[178,179] and a history of psychiatric illness.[180]

Discussing the diagnosis

Being diagnosed with DCIS often involves undergoing many tests and procedures, such as mammographic screening and assessment processes, biopsy, ultrasound, and hook wire localisation. Providing information and explanation before, during and after such procedures is important to alleviate anxiety and ensure the woman is fully informed.

The availability of written information about DCIS has been identified by women as crucial in assisting their understanding of the disease, and the risk of recurrence of DCIS or subsequent invasive breast cancer (**Level IV**).[172] Studies of women with early breast cancer have indicated that satisfaction with treatment is influenced by the amount of information received, as well as the style, comprehensibility and delivery method of the material (**Level II**).[181,182] Verbal information provided by clinicians, supplemented by written information and diagrams, may assist in meeting a woman's information needs.[183]

Clinicians should be aware that, while some women will accept a diagnosis of DCIS with little concern, others will become anxious about the current situation and long-term implication of their diagnosis. Women should be offered the opportunity to discuss openly their fears and concerns about the diagnosis and its implications. Although studies that specifically address the psychological needs of women with DCIS are required, studies of women with invasive breast cancer show that appropriate counselling improves the wellbeing of women and that the opportunity to discuss their feelings with a member of the treatment team or counsellor decreases psychosocial distress (**Level I**).[6]

Women diagnosed with DCIS consider psychosocial support to be a very important component of their care.[172] Women who are satisfied with their psychosocial support are less anxious and depressed and have a more positive outlook about their prognosis.[172] Such support should be offered at the time of diagnosis and on a continuing basis where appropriate. Sources of psychosocial support may include the surgeon, other members of the treatment team, the woman's GP, breast cancer support services, a breast care nurse, a counsellor, other women diagnosed with breast cancer or DCIS, family members and close friends.

Women should be advised of available support services, and encouraged to use them as necessary. Matching of women diagnosed with DCIS with volunteers (through State and Territory cancer organisations) may be difficult, but should be encouraged.

For further general information on providing information and psychosocial support, refer to the NHMRC *Psychosocial clinical practice guidelines: providing information, support and counselling for women with breast cancer*.[68]

Discussing treatment options

Women with DCIS should be given information about the natural history of the disease and available treatment. They should also be informed that the primary goal of treatment is the removal of all DCIS using the most appropriate method, as it is currently unclear which forms of DCIS are associated with a risk of subsequent invasive breast cancer.

It should be emphasised that the most appropriate treatment for each woman may be influenced by factors such as age, extent of disease, past history, size and grade of lesion and patient preference. Treatment must therefore be tailored to the individual woman's needs. The benefits and risks of each treatment, and of no treatment, should be discussed with the woman. The current level of knowledge about the relative risk of recurrence of DCIS and subsequent invasive breast cancer should also be discussed. Repeated opportunities for the woman to ask questions should be provided. Studies have shown that women do not remember much of their initial consultation and a second consultation should therefore be offered.[184]

It should be recognised that:

- each woman will have a preferred way of making decisions (some women prefer to be the decision makers, others prefer to share the decision making, and some prefer their clinician to make the decision for them)
- each woman's preferred way of making decisions may vary over time
- clinicians should ask each woman which decision making process she prefers
- given that many women will discuss their treatment alternatives with their GP, it is important that the GP receives timely and specific information to inform his or her discussion with the woman.

Second opinion

Women should be assisted in seeking a second opinion if they request one. Clinicians should cooperate fully in providing all the necessary information to the second clinician. A woman who decides to seek a second opinion, should be reassured that taking a week or two to decide on treatment will not adversely affect her outcome. At the same time, she should be cautioned that it is not wise to take months to decide.[71]

Practical support

Women should be advised about practical issues, such as being fitted for a prosthesis, eligibility for travel assistance, access to support groups, and where to receive counselling, if needed.

Psychosocial follow-up

There are no longitudinal data on the long-term course of psychological adjustment or psychological and coping problems in women with DCIS. However, clinicians should be aware that follow-up provides an opportunity to assess the emotional adjustment of both the woman and her partner. Since it is rare for women to seek psychological assistance themselves, doctors should inquire about the woman's psychological wellbeing at each visit.[185,186] Where appropriate, the woman should be referred for counselling and/or treatment by a trained professional (eg a clinical psychologist or psychiatrist). It is important to assess the woman's psychological and practical support needs at each follow-up visit, as these needs may change over time.

Key points

- Women diagnosed with DCIS should be offered relevant information and given practical and psychological support.
- Clinicians should be aware that the information and support needs of women diagnosed with DCIS may change over time.
- Women diagnosed with DCIS should be given the opportunity to openly discuss their fears and concerns about diagnosis, prognosis, procedures and treatment options.

3.2 INFORMATION AND SUPPORT NEEDS OF WOMEN WITH ATYPICAL DUCTAL HYPERPLASIA, LOBULAR CARCINOMA IN SITU AND ATYPICAL LOBULAR HYPERPLASIA

Although there are no published data about the information and support needs of women with ADH, LCIS and ALH, a large body of literature is available about women at increased risk of invasive breast cancer on the basis of family history. Women in this latter group have been found to have unmet information needs,[187] high levels of psychological distress, and inaccurate perceptions of their risk of breast cancer (**Level III**).[188]

On this basis, clinicians must ensure that women diagnosed with ADH, LCIS or ALH receive adequate information. This should include an explanation of the meaning of the diagnosis in terms of risk of invasive breast cancer, and the importance of 'watchful waiting'. Although the true size of the increased risk of subsequent invasive breast cancer is unknown (see Section 2.2, page 61), women with ADH, LCIS or ALH should be informed that they are at greater risk than the general population.

The NHMRC publication, *Psychosocial clinical practice guidelines: providing information, support and counselling for women with breast cancer*[68] provides a comprehensive description of how best to inform women, along with psychosocial support strategies that can be used when discussing a diagnosis of DCIS, ADH, LCIS or ALH.

Consumer guides for DCIS, ALH, LCIS and ALH are being developed by the National Breast Cancer Centre and will be available in early 2004.

CHAPTER 4 FUTURE RESEARCH

The research needs outined below have been identified.

Natural history of ductal carcinoma in situ, atypical ductal hyperplasia, lobular carcinoma in situ and atypical lobular hyperplasia

An important issue to be addressed by research is establishing the natural history of DCIS, ADH, LCIS and ALH. A national register of all women with these conditions could assist in assessing the natural history of these diseases, as well as clinical, pathological and other features that may affect patient outcomes. In the meantime, knowledge about DCIS, ADH, LCIS and ALH can be expanded by following cases from breast screening units or clinical trials.

Effectiveness of treatments

Further research is needed to determine the effectiveness of different treatments and screening schedules, the associated costs, and the impact of different treatments on women's quality of life. Research aimed at establishing the natural history of DCIS, ADH, LCIS and ALH would help clinicians determine appropriate surveillance strategies.

Information and support needs

Further research is needed to:

- determine the information needs of women diagnosed with DCIS, ADH, LCIS and ALH
- identify women's decision making needs regarding treatment
- develop appropriate information resources
- determine counselling needs following diagnosis

- determine the psychological impact of DCIS on women's quality of life
- understand the experience of specific groups, such as non-English-speaking and Aboriginal and Torres Strait Islander women
- improve women's understanding of the concept of non-invasive carcinoma.

Clinical trials

Randomised clinical trials to improve understanding of the management of DCIS, ADH, LCIS and ALH should be supported, and women should be encouraged to participate.

Two recent trials investigated the effectiveness of tamoxifen in the prevention of invasive breast cancer in women with DCIS, ADH, LCIS and ALH:

- NSABP P-1 involved women with DCIS and LCIS[169,170]
- IBIS involved women with LCIS and AH.[171]

Findings from these trials are discussed in Section 2.5, page 70.

Future clinical trials and research should be performed to:

- determine the impact of exogenous oestrogen and combined oestrogen–progestin preparations on the risk of invasive breast cancer in women with DCIS, ADH, LCIS and ALH
- identify women at high risk of recurrence of these conditions
- identify variations in the methods used by different pathology facilities to distinguish between ADH and DCIS
- determine the effectiveness of using tamoxifen to treat women with DCIS
- identify indicators of likely progression from DCIS, ADH, LCIS and ALH to invasive breast cancer

- determine the significance of several molecular and biological markers in women with ADH and ALH, such as:
  - *ra*s oncogene *p21* expression and its correlation with levels of atypia and proliferation[189]
  - increased carcinoembryonic antigen (CEA) reactivity in ADH compared with hyperplasia[190]
  - association between histologic progression of breast tissue from normal to proliferative, to ADH and ALH, and increasing concentrations of cholesterol and cholesterol ß-epoxide[191]
- identify ancillary techniques that could improve the reproducibility of diagnostic reporting.

APPENDICES

APPENDIX A MEMBERSHIP OF THE DCIS, LCIS AND AH WORKING GROUPS AND TERMS OF REFERENCE

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Terms of reference

- To undertake development and subsequent implementation of the evidence-based: *The clinical management of ductal carcinoma in situ, lobular carcinoma in situ and atypical hyperplasia of the breast.*
- To develop recommendations following the procedures outlined in *A guide to the development, implementation and evaluation of clinical practice guidelines*.[3]
- To ensure the recommendations can be clearly understood and applied (with modifications when necessary) in the diagnosis and treatment of women with DCIS, ADH, LCIS and ALH.

APPENDIX B EORTC TRIAL UNIVARIATE ANALYSIS OF CLINICAL AND HISTOLOGICAL CHARACTERISTICS RELATED TO LOCAL RECURRENCE OF DUCTAL CARCINOMA IN SITU[9]

		LOCAL RECURRENCE (%)			
	Characteristic	**Local excision**	**Local excision and RT[1]**	**Hazard ratio**	**p value**
Age	> 40 years	18	12	1	0.001
	≤ 40 years	45	23	2.54	
Method of detection	X-ray alone	16	11	1	0.0147
	clinical symptoms	27	17	1.55	
Pathological diagnosis	benign/LCIS[2]	0	8	1	0.0230
	DCIS[3]	20	12	3.7	
	suspicion of invasion	29	19	6.01	
Nuclear grade	low	13	4	1	0.0011
	moderate	22	14	1.77	
	high	28	18	2.23	
Necrosis	none	16	4	1	0.0183
	moderate/marked	20	16	1.80	
Architecture	clinging/micropapillary	8	3	1	0.0001
	cribriform	21	16	3.74	
	solid/comedo	28	15	4.40	
Size	< 10mm	16	11	1	0.2127
	10–20mm	35	5	1.15	
	> 20mm	71	10	2.46	
Margins	re-excision, no DCIS in residual	18	7	1	0.0223
	free, distance specified	18	12	1.36	
	free, not otherwise specified	14	12	1.07	
	close/involved	32	16	2.01	
	not specified	33	22	2.11	

	Characteristic	LOCAL RECURRENCE (%) Local excision	Local excision and RT[1]	Hazard ratio	p value
Histological type	well	13	7	1	0.0007
	intermediate	20	18	2.10	
	poor	28	14	2.19	
VNPI[4] score	1	15	4	1	0.0042
	2	20	18	2.06	
	3	28	18	2.22	

[1] RT radiotherapy
[2] LCIS lobular carcinoma in situ
[3] DCIS ductal carcinoma in situ
[4] VNPI Van Nuys Prognostic Index

APPENDIX C LOCAL RECURRENCE OF DUCTAL CARCINOMA IN SITU ACCORDING TO TREATMENT AND PATHOLOGIC FACTORS – SUMMARY[21]

A recent overview of all published series analysed various predictors for local recurrence of DCIS and occurrences of invasive breast cancer according to treatment.[21] Differences in local recurrence between patients treated with lumpectomy alone versus those also receiving radiotherapy were greatest for high-grade DCIS or DCIS with necrosis, or of the comedo subtype, or those lesions with close or positive surgical margins.

This overview requires some caution in interpretation, as most of the studies included in the analysis were single-arm or single-institution studies and therefore prone to selection biases. In addition, surgical techniques and pathologic assessments may vary considerably between studies. Insufficient data were available to show whether recurrences were more likely to occur in the immediate vicinity of the primary lesion.

	Conservative surgery alone			Conservative surgery & radiotherapy			
Pathological factor	**No. treated**	**No. of recurrent tumours**	**%**	**No. treated**	**No. of recurrent tumours**	**%**	**p-value**
Comedo	96	33	34.4	119	17	14.3	0.0005
Non-comedo	193	16	8.3	158	11	5.9	NS*
Necrosis							
• present	150	37	24.7	213	18	8.5	< 0.0001
• absent	236	26	11.0	216	11	5.1	0.05
Grade							
• high	209	48	23.0	241	23	9.5	0.0001
• intermediate	66	15	22.7	107	8	7.5	0.01
• low	221	18	8.1	218	8	3.7	NS* (0.06)
Tumour diameter							
• 0–10mm	322	46	14.3	275	17	6.2	0.001
• > 10mm	136	32	23.5	51	1	2.0	0.0007
Combination of factors							
Negative margins with:							
• absent/slight necrosis	125	9	7.2	144	6	4.1	NS*
• moderate/marked necrosis	98	16	16.0	105	4	3.8	0.003
Positive or uncertain margins with:							
• absent/slight necrosis	26	5	19.2	24	2	8.3	NS*
• moderate/marked necrosis	25	8	32.0	26	3	11.5	NS* (0.08)

* NS non-significant

APPENDIX D UNDERSTANDING RELATIVE AND ABSOLUTE RISK

Relative risk is the most common statistic used to quantify the risk of death or other morbid outcomes associated with different groups of individuals and therapeutic interventions. For any one individual, the absolute risk is of more relevance than relative risk. For example, in deciding whether to recommend prophylactic mastectomy to a woman, it is more valuable to know her chance of developing breast cancer than to know how much more likely she is to develop this disease than any other woman.

Relative risk

A woman with a relative risk of 10 compared with the general population has a risk of developing breast cancer that is 10 times higher than the corresponding risk for a woman of the same age from the general population for a given time interval.[192]

Absolute risk

The absolute risk of a woman's developing invasive breast cancer is a complicated function of her relative risk, her age, and the age-specific incidence of breast cancer and death from causes other than breast cancer in the general population. Estimating absolute risk is further complicated by the fact that the relative risk itself may vary with time.

For women diagnosed with *in situ* cancer at 60 years, a constant relative risk of 10 for developing invasive breast cancer is associated with a 20-year absolute risk of 40% for developing the disease. For 80-year-old women, this absolute risk drops to about 30%. This reduction in absolute risk occurs because the shorter remaining life expectancy of 80-year-old women outweighs their increased age-specific breast cancer incidence in the calculation of their absolute risk of invasive breast cancer.[193]

APPENDIX E CHECKLIST OF ISSUES OF CONCERN TO WOMEN DIAGNOSED WITH DUCTAL CARCINOMA IN SITU

Women are often stressed by the diagnosis and treatment of DCIS, but they may not be able to express their questions or concerns adequately. This checklist identifies issues appropriate for consideration when speaking to women about DCIS. These issues may be of interest to women, even if they do not ask the questions themselves.

Diagnosis

- What is DCIS?
- How does DCIS differ from invasive breast cancer?
- How does DCIS differ from other breast disease?
- Can I die from DCIS?
- Why did I get DCIS?
- How long has the DCIS been present?
- Can DCIS be inherited?
- Should my daughter be tested?
- Does DCIS always become invasive?
- Why did I need a mammogram and a biopsy?
- Why was a fine needle aspiration /core biopsy/surgical biopsy chosen?
- Can a biopsy lead to invasive breast cancer by breaking the ducts?

Treatment

- What are my treatment options?
- Will I need a lumpectomy or a mastectomy?
- Why has this particular option (or range of options) been suggested?
- What are the risks and benefits associated with each of the treatment options?
- What is the risk associated with choosing not to be treated?
- Will regular mammograms pick up invasive breast cancer if it develops?
- Is axillary dissection necessary?
- What are the chances of DCIS recurring in the same breast?
- What are the chances of developing an invasive cancer in the same breast?
- What are the chances of either an invasive cancer or DCIS in the other breast?
- Is it still possible to have children and breastfeed after treatment for DCIS?
- How often will I need to have follow-up?
- What will the follow-up involve?

Support

- Who can provide me with more information?
- Where can I find another woman diagnosed with DCIS to talk to?
- Are there support groups for women with DCIS?
- Are there any support groups for partners of women with DCIS?
- Are professional counselling or psychiatric services available?
- Where can I get a prosthesis if I need one?
- Can I get any financial assistance to help with treatment costs or prostheses?
- Can I get assistance with childcare while I'm having radiotherapy?
- What implications does this disease have for my job?
- Is it normal to feel anxious about the future?
- Is it normal to feel a sense of loss after a mastectomy?

GLOSSARY

absolute risk

The observed or calculated probability of an event, such as developing breast cancer, occurring in the population under study over a specified timeframe.

aneuploidy

Any deviation from an exact multiple of 23 chromosomes, whether fewer or more.

architectural distortions

The normal architecture is distorted with no definite mass visible. This includes spiculations radiating from a point and focal retraction or distortion of the edge of the parenchyma.

carcinoembryonic antigen (CEA)

A glycoprotein that is usually present only during foetal development but may appear in the plasma of adults with certain types of cancer, including breast cancer.

comparative genomic hybridisation (CGH)

A cytogenetic technique in which reference DNA and the DNA to be studied, are labelled with green- and red-fluorescing fluorochromes, respectively. Genetic abnormalities are detected by changes in the green-to-red ratio.

cranio-caudal

One of the two standard views for two-view mammography. The cranio-caudal view will show virtually all but the most lateral and axillary part of the breast. The cranio-caudal view should show the medial border of the breast, some of the axillary tail of the breast and the nipple in profile, and sometimes the pectoral muscle shadow on posterior edge of the breast.

cribriform

Changes in which normal cells appear to be perforated like a sieve.

diathermy

Surgery or heat treatment using high-frequency electromagnetic radiation, electric currents or ultrasound waves.

EORTC

European Organization for Research and Treatment of Cancer.
An oncology cooperative that carries out laboratory and clinical research across Europe to improve the management of cancer and related problems.

*erb*B-2

Also known as HER2/*neu*. A cell surface receptor related to the epidermal growth factor receptor (EGF-R). Activation of EGF-R and *erb*B-2 signal transduction pathways results in a mitogenic response. High expression of *erb*B-2 is associated with a poor prognosis.

fibroadenoma

A benign epithelial tumour containing fibrous tissue in which the cells form recognisable glandular structures or in which the cells are clearly derived from glandular epithelium.

HER2/*neu*

See *erb*B-2.

IBIS

International Breast Cancer Intervention Study. A major research study investigating whether the drug tamoxifen can prevent breast cancer.

mediolateral oblique

One of the two standard views for mammography in which the X-ray beam passes obliquely from medial to lateral in the breast. This view aims to show a wedge of the pectoral muscle to nipple level, the nipple in profile and the infra-mammary angle clearly demonstrated.

meta-analysis

A quantitative synthesis of the results of two or more primary studies that have addressed the same hypothesis in the same way.

multivariate analysis

A branch of statistics concerned with the analysis of multiple measurements, made on one or several samples of individuals.

NSABP

National Surgical Adjuvant Breast and Bowel Project. A multi-site clinical trials cooperative group supported by the American National Cancer Institute.

oncogene

Literally, a cancer-causing gene. A gene, often with a normal function in controlling growth or differentiation, which when functioning abnormally (activated, for example, by amplification or mutation) confers on normal cells immortality or the ability to form tumours (transformation). Oncogenes that are commonly overexpressed or amplified in breast cancer include EGF-R, *erb*B-2, c-*myc*, c-*myb* and *int*-2/cyclin D1.

p53

A protein with complex functions that include mediating cell cycle arrest after DNA damage. Li-Fraumeni syndrome (which results in a marked increase in the risk of breast cancer) is associated with inherited mutations of the *p53* gene. Most *p53* mutations result in an abnormal protein that accumulates in cells and is thus easily identified immunohistochemically. Acquired (somatic) mutations of *p53* are found in approximately 50% of breast cancers.

pleomorphic

Distinct forms of variation in the size and shape of cells or nuclei.

relative risk

The risk that a patient has of an event occurring, compared with that of a reference group.

sentinel node biopsy

Sampling of the first set of lymph nodes that receives drainage from a tumour. A combination of radioactive tracer and coloured dye is used to localise the nodes. The biopsy technique is less extensive than, and can reduce the need for, axillary clearance in node-negative patients. It is not, at present, a standard procedure.

spot compression magnification

X-ray of a small area of the breast that has been compressed by a paddle device and magnified to assess calcification and other fine detail.

stereotaxis

A radiological technique used to localise a lesion accurately in the breast. Permits precise insertion of a needle in order to obtain material for cytology (fine needle) or histology (core biopsy), or as an aid to surgical excision of an impalpable lesion.

univariate analysis

Statistical analysis in which each variable in a data set is explored separately.

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