BMJ Best Practice

Breast cancer in situ

Straight to the point of care

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Summary

Breast cancer in situ comprises ductal carcinoma in situ (DCIS), a non-invasive breast cancer that is confined to the duct in which it originates, and lobular carcinoma in situ (LCIS), a neoplastic proliferation of cells that is a risk factor for invasive breast cancer.

Typically asymptomatic and diagnosed at screening.

Breast cancer guideline recommendations differ on when to start screening and screening frequency. In the US, recommendations for bilateral mammography screening in average-risk women range from yearly starting at age 40 years (National Comprehensive Cancer Network) to every 2 years starting at age 50 years (US Preventive Services Task Force). The UK NHS Breast Screening Programme offers routine mammographic screening every 3 years to all women from age 50 years. The UK National Institute for Health and Care Excellence recommends annual mammogram screening from age 40 years in women at moderate risk of breast cancer. The European Society for Medical Oncology recommends annual or biennial mammogram screening in all women from age 50 years.

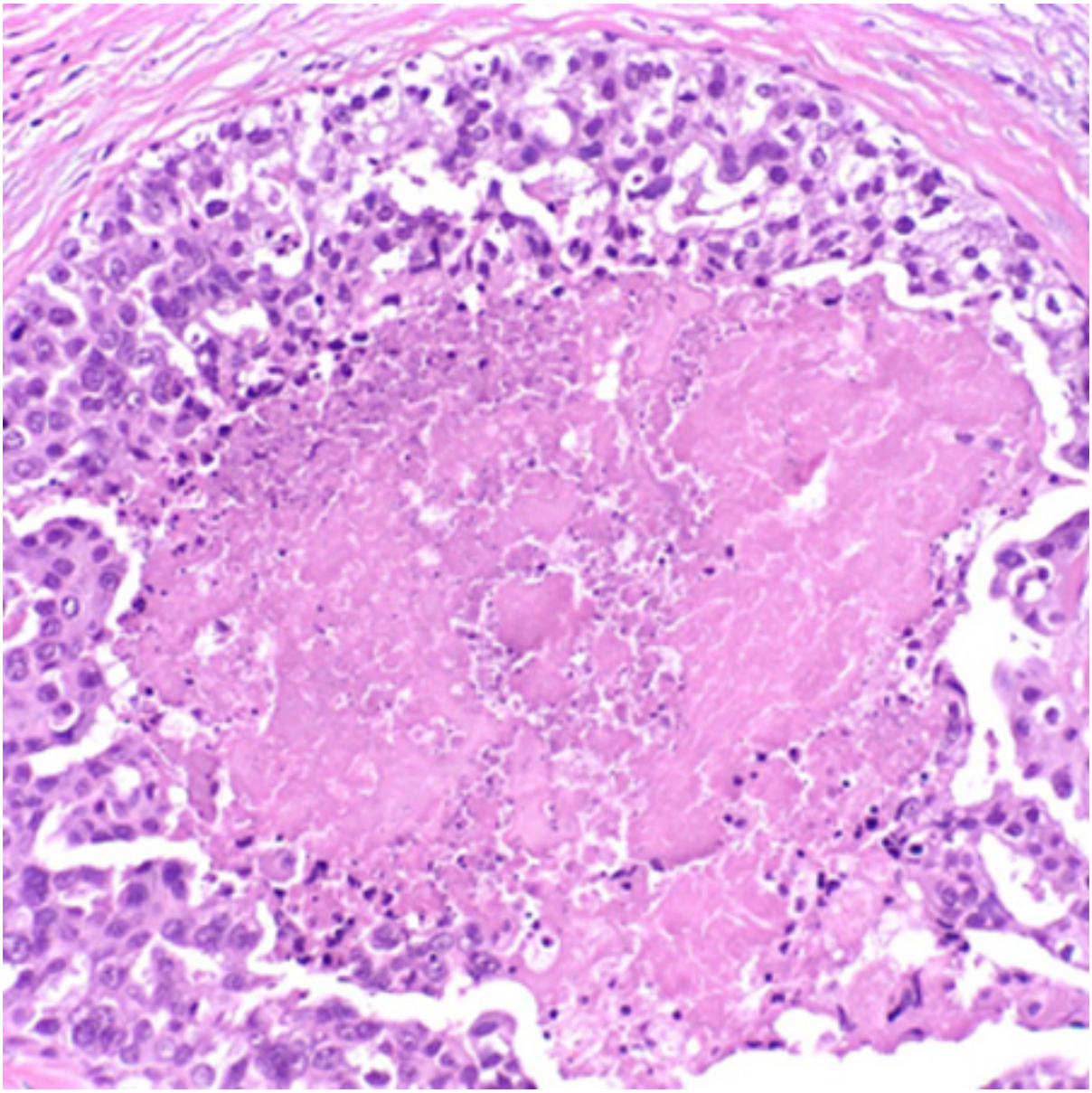
Diagnosis is with mammography, supplemented with other imaging, such as ultrasound or magnetic resonance imaging, and biopsy.

Chemoprophylaxis (e.g., with tamoxifen, raloxifene, or an aromatase inhibitor [anastrozole or exemestane]) can be used in high-risk patients. Some high-risk patients may choose to undergo preventive bilateral total mastectomy.

Treatment is usually lumpectomy (breast-conserving surgery) followed by radiotherapy.

Definition

Breast cancer in situ is a non-invasive breast cancer that is confined to the duct or lobule in which it originated and does not extend beyond the basement membrane. The cancer does not have access to distant spread through lymphatics or the bloodstream. Ductal carcinoma in situ (DCIS) is a potential precursor of invasive carcinoma and suggests that cancer will become invasive at that site.[1]



Ductal carcinoma in situ

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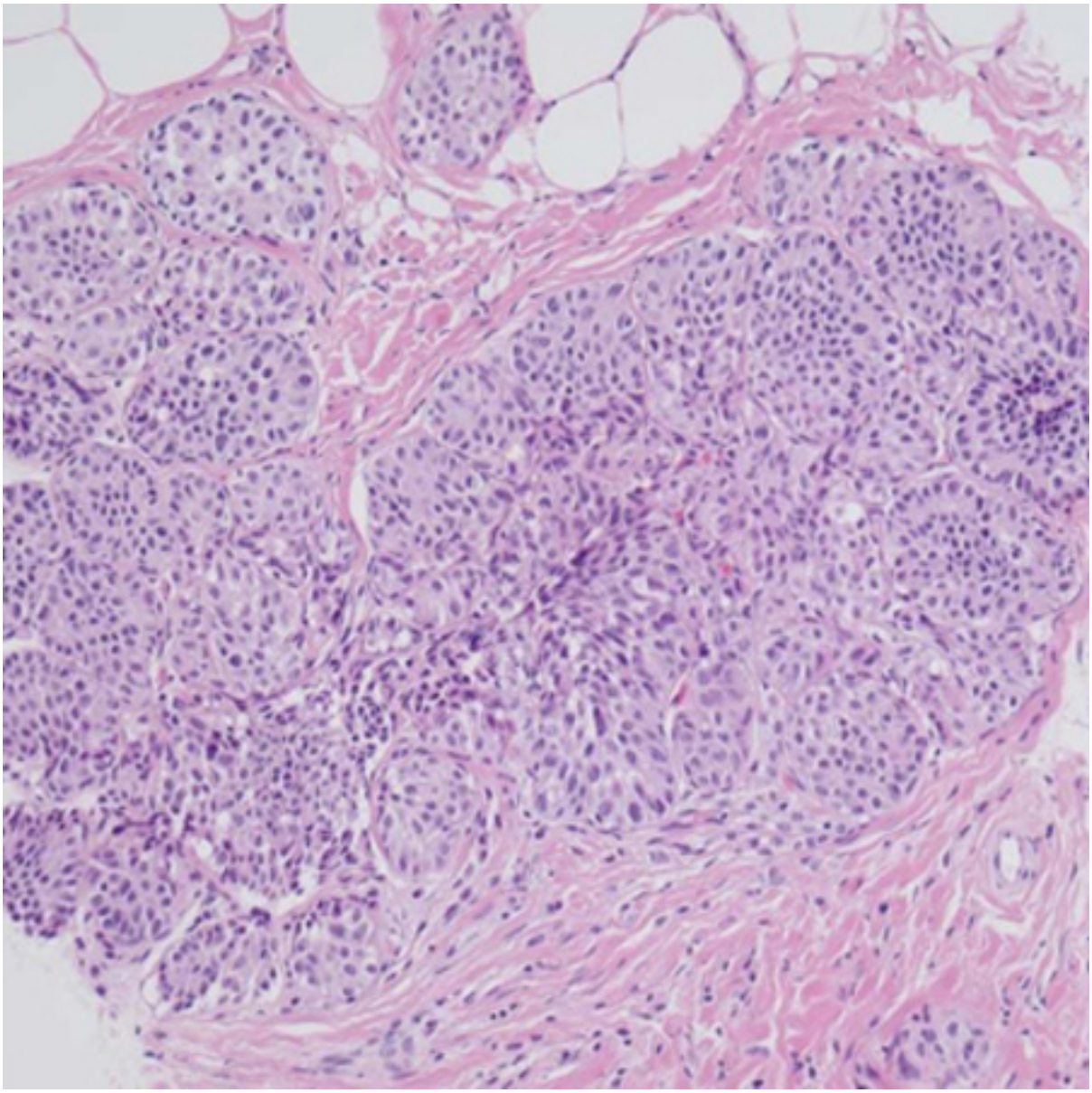
Lobular carcinoma in situ (LCIS) develops in breast lobule(s) and/or terminal ducts and is usually found incidentally. Whereas DCIS predicts an increased risk of invasive ductal carcinoma developing at the site of a biopsy demonstrating DCIS, LCIS implies increased risk of invasive ductal or lobular carcinoma developing in either breast.[2] LCIS is not cancer but a pathological description of a neoplastic proliferation of cells within lobules and/or terminal ducts, which is a risk factor for invasive breast cancer.[3] A finding of LCIS does not imply that cancer will form at the diagnostic site. Consequently, treatment for LCIS is less formalised than for DCIS.



Lobular carcinoma in situ

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Epidemiology

In the US, it has been estimated that in 2020 there will be 48,530 new cases of ductal carcinoma in situ (DCIS) in women. DCIS comprises approximately 85% and lobular carcinoma in situ (LCIS) is approximately 15% of in situ carcinomas of the breast. DCIS represents approximately one fifth of all new cases of breast cancer.[5]

The reported percentage of untreated cases of DCIS that will eventually progress to invasive disease varies widely, from 14% to 75%.[6] A diagnosis of LCIS confers an approximately 8- to 10-fold increased risk of breast cancer and the risk of invasive disease is equally distributed between both breasts.[7]

DCIS diagnosis peaks at age 70-74 years. Black, Hispanic, Chinese, and Korean women have a lower incidence of DCIS as compared with white women. The rate of diagnosis of DCIS in the US and Europe increased dramatically through the 1990s due to the widespread use of mammography, and has levelled off since. DCIS in men is uncommon, accounting for approximately 7% of all male breast carcinomas. Compared with invasive carcinomas of the breast, the prognosis associated with DCIS in men is excellent; however, clinical features, pathology, and treatment of this disease are not well defined in the literature.[8]

While it is well established that hormone replacement therapy (HRT) is associated with an increased risk of invasive breast cancer, there is not a similar association with HRT and DCIS.[9] The lack of association is consistent across five observational studies and one large randomised trial.[9]

The true incidence of LCIS is difficult to determine, with reports ranging from 0.07% to 3% in core biopsy specimens.[3] Multiple publications indicate that the incidence of LCIS is increasing, which may be attributed to better screening techniques, more core biopsies being carried out, and better recognition by pathologists. The incidence of LCIS increased from 0.9 in 100,000 person-years between 1978-1980, to 3.19 in 100,000 person-years from 1996-1998.[10] [3] Analysis of the Surveillance, Epidemiology, and End Results (SEER) data showed an increase the incidence of LCIS increased from 2.00 in 100,000 in 2000, to 2.75 in 100,000 in 2009.[7]

SEER data from 18,835 women diagnosed with LCIS from 1990-2015 demonstrated that, compared to white women, black women had a 30% higher risk of developing hormone receptor (HR) positive breast cancer and an 85% higher risk of developing HR-negative breast cancer.[11]

Lobular carcinoma, both in situ and invasive, is rare in males, with an incidence of about 0.5% to 1%.[12] [13]

Aetiology

Ductal carcinoma in situ (DCIS) is proliferation of malignant-appearing epithelial cells that have not penetrated the basement membrane.[14] The terminal duct lobular unit is the origin of most lesions. DCIS is part of a continuum of progression from benign disease to invasive cancer, which includes typical hyperplasia, atypical hyperplasia, DCIS, and invasive breast cancer.[15]

Similarly to invasive breast cancer, approximately two-thirds of DCIS specimens express oestrogen receptor, with the fraction of tumours expressing oestrogen receptor depending on the degree of differentiation.[6] HER2, a cell surface marker in the epidermal growth factor family that is used to guide therapy of invasive breast cancer, is expressed in both DCIS and invasive breast cancer, with higher rates of expression in DCIS.[16] A variety of other markers are differentially expressed in DCIS and invasive breast cancer compared with benign breast disease, including p53, vascular endothelial growth factor, and cyclin D1.[6]

Oestrogen levels, which are higher in women than in men, stimulate proliferation of breast epithelial cells in the lobules and ducts. Spontaneous mutations in epithelial cells, some of which provide a survival advantage to the cell, lead to precancerous changes. Further mutations lead to in situ or invasive breast cancer.[17]

Pathophysiology

Microarrays have been used to investigate the association of ductal carcinoma in situ (DCIS) and invasive breast cancer. There were greater associations seen between low-grade DCIS and low-grade invasive disease and high-grade DCIS and high-grade invasive disease, than between low- and high-grade DCIS.[6] This suggests that low-grade DCIS may progress to low-grade invasive cancer, and high-grade DCIS to high-grade invasive cancer.

Lobular carcinoma in situ (LCIS) develops in breast lobule(s) and/or terminal ducts and is usually found incidentally. Whereas DCIS predicts an increased risk of invasive duct carcinoma developing at the site of a biopsy demonstrating DCIS, LCIS implies increased risk of invasive ductal or lobular carcinoma developing in the future in either breast.[2] LCIS is not cancer but a pathologic description of a neoplastic proliferation of cells within lobules and/or terminal ducts, which is a risk factor for invasive breast cancer.[3] A finding of LCIS does not imply that cancer will form at the diagnostic site. Consequently, treatment for LCIS is less formalised than for DCIS.

Classification

Architectural classification of ductal carcinoma in situ (DCIS)[4]

Pathological analysis is necessary to determine the histological subtype. Architectural subtypes of DCIS are comedo and non-comedo. Non-comedo subtypes are further subdivided: the classification is descriptive, and there are no consistently associated clinical implications.

- Comedo
- Non-comedo
    - Cribriform
    - Micropapillary
    - Papillary
    - Solid
    - Clinging.

Case history

Case history #1

A 58-year-old white woman has clustered microcalcifications in the right breast on routine mammography screening, which were not seen on her previous mammogram. She is post-menopausal, has used hormone replacement therapy for 6 years, and has a BMI of 26. She has one sister who was diagnosed with breast cancer.

THEORY

Case history #2

A 55-year-old post-menopausal black woman presents with 2 new areas of breast nodularity that do not resolve. Mammography is negative.

Other presentations

Sixty percent of pure ductal carcinoma in situ is detected mammographically, most commonly in association with clustered microcalcifications. Other cases are found in women presenting with symptoms, such as nipple discharge (which may be bloody) or Paget's disease. There is no classic mammographic pattern for lobular carcinoma in situ. The disease is multi-focal or multi-centric in 40% to 90% of cases, and similar findings are present in the opposite breast in up to 50% of cases.

Approach

Ductal carcinoma in situ (DCIS) in women is typically asymptomatic and diagnosed during routine screening mammography. Less commonly, women with DCIS may present with a breast lump, nipple discharge, or Paget's disease of the breast. Lobular carcinoma in situ (LCIS) is usually discovered incidentally, often in conjunction with other clinically identified malignant or benign lesions such as fibroadenoma, cysts, papilloma, papillomatosis, fat necrosis, or breast abscesses.

There are no classic mammographic findings for LCIS, whereas DCIS often presents with clustered microcalcifications.[2]

Clinical assessment

DCIS and LCIS are typically asymptomatic.

Rarely, DCIS may present as an eczematous-like rash if presenting as Paget's disease. In the absence of medical attention, a woman may present with ulceration. Other uncommon presenting symptoms of DCIS include nipple discharge or a breast lump.

The first symptom in males diagnosed with DCIS is generally bloody nipple discharge.[44]

Imaging

A mammographic finding in one breast of clustered microcalcifications and absence of a soft tissue abnormality indicates DCIS. Calcifications may be linear, branching, or bizarre in comedo DCIS. Non-comedo DCIS may not be calcified or may present as fine granular powdery calcifications.

LCIS does not have classic mammographic findings.

In the absence of microcalcifications detected by mammography, either compression mammography, mammographic magnification views, ultrasonography, and/or magnetic resonance imaging (MRI) may be necessary. For non-specific lesions magnification views, with or without ultrasound, are generally performed. To differentiate cystic from solid lesions, ultrasound is performed.

Breast density, particularly in younger women, may render mammography ineffective and warrant supplemental ultrasonography or MRI.[45] [46]

MRI seems to be especially helpful in detecting high-grade DCIS, and is recommended for screening of high-risk women.[46] [47] [48] Available data are insufficient to recommend for or against using screening MRI for women with a history of breast carcinoma in situ.[49] Breast MRI should not be used routinely for the preoperative work-up of patients with DCIS.[50] [51] [52] Although MRI can detect accurately additional lesions and contralateral cancer not identified using conventional imaging in primary breast cancer, MRI findings should be pathologically verified because of the high false-positive rate.[53]

Biopsy

Fine-needle aspiration, core needle, or excisional biopsy techniques are used when breast cancer is suspected. The choice depends on the purpose of the procedure. Fine and core needle are performed for diagnostic purposes only, whereas excisional biopsy also removes the lesion. For a non-palpable mass, ultrasound-guided biopsy is preferred. For a palpable mass, biopsy may be guided by palpation.

Choice of technique is a matter of patient and surgeon preference to some extent. Radiologists perform only core or fine-needle biopsies, while surgeons perform all three.

- Fine-needle biopsy provides cytology, allows for rapid diagnosis (often within 24 hours), and yields good cosmesis. A disadvantage is that while cancer can be diagnosed, invasiveness, hormone receptor status, and HER2 expression cannot be assessed. There is a risk of false-positives and negatives. Fine-needle aspiration is not ideal, as it does not distinguish DCIS from invasive cancer, because tissue is required to assess architecture. For a patient desiring a rapid diagnosis, especially in a setting with cytological expertise, fine-needle biopsy may be a satisfactory choice.
- Core biopsy is often a good option. It causes more bruising than fine-needle biopsy, but less chance of false negatives or positives. However, results are also only diagnostic and not definitive, and may underestimate the extent of disease.[54] Architecturally, papillomas can cause false-positives. Furthermore, many breast malignancies contain elements of both in situ and invasive carcinoma. As such, a core biopsy demonstrating one component does not exclude the other when excisional biopsy is performed. Stereotactic (mammographically guided) biopsy is a form of core needle biopsy and is the diagnostic procedure of choice in the setting of microcalcifications, as it is nearly as accurate as excisional biopsy, with fewer complications.[55]
- Excisional biopsy provides a complete diagnosis and the opportunity for treatment. However, it is associated with poorer cosmesis than needle biopsies, is more costly, and necessitates surgery.

Pathological analysis of biopsy is necessary for scoring by nuclear grade and architecture.

Emerging procedures, such as ductal lavage or nipple aspirate fluid collection analysis, may prove to be useful for diagnosis.[56] However, concomitant use of detection markers may be required to improve sensitivity (e.g., basic fibroblast growth factor). More evidence is needed.

Sentinel lymph node biopsy (SNLB)

The use of SNLB is controversial. The incidence of positive lymph nodes is between 1% and 8%, depending on the characteristics of the DCIS (grade, tumour size). SNLB is frequently recommended if the DCIS is high grade and measures >2.5 cm in extent based on imaging.[57] This is because missed invasive disease is more likely under these circumstances. Many centres do not recommend SNLB in DCIS and reserve this procedure for use only if invasive disease is noted after excision. NCCN guidelines do not recommend in women with DCIS who are undergoing breast conserving surgery (unless when SLNB would be difficult to perform after surgery).[58] SLNB should be considered in women undergoing mastectomy due to the difficulty in performing the procedure after mastectomy.[58]

Hormone receptor testing

Oestrogen and progesterone receptor status is measured by immunohistochemical staining of fixed tumour tissue. Results can help to guide treatment.[59]

Genetic testing

The NCCN recommends genetic testing for breast cancer susceptibility genes (e.g., BRCA1, BRCA2, CDH1, PALB2, PTEN, TP53) in the following individuals:[60]

- Those with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene
- Those with a personal history of cancer who meet the following criteria:

- Breast cancer diagnosed at age ≤45 years
- Breast cancer diagnosed at age 46-50 years with: unknown or limited family history; or a second breast cancer diagnosed at any age; or at least one close blood relative with breast, ovarian, pancreatic, or high-grade (Gleason score ≥7) or intraductal prostate cancer at any age
- Triple-negative breast cancer diagnosed at age ≤60 years
- Breast cancer diagnosed at any age with: Ashkenazi Jewish ancestry; or at least one close blood relative with breast cancer at age ≤50 year, or ovarian, pancreatic, or metastatic or intraductal prostate cancer at any age; or three or more breast cancer diagnoses in the patient and/or close blood relatives
- Male breast cancer diagnosed at any age
- Epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age
- Exocrine pancreatic cancer at any age
- Metastatic or intraductal prostate cancer at any age
- High-grade (Gleason score ≥7) prostate cancer with: Ashkenazi Jewish ancestry; or at least one close relative with breast cancer at age ≤50 years, or ovarian, pancreatic, or metastatic or intraductal prostate cancer at any age; or two or more close relatives with breast or prostate cancer (any grade) at any age.

- Those with a family history of cancer who meet the following criteria:

  - An affected or unaffected individual with a first- or second-degree blood relative meeting any of the criteria above
  - An affected or unaffected individual who otherwise does not meet the criteria above, but has a >5% probability of a BRCA mutation.

The American Society of Breast Surgeons and the US Preventive Services Task Force have also published recommendations for genetic testing for breast cancer.[61] [62]

History and exam

Key diagnostic factors

presence of risk factors (common)

- Key factors include family history of breast cancer, benign breast disease on prior biopsy or hereditary syndromes such as Li-Fraumeni syndrome, Cowden's syndrome, or hereditary breast ovarian cancer syndrome.

family history of breast cancer (common)

- Increases risk for ductal carcinoma in situ (DCIS) 1.5-fold and for lobular carcinoma in situ (LCIS) 1.7-fold.[18]
- Some genetically defined syndromes increase risk of multiple cancers, including breast cancer: BRCA-related genes 1 and 2 (cancers of breast, fallopian tube, prostate, and ovary)[20] and Li-Fraumeni syndrome (breast cancer, osteosarcoma, and soft tissue sarcomas).

Other diagnostic factors

nipple discharge (common)

- Unilateral discharge, whether bloody or not, may indicate a benign tumour such as a papilloma, or less commonly ductal carcinoma in situ or invasive breast cancer.
- The first symptom in males diagnosed with DCIS is generally bloody nipple discharge.[44]

breast lump (uncommon)

- Can be smooth or nodular.

eczema-like rash on breast (uncommon)

- Bleeding from or excoriation of the nipple are typical presenting signs of Paget's disease of the breast.

ulceration (uncommon)

- Breast cancer that is ignored can present as an ulcerating skin lesion.

Risk factors

Strong

family history of breast cancer

- Increases risk for ductal carcinoma in situ (DCIS) 1.5-fold and for lobular carcinoma in situ (LCIS) 1.7-fold.[18]
- May increase risk of DCIS because of genetic factors, shared exposures to other risk factors, or because women with a positive family history are more likely to have regular mammography.
- Because DCIS is most often first detected mammographically, mammography frequency often confounds studies of DCIS incidence.[19]
- Some genetically defined syndromes increase risk of multiple cancers, including breast cancer: BRCA-related genes 1 and 2 (cancers of breast, fallopian tube, prostate, and ovary)[20] and Li-Fraumeni syndrome (breast cancer, osteosarcoma, and soft tissue sarcomas).

benign breast disease on prior biopsy

- Increases risk for ductal carcinoma in situ up to 3.5-fold and for lobular carcinoma in situ up to 4.2-fold.[18]

hereditary breast ovarian cancer syndrome

- Approximately 85% of hereditary breast and ovarian cancers are caused by mutations in BRCA1 or BRCA2 genes.[21]
- In one prospective cohort study, the cumulative risk of breast cancer up to age 80 years was found to be similar for BRCA1 carriers (72%, 95% confidence interval [CI] 65% to 79%) and BRCA2 carriers (69%, 95% CI 61% to 77%). However, up to age 50 years, the cumulative risk was found to be higher for BRCA1 carriers.[20]

Li-Fraumeni syndrome

- Li-Fraumeni syndrome, caused by mutations in the TP53 gene; it is characterised by early-onset (<40 years old) breast cancer, soft tissue sarcomas, leukaemia, primary brain tumours, and adrenocortical

carcinomas. Among patients with Li-Fraumeni syndrome, up to one third of the cancers are of breast origin.[22]

Cowden syndrome

- Cowden syndrome is caused by mutations in the PTEN gene.
- Approximately 75% of women with the syndrome have benign breast disease and 25% to 50% will develop breast cancer.[23]

hereditary diffuse gastric cancer (HDGC)

- HDGC is caused by germline mutations in the CDH1 (E-cadherin) gene and predisposes an individual to breast and colorectal cancer.[24] In one study, the cumulative risk of breast cancer in women with CDH1 mutations was 39%. The breast tumours tend to be of the lobular subtype.[24]

Peutz-Jeghers syndrome

- Peutz-Jeghers syndrome is caused by mutations in the STK11 gene and predisposes to cancers, particularly breast and gynaecological cancers.[25] [26] One study reported a relative risk of 20.3 for breast and gynaecological cancer in women with Peutz-Jeghers.[27]

Klinefelter's syndrome

- There is an increased risk of breast cancer in males with Klinefelter's syndrome.[28]

Weak

older age at menopause

- Increases the risk of both ductal carcinoma in situ and lobular carcinoma in situ[18]

older age at first full-term pregnancy

- Age at first birth influences risk of ductal carcinoma in situ but not so clearly lobular carcinoma in situ.[18]

nulliparity

- May be associated with an increased risk of ductal carcinoma in situ but not clearly lobular carcinoma in situ.[18]

low physical activity

- Lifetime physical activity is associated with an approximately 35% lower risk of in situ carcinoma compared to women with an inactive lifestyle.[29]

high vitamin A intake

- High vitamin A intake may be associated with increased risk of ductal carcinoma in situ but not lobular carcinoma in situ.[30]

ataxia telangiectasia

- This autosomal-recessive condition, which results in cerebellar ataxia, immune defects, telangiectasias, radiosensitivity, and a predisposition to malignancy, is caused by mutations in the ATM gene.[31]
- Study results vary regarding the influence of this mutation on breast cancer risk.[32]

Investigations

1st test to order

Test	Result
mammography • Mammography is recommended for screening and diagnosis. • Guideline recommendations differ on when to start screening and on screening frequency. In the US, recommendations for bilateral mammography screening in average-risk women range from yearly starting at age 40 years (National Comprehensive Cancer Network) to every 2 years starting at age 50 years (US Preventive Services Task Force).[63] [64] • The UK NHS Breast Screening Programme offers routine mammographic screening every 3 years to all women from age 50 years. [Public Health England: NHS breast screening (BSP) programme] (https://www.gov.uk/topic/population-screening-programmes/breast) The UK National Institute for Health and Care Excellence recommends annual mammographic screening from age 40 years in women at moderate risk of breast cancer.[65] The European Society for Medical Oncology recommends annual or biennial mammographic screening in all women from age 50 years. • Screening may be performed in younger women who have a family history of the disease or who present with a breast mass, unilateral nipple discharge, or Paget's disease. • A mammographical finding of clustered calcifications, either focal or diffuse, and absence of a soft tissue abnormality suggests ductal carcinoma in situ. Compression views may be performed to determine if a mammographical finding is real or an artifact. Magnification views are indicated in non-specific lesions. • Lobular carcinoma in situ does not have classic mammographical findings.	**calcifications**

Other tests to consider

Test	Result
biopsy (fine-needle or core) • Comedo lesion and high nuclear grade indicate more aggressive ductal carcinoma in situ. Size of lesion, margin size, comedo, nuclear grade, and age are used to determine Van Nuys score.	**necrosis and high nuclear grade**
stereotactic biopsy • Preferred method of biopsy if microcalcifications are present. • Performed with a patient prone on a metal table through which the breast descends. The lesion is then localised in two planes and the biopsy carried out.	**necrosis and high nuclear grade**
sentinel lymph node biopsy (SNLB) • Should be strongly considered in women diagnosed with ductal carcinoma in situ who are scheduled to undergo mastectomy, or breast conserving surgery when SLNB after surgery will be difficult to perform.[57]	**may show metastasis, indicating missed invasive carcinoma**
ultrasound-guided biopsy • Preferred if a non-palpable mass is found on imaging. • A handheld ultrasound is used to guide the biopsy needle and the biopsy carried out.	**necrosis and high nuclear grade**
magnetic resonance imaging (MRI) • Breast density, particularly in younger women, may render mammography ineffective and warrant supplemental ultrasonography or MRI.[45] [46] • MRI seems to be especially helpful in detecting high-grade ductal carcinoma in situ, and is recommended for screening of high-risk women.[46] [47]	**tissue enhancement, especially with high grade ductal carcinoma in situ**
ultrasonography • Ductal carcinoma in situ presenting as a mass may be detected ultrasonographically. For solid lesions, a taller-than-wide shape is more suspicious than wider-than-tall. Indicated if mammogram is non-specific or shows no microcalcification or to distinguish between solid or cystic lesions.	**cystic versus solid lesion; shape of solid lesion**
hormone receptor testing • Oestrogen and progesterone receptor status is measured by immunohistochemical staining of fixed tumour tissue. Results can help to guide treatment.	**positive or negative**
genetic testing • The NCCN recommends genetic testing for breast cancer susceptibility genes (e.g., BRCA1, BRCA2, CDH1, PALB2, PTEN, TP53) in a range of individuals with a personal or family history of various cancers.[60]	**may be positive**

Emerging tests

Test	Result
nipple aspirate fluid • Cytology is very specific but not sensitive in detecting breast cancer.[56] • Other detection markers, in combination with cytology, may improve sensitivity: for example, basic fibroblast growth factor. However, more evidence is needed.	**may show malignant cells**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Locally invasive breast cancer	• More commonly presents as a breast lump with or without nipple inversion, discharge, or tenderness.	• Mammographic microcalcifications may be pure ductal carcinoma in situ (DCIS) or have an invasive component, which can be detected on core or excisional biopsy.[66] • Lesions are not confined to the duct but have invaded surrounding tissue.
Atypical hyperplasia	• Difficult to distinguish clinically, as it is generally asymptomatic.	• Atypical hyperplasia on pathology.
Fibroadenoma	• Presents as a breast lump on examination. • If lump is palpable, it is typically freely mobile.	• Mammographic calcifications that are large, are round, have sharp edges, and are diffuse are typically benign.[66]
Breast cyst	• Most commonly presents as a breast lump and tenderness. • May occur in association with menstrual cycle.	• Mammographic calcifications that are large, are round, have sharp edges, and are diffuse are typically benign.[66]

Criteria

University of Southern California (USC)/Van Nuys prognostic index for ductal carcinoma in situ (DCIS)[67]

The Van Nuys classification system incorporates nuclear grade and necrosis into a pathology score of high nuclear grade, non-high grade with necrosis, and non-high grade without necrosis. The pathology score is then combined with margin size, tumour size, and age for prognostic classification. A low score is 4-6, intermediate score is 7-9, and high score is 10-12.

Size (score):

- <15 mm (1)
- 16-40 mm (2)
- >41 mm (3).

Margin (score):

- >10 mm (1)
- 1-9 mm (2)
- <1 mm (3).

Age (score):

- >61 years (1)
- 40-61 years (2)
- <39 years (3).

Pathological classification (score):

- NG1 non-high grade without necrosis (1)
- NG2 non-high grade with necrosis (2)
- NG3 high grade (3).

Gail model of breast cancer risk assessment[68]

Combines the number of previous breast biopsies, presence of atypical hyperplasia in any previous breast biopsy specimen, reproductive history (age at the start of menstruation and age at the first live birth of a child), and history of breast cancer among first-degree relatives (mother, sisters, daughters) to estimate risk of developing invasive breast cancer over specific periods of time. Applies to women aged 35-74 years. Not accurate in the setting of prior DCIS, lobular carcinoma in situ (LCIS), or invasive breast cancer.

Claus (CASH) model of breast cancer risk assessment[68]

Genetic models were adapted to age-specific familial recurrence data. Less commonly used in practice than the Gail model, but better at factoring in second-degree relatives and lobular neoplasia.

Screening

Mammography

Early detection is highly effective in reducing mortality associated with breast cancer. Nonetheless, screening leads to over-diagnosis and over-treatment of breast disease in many women, and women invited to screening should be informed of both the benefits and harms.[69]

Breast cancer guideline recommendations differ on when to start screening and screening frequency.

- The American Cancer Society (ACS) guidelines recommend regular screening mammography for all women 45 years and older.[47] The ACS suggests annual screening between 45-54 years, and biennial screening for women 55 and older (with the opportunity to continue annual screening) so long

as they are in good health and their life expectancy is 10 years or more. Women aged 40-44 years should be offered the opportunity to begin annual screening. The ACS recommends both bilateral mammography and breast magnetic resonance imaging (MRI) for women with a >20% lifetime breast cancer risk.[47] This includes women with a known BRCA1 or BRCA2 gene mutation, women with a first-degree relative (mother, father, brother, sister, or child) with a BRCA1 or BRCA2 gene mutation, women with a Gail or Claus model lifetime risk of ≥20%, women with a history of chest irradiation between the ages of 10-30 years, and women with a personal or family history of one of the following hereditary conditions: breast ovarian cancer syndrome, Li-Fraumeni syndrome, Cowden syndrome, Peutz-Jeghers syndrome, hereditary diffuse gastric cancer, or ataxia telangiectasia.[18] [38] [National Cancer Institute: breast cancer risk assessment tool] (http://www.cancer.gov/bcrisktool)

- The US Preventive Services Task Force recommends starting regular, biennial screening mammography between the ages of 50-74 years.[63] Screening prior to 50 years of age should be decided by women on an individual basis.[63]
- The American College of Obstetricians and Gynecologists revised breast cancer screening guidelines recommend that women of average breast cancer risk should be offered screening mammography at age 40 years.[70] If screening is not started at age 40 years, then it should start no later than age 50 years. The decision about the age to begin screening should be a shared decision between the patient and her healthcare provider. The discussion should include information on potential benefits and harms. Once started, screening should occur every one to two years and continue until age 75 years, after which continued screening should be a shared decision between the patient and her healthcare provider regarding potential benefits and harms.
- The National Comprehensive Cancer Network guidelines recommend that women of average breast cancer risk should be offered screening mammography at age 40 years.[64] An upper age limit for screening is not specified in the guidelines, but it is suggested that screening should be stopped if a woman has severe comorbidities that limit life expectancy and no further intervention would occur based on the screening results.
- In the UK, the NHS Breast Screening Programme offers routine breast screening every 3 years for all women between 50-70 years of age. In England, by the end of 2016, the age range for routine breast screening will be extended to cover ages 47-73 years. [Public Health England: NHS breast screening (BSP) programme] (https://www.gov.uk/topic/population-screening-programmes/breast)
- The National Institute for Health and Care Excellence makes the following recommendations for surveillance of women at increased risk of breast cancer:[71]
    - Surveillance for women with no personal history of breast cancer
        - Offer annual mammographic surveillance to women:
            - Aged 40-49 years at moderate risk of breast cancer
            - Aged 40-59 years at high risk of breast cancer but with a ≤30% probability of being a BRCA or TP53 carrier
            - Aged 40-59 years who have not had genetic testing but have a >30% probability of being a BRCA carrier
            - Aged 40-69 years with a known BRCA1 or BRCA2 mutation.
        - Offer annual MRI surveillance to women:
            - Aged 30-49 years who have not had genetic testing but have a >30% probability of being a BRCA carrier
            - Aged 30-49 years with a known BRCA1 or BRCA2 mutation
            - Aged 20-49 years who have not had genetic testing but have a >30% probability of being a TP53 carrier
            - Aged 20-49 years with a known TP53 mutation.
    - Surveillance for women with a personal and family history of breast cancer

- Offer annual mammographic surveillance to all women aged 50-69 years with a personal history of breast cancer who:
    - Remain at high risk of breast cancer (including those who have a BRCA1 or BRCA2 mutation) and
    - Do not have a TP53 mutation.
- Offer annual MRI surveillance to all women aged 30-49 years with a personal history of breast cancer who remain at high risk of breast cancer, including those who have a BRCA1 or BRCA2 mutation.

- The 2019 European Society for Medical Oncology (ESMO) guidelines recommend annual or biennial screening with mammography in all women aged 50-69 years. This may also be offered to women aged 40-49 years and women aged 70-74 years. If there is a strong family history of breast cancer, with or without known BRCA mutations, annual MRI and mammography are recommended.[48]

In younger women, breast density limits mammographic sensitivity and MRI or ultrasound may be useful screening tools. A cohort study in the US suggests that combining a measure of breast density (BI-RADS) with breast cancer risk (Breast Cancer Surveillance Consortium 5-year risk) is a possible strategy for identifying women at the highest risk of advanced cancer, who may benefit from supplemental imaging.[72]

Screening mammography is not routinely performed in men.

Breast examination

All adult women can perform a monthly breast self-examination to detect lumps. However, ductal carcinoma in situ is generally detected by mammography before it is palpable, so this physical examination of the breast is more likely to detect invasive cancer. Breast examination is rarely of benefit to detect lobular carcinoma in situ.

Approach

The treatment for breast cancer is complex and highly individualised, and takes into consideration many different factors, including age, performance status, disease stage, tumour type, tumour biology (e.g., hormone-receptor status), and prognosis (risk of recurrence).

Due to the complexities of treatment, patients are best managed by a multidisciplinary team of breast cancer specialists comprised of medical oncologists, surgeons, radiation oncologists, radiologists, pathologists, and nurses. Patients should be involved in decision making and treatment planning throughout the course of treatment.

The main goal of primary treatment for patients with breast cancer in situ is to prevent progression to invasive breast cancer.

The treatment approach differs for low-risk and high-risk ductal carcinoma in situ and for lobular carcinoma in situ.

Primary treatment: low-risk ductal carcinoma in situ (DCIS)

The primary treatment options for patients with low-risk DCIS (e.g., DCIS that is screen detected, unifocal, unicentric, low to intermediate grade, and <2.5 cm) are breast-conserving therapy (involving wide local surgical excision of the tumour [lumpectomy] followed by adjuvant radiotherapy), or total mastectomy (with or without breast reconstruction). The approach to undertake should be a shared decision between the patient and treating clinicians. Both approaches have demonstrated equivalent outcomes in terms of overall survival.[58] [73]

Guidelines generally recommend breast conserving therapy as the primary treatment for most patients with low-risk DCIS.[58] [48] The optimal post-surgical margin following breast-conserving therapy for DCIS is ≥2 mm.[48] [74] If one or more of the post-surgical margins is <2 mm, re-excision or mastectomy is recommended.[75]

Breast reconstruction should be discussed with all patients who plan to undergo mastectomy. It can be performed at the time of mastectomy (immediate reconstruction) or a later time (delayed reconstruction).

Some patients with low-grade DCIS may be considered for lumpectomy alone (e.g., if there are clear margins >1 cm in all directions).[76] [77] However, this approach is controversial as most studies show that adjuvant radiation therapy decreases the risk of disease recurrence (local and distant) in all subgroups of women with DCIS.[78] [79] [80] Guidelines advise that lumpectomy alone is only appropriate for patients with a low risk of recurrence and following a discussion between the physician and patient on the risks and benefits.[58] If surgery alone is undertaken, then frequent follow-up should be performed during the first 3-5 years in order to detect disease recurrence early.

Axillary lymph node surgical staging:

Axillary lymph node surgical staging is controversial in patients with DCIS. Guidelines recommend against sentinel lymph node biopsy (SLNB) for women with DCIS who are undergoing lumpectomy, unless the lumpectomy procedure includes the axilla making it difficult to perform a SLNB in the future.[58] SLNB should be strongly considered in patients undergoing mastectomy, in case invasive disease is found in the excised specimen.[58] Performing a SLNB after mastectomy is impractical.

Adjuvant radiotherapy:

Most patients receive adjuvant whole breast radiation therapy (WBRT) following lumpectomy in order to treat microscopic disease and to reduce the risk of ipsilateral recurrence.[58] Approximately 50% of ipsilateral recurrences are DCIS (i.e., noninvasive) and 50% are invasive.[81]

In an observational study, the use of adjuvant WBRT in women with DCIS who underwent breast conserving surgery was associated with an approximately 50% decrease in the ipsilateral recurrence rate compared with no adjuvant radiotherapy.[73]

Although radiotherapy decreases the risk of ipsilateral recurrence (non-invasive and invasive), it does not decrease the risk of distant recurrence or breast cancer specific mortality.[58] [73]

Radiotherapy boost to the tumour bed may be offered along with adjuvant WBRT, depending on individual patient factors and patient preference.[58] [48] In an observational study, the use of a radiotherapy boost after WBRT in patients with DCIS was associated with a reduction in the risk of ipsilateral recurrence.[82] Studies evaluating a radiotherapy boost in DCIS are ongoing to determine which patients are most likely to benefit from boost therapy.[83] [84]

Accelerated partial breast irradiation (APBI) is an alternative to WBRT in certain patients with low-risk DCIS (e.g., those aged ≥50 years who have all of the following tumour characteristics: screen-detected DCIS, low to intermediate nuclear grade, tumour size ≤2.5 cm, and surgical resection with negative margins >3 mm).[58] [48] [85] [81] [86] [87] [88]

APBI delivers higher doses of radiation over a shorter time period specifically to the tumour or tumour bed and surrounding breast tissue, therefore, sparing healthy breast tissue and reducing treatment time and some treatment-related adverse effects.[89] [85] Several approaches can be used for APBI (e.g., intra-operative radiotherapy; 3D conformal radiotherapy; intensity-modulated radiotherapy; or brachytherapy).

One randomised controlled trial comparing adjuvant APBI with adjuvant WBRT in women with DCIS or early stage invasive breast cancer reported similar efficacy in preventing local recurrence.[90] WBRT was associated with a higher risk for early complications (e.g., radiation dermatitis, breast pain, and pneumonitis), whereas long term complications were more common following APBI (e.g., breast pain, skin telangiectasia, and breast fibrosis with poor cosmesis.[90]

Radiotherapy delivers local or local and regional therapy, and adverse effects are localised to the area(s) through which the radiation passes. The most common acute adverse effects are skin changes (similar to sunburn) and fatigue. The skin may tan, either temporarily or permanently. The irradiated breast may appear smaller due to both surgical and radiotherapy. In patients receiving WBRT, a small portion of the lung and ribs receive radiation, which can induce lung scarring and slightly increase the risk of rib fracture. Furthermore, the heart is incidentally exposed to small doses of radiation when treating left sided breast cancers, which may increase the risk of ischaemic heart disease.[91] Risk of ischaemic heart disease may increase with increasing doses of radiation to the heart.[91] Newer techniques minimise the dose and, therefore, sequelae.

Primary treatment: high-risk DCIS

Mastectomy is generally recommended for high-risk patients, for example those with DCIS in two or more quadrants (multicentric disease). If there are two or more sites of disease in the same quadrant (multifocal disease), mastectomy should be considered because it may not be feasible to surgically clear the disease and achieve a good cosmetic outcome with breast-conserving therapy.[58]

Patients who present with a palpable mass and/or imaging showing a formed lesion, and those with histologically high grade DCIS are considered high risk and should be considered for mastectomy.[92]

DCIS in males is generally treated with mastectomy.[93]

Disease recurrence is low following total mastectomy for DCIS.[94] [95]

Axillary lymph node surgical staging:

SLNB should be strongly considered in patients undergoing mastectomy, in case invasive disease is found in the excised specimen.[58] Performing a SLNB after mastectomy is impractical. The chance that an initial diagnosis of DCIS will be upgraded to invasive breast cancer is more likely if the disease is high grade and/or >2.5 cm (based on imaging).[48] [58] [96]

Adjuvant radiotherapy:

Adjuvant radiotherapy is not needed for DCIS treated with mastectomy unless disease is present near or at the chest wall, or if there is a substantial positive surgical margin.

Adjuvant (postoperative) systemic treatment for DCIS

The hormone receptor status of the tumour is determined to guide decision making about adjuvant systemic treatment with endocrine therapy. Most patients with hormone receptor-positive DCIS receive adjuvant endocrine therapy to reduce the risk of ipsilateral and/or contralateral invasive breast cancer.

For pre-menopausal women and women aged ≥60 years, tamoxifen is considered first-line therapy for risk reduction of the ipsilateral breast after breast-conserving therapy (i.e., lumpectomy followed by adjuvant radiotherapy), and for risk reduction of the contralateral breast after either mastectomy or breast-conserving therapy has been completed.[58] Tamoxifen is effective in preventing recurrence in patients with oestrogen receptor-positive breast cancer (both invasive and noninvasive), as well as in decreasing the risk of oestrogen receptor-positive cancers developing in the contralateral breast.[97] The duration of tamoxifen treatment is 5 years.

For postmenopausal women aged <60 years and those with increased risk of thromboembolism, an aromatase inhibitor (e.g., anastrozole or exemestane) is considered first line therapy for risk reduction after surgery.[58] [48] [98] The duration of aromatase inhibitor treatment is 5 years.

There are no strong data available for the treatment of older women with DCIS. Guidelines from the European Society of Breast Cancer Specialists suggest that healthy women >70 years of age with localised DCIS should be considered for breast conserving therapy.[99] Tamoxifen after breast conserving therapy decreases local failure independent of age.[100] The duration of tamoxifen treatment is 5 years.

Lobular carcinoma in situ (LCIS)

Treatment for LCIS includes observation and counselling, with or without long-term endocrine therapy with tamoxifen (in pre-menopausal and postmenopausal women), or raloxifene, anastrozole, or exemestane (in postmenopausal women); or bilateral preventive (prophylactic) mastectomy. Tamoxifen and raloxifene have been found to decrease the risk of LCIS progression to invasive breast cancer.[33] [101] [102] Duration of endocrine therapy is 5 years.

The choice of observation versus bilateral mastectomy for women with LCIS is based on patient preference and assessment of risk of developing invasive disease.[33]

Patients who are anxious about the future risk of developing invasive breast cancer, have a strong family history of breast cancer, or who otherwise are at high risk may opt for bilateral mastectomy. Those with incidentally found LCIS, who are otherwise at low risk and have a low level of anxiety may opt for observation and counselling, with or without long-term endocrine therapy. If there is concern about progression of LCIS in patients undergoing observation, the management approach might be revised, based on clinical, imaging and pathology results.

Lobular carcinoma, both in situ and invasive, is rare in males.[13]

Local recurrence of DCIS

Patients with local recurrence of DCIS following breast conserving therapy are treated with mastectomy (with or without breast reconstruction) and SLNB if not previously done.[33] Re-excision followed by adjuvant radiotherapy is an option in patients who have had surgical excision without prior radiotherapy.

Patients with local recurrence of DCIS following mastectomy may undergo re-excision (if clear margins and acceptable cosmesis can be obtained) followed by adjuvant radiotherapy (if not previously given).[33]

A decision about endocrine therapy is made in the context of the previous treatment the patient has received, the hormone receptor status of the disease (if this information is available), and following discussion about the risks and benefits of the treatment options.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)		
women with low-risk ductal carcinoma in situ		
	1st	surgical excision or mastectomy ± breast reconstruction
	adjunct	axillary lymph node surgical staging
	adjunct	radiotherapy
	adjunct	endocrine therapy
women with high-risk DCIS; all men with DCIS		
	1st	mastectomy ± breast reconstruction
	adjunct	axillary lymph node surgical staging
	adjunct	radiotherapy
	adjunct	endocrine therapy
lobular carcinoma in situ		
▪ low risk and low patient anxiety	1st	observation and counselling
	adjunct	endocrine therapy
▪ high risk or high patient anxiety	1st	bilateral (prophylactic) mastectomy

Ongoing (summary)		
local recurrence of DCIS		
▪ following surgical excision with radiotherapy (breast-conserving therapy, surgical excision with radiotherapy)	1st	mastectomy ± breast reconstruction
	adjunct	axillary lymph node surgical staging
▪ following surgical excision without prior radiotherapy	1st	re-excision plus radiotherapy
▪ following mastectomy	1st	re-excision ± adjuvant radiotherapy

MANAGEMENT

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

women with low-risk ductal carcinoma in situ

1st **surgical excision or mastectomy ± breast reconstruction**

» The primary treatment options for women with low risk ductal carcinoma in situ (DCIS; e.g., DCIS that is screen detected, unifocal, unicentric, low to intermediate grade, and <2.5 cm) are breast-conserving therapy (involving wide local surgical excision of the tumour [lumpectomy] followed by adjuvant radiotherapy), or total mastectomy (with or without breast reconstruction).

» The approach to undertake should be a shared decision between the patient and treating clinicians. Both approaches have demonstrated equivalent outcomes in terms of overall survival.[58] [73]

» Guidelines generally recommend breast conserving therapy as the primary treatment for most patients with low-risk DCIS.[58] [48] The optimal post-surgical margin following breast-conserving therapy for DCIS is ≥2 mm.[48] [74] If one or more of the post-surgical margins is <2 mm, re-excision or mastectomy is recommended.[75]

» Breast reconstruction should be discussed with all patients who plan to undergo mastectomy. It can be performed at the time of mastectomy (immediate reconstruction) or a later time (delayed reconstruction).

» Some patients with low-grade DCIS may be considered for lumpectomy alone (e.g., if there are clear margins >1 cm in all directions).[76] [77] However, this approach is controversial as most studies show that adjuvant radiation therapy decreases the risk of disease recurrence (local and distant) in all subgroups of women with DCIS.[78] [79] [80]

» Guidelines advise that lumpectomy alone is only appropriate for patients with a low risk of recurrence and following a discussion between the physician and patient on the risks and benefits.[58] If surgery alone is undertaken, then frequent follow-up should be performed during the first 3-5 years in order to detect disease recurrence early.

adjunct **axillary lymph node surgical staging**

Acute

Treatment recommended for SOME patients in selected patient group

» [103]

» Axillary lymph node surgical staging is controversial in patients with DCIS. Guidelines recommend against sentinel lymph node biopsy (SLNB) for women with DCIS who are undergoing lumpectomy, unless the lumpectomy procedure includes the axilla making it difficult to perform a SLNB in the future.[58] SLNB should be strongly considered in patients undergoing mastectomy, in case invasive disease is found in the excised specimen.[58] Performing a SLNB after mastectomy is impractical.

adjunct **radiotherapy**

Treatment recommended for SOME patients in selected patient group

» Most patients receive adjuvant whole breast radiation therapy (WBRT) following lumpectomy in order to treat microscopic disease and to reduce the risk of ipsilateral recurrence.[58] Approximately 50% of ipsilateral recurrences are DCIS (i.e., noninvasive) and 50% are invasive.[81]

» In an observational study, the use of adjuvant WBRT in women with DCIS who underwent breast conserving surgery was associated with an approximately 50% decrease in the ipsilateral recurrence rate compared with no adjuvant radiotherapy.[73]

» Although radiotherapy decreases the risk of ipsilateral recurrence (non-invasive and invasive), it does not decrease the risk of distant recurrence or breast cancer specific mortality.[58] [73]

» Radiotherapy boost to the tumour bed may be offered along with adjuvant WBRT, depending on individual patient factors and patient preference.[58] [48] In an observational study, the use of a radiotherapy boost after WBRT in patients with DCIS was associated with a reduction in the risk of ipsilateral recurrence.[82] Studies evaluating a radiotherapy boost in DCIS are ongoing to determine which patients are most likely to benefit from boost therapy.[83] [84]

» Accelerated partial breast irradiation (APBI) is an alternative to WBRT in certain patients with low-risk DCIS (e.g., those aged ≥50 years who have all of the following tumour characteristics: screen-detected DCIS, low to intermediate nuclear grade, tumour size ≤2.5 cm, and surgical

Acute

resection with negative margins >3 mm).[58] [48] [85] [81] [86] [87] [88]

» APBI delivers higher doses of radiation over a shorter time period specifically to the tumour or tumour bed and surrounding breast tissue, therefore, sparing healthy breast tissue and reducing treatment time and some treatment-related adverse effects.[89] [85] Several approaches can be used for APBI (e.g., intra-operative radiotherapy; 3D conformal radiotherapy; intensity-modulated radiotherapy; or brachytherapy).

» One randomised controlled trial comparing adjuvant APBI with adjuvant WBRT in women with DCIS or early stage invasive breast cancer reported similar efficacy in preventing local recurrence.[90] WBRT was associated with a higher risk for early complications (e.g., radiation dermatitis, breast pain, and pneumonitis), whereas long term complications were more common following APBI (e.g., breast pain, skin telangiectasia, and breast fibrosis with poor cosmesis.[90]

» Radiotherapy delivers local or local and regional therapy, and adverse effects are localised to the area(s) through which the radiation passes. The most common acute adverse effects are skin changes (similar to sunburn) and fatigue. The skin may tan, either temporarily or permanently. The irradiated breast may appear smaller due to both surgical and radiotherapy. In patients receiving WBRT, a small portion of the lung and ribs receive radiation, which can induce lung scarring and slightly increase the risk of rib fracture. Furthermore, the heart is incidentally exposed to small doses of radiation when treating left sided breast cancers, which may increase the risk of ischaemic heart disease.[91] Risk of ischaemic heart disease may increase with increasing doses of radiation to the heart.[91] Newer techniques minimise the dose and, therefore, sequelae.

adjunct **endocrine therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» tamoxifen: 20 mg orally once daily

OR

» anastrozole: 1 mg orally once daily

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OR

» exemestane: 25 mg orally once daily

» Most patients with hormone receptor-positive DCIS receive adjuvant endocrine therapy to reduce the risk of ipsilateral and/or contralateral invasive breast cancer.

» For pre-menopausal women and women aged ≥60 years, tamoxifen is considered first-line therapy for risk reduction of the ipsilateral breast after breast-conserving therapy (i.e., lumpectomy followed by adjuvant radiotherapy), and for risk reduction of the contralateral breast after either mastectomy or breast-conserving therapy has been completed.[58] Tamoxifen is effective in preventing recurrence in patients with oestrogen receptor-positive breast cancer (both invasive and noninvasive), as well as in decreasing the risk of oestrogen receptor-positive cancers developing in the contralateral breast.[97] The duration of tamoxifen treatment is 5 years.

» For postmenopausal women aged <60 years and those with increased risk of thromboembolism, an aromatase inhibitor (e.g., anastrozole or exemestane) is considered first line therapy for risk reduction after surgery.[58] [48] [98] The duration of aromatase inhibitor treatment is 5 years.

» There are no strong data available for the treatment of older women with DCIS. Guidelines from the European Society of Breast Cancer Specialists suggest that healthy women >70 years of age with localised DCIS should be considered for breast conserving therapy.[99] Tamoxifen after breast conserving therapy decreases local failure independent of age.[100]

women with high-risk DCIS; all men with DCIS

1st **mastectomy ± breast reconstruction**

» Mastectomy is generally recommended for high-risk patients, for example those with DCIS in two or more quadrants (multicentric disease). If there are two or more sites of disease in the same quadrant (multifocal disease), mastectomy should be considered because it may not be feasible to surgically clear the disease and achieve a good cosmetic outcome with breast-conserving therapy.[58]

Acute

» Patients who present with a palpable mass and/or imaging showing a formed lesion, and those with histologically high grade DCIS are considered high risk and should be considered for mastectomy.[92]

» DCIS in males is generally treated with mastectomy.[93]

» Disease recurrence is low following total mastectomy for DCIS.[104] [95]

» Breast reconstruction should be discussed with all patients who plan to undergo mastectomy. It can be performed at the time of mastectomy (immediate reconstruction) or a later time (delayed reconstruction).

adjunct **axillary lymph node surgical staging**

Treatment recommended for SOME patients in selected patient group

» SLNB should be strongly considered in patients undergoing mastectomy, in case invasive disease is found in the excised specimen.[58] Performing a SLNB after mastectomy is impractical. The chance that an initial diagnosis of DCIS will be upgraded to invasive breast cancer is more likely if the disease is high grade and/or >2.5 cm (based on imaging).[48] [58] [96]

adjunct **radiotherapy**

Treatment recommended for SOME patients in selected patient group

» Adjuvant radiotherapy is not needed for DCIS treated with mastectomy unless disease is present near or at the chest wall, or if there is a substantial positive surgical margin.

» Radiotherapy delivers local or local and regional therapy, and adverse effects are localised to the area(s) through which the radiation passes. The most common acute adverse effects are skin changes (similar to sunburn) and fatigue. The skin may tan, either temporarily or permanently. The irradiated breast may appear smaller due to both surgical and radiotherapy. In patients receiving WBRT, a small portion of the lung and ribs receive radiation, which can induce lung scarring and slightly increase the risk of rib fracture. Furthermore, the heart is incidentally exposed to small doses of radiation when treating left sided breast cancers, which may increase the risk of ischaemic heart disease.[91] Risk of ischaemic heart disease may increase with increasing

Acute

doses of radiation to the heart.[91] Newer techniques minimise the dose and, therefore, sequelae.

adjunct **endocrine therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» tamoxifen: 20 mg orally once daily

OR

» anastrozole: 1 mg orally once daily

OR

» exemestane: 25 mg orally once daily

» Most patients with hormone receptor-positive DCIS receive adjuvant endocrine therapy to reduce the risk of ipsilateral and/or contralateral invasive breast cancer.

» For pre-menopausal women and women aged ≥60 years, tamoxifen is considered first-line therapy for risk reduction of the ipsilateral breast after breast-conserving therapy (i.e., lumpectomy followed by adjuvant radiotherapy), and for risk reduction of the contralateral breast after either mastectomy or breast-conserving therapy has been completed.[58] Tamoxifen is effective in preventing recurrence in patients with oestrogen receptor-positive breast cancer (both invasive and noninvasive), as well as in decreasing the risk of oestrogen receptor-positive cancers developing in the contralateral breast.[97] The duration of tamoxifen treatment is 5 years.

» For postmenopausal women aged <60 years and those with increased risk of thromboembolism, an aromatase inhibitor (e.g., anastrozole or exemestane) is considered first line therapy for risk reduction after surgery.[58] [48] [98] The duration of aromatase inhibitor treatment is 5 years.

» There are no strong data available for the treatment of older women with DCIS. Guidelines from the European Society of Breast Cancer Specialists suggest that healthy women >70 years of age with localised DCIS should be considered for breast conserving therapy.[99] Tamoxifen after breast conserving therapy

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decreases local failure independent of age.[100] The duration of tamoxifen treatment is 5 years.

lobular carcinoma in situ

low risk and low patient anxiety

1st **observation and counselling**

» The choice of observation versus bilateral mastectomy for women with LCIS is based on patient preference and assessment of risk of developing invasive disease.

» Patients with incidentally found LCIS, who are otherwise at low risk and have a low level of anxiety may opt for observation and counselling, with or without long-term endocrine therapy.

» Lobular carcinoma, both in situ and invasive, is rare in males.[13]

adjunct **endocrine therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» tamoxifen: 20 mg orally once daily

OR

» raloxifene: 60 mg orally once daily

OR

» anastrozole: 1 mg orally once daily

OR

» exemestane: 25 mg orally once daily

» Those with incidentally found LCIS, who are otherwise at low risk and have a low level of anxiety may opt for observation and counselling, with or without long-term endocrine therapy with tamoxifen (in pre-menopausal and postmenopausal women), or raloxifene, anastrozole, or exemestane (in postmenopausal women).[33]

» Tamoxifen and raloxifene have been found to decrease the risk of LCIS progression to invasive breast cancer.[33] [101] [102]

» Duration of endocrine therapy is 5 years.

high risk or high patient anxiety

1st **bilateral (prophylactic) mastectomy**

Acute

» The choice of bilateral preventive (prophylactic) mastectomy versus observation and counselling for women with LCIS is based on patient preference and assessment of risk of developing invasive disease.

» Patients who are anxious about the future risk of developing invasive breast cancer, have a strong family history of breast cancer, or who otherwise are at high risk may opt for bilateral mastectomy.

» Lobular carcinoma, both in situ and invasive, is rare in males.[13]

Ongoing

local recurrence of DCIS

following surgical excision with radiotherapy (breast-conserving therapy, surgical excision with radiotherapy)

1st **mastectomy ± breast reconstruction**

» Patients with local recurrence of DCIS following breast conserving therapy are treated with mastectomy (with or without breast reconstruction).

» Reconstruction can be performed at the time of mastectomy (immediate reconstruction) or at a later time (delayed reconstruction).

adjunct **axillary lymph node surgical staging**

Treatment recommended for SOME patients in selected patient group

» SLNB (if not previously done) should be strongly considered in patients undergoing mastectomy, in case invasive disease is found in the excised specimen.[58] Performing a SLNB after mastectomy is impractical.

» The chance that an initial diagnosis of DCIS will be upgraded to invasive breast cancer is more likely if the disease is high grade and/or >2.5 cm (based on imaging).[48] [58] [96]

following surgical excision without prior radiotherapy

1st **re-excision plus radiotherapy**

» Re-excision followed by adjuvant radiotherapy is an option in patients who have had surgical excision without prior radiotherapy.

» Radiotherapy delivers local or local and regional therapy, and adverse effects are localised to the area(s) through which the radiation passes. The most common acute adverse effects are skin changes (similar to sunburn) and fatigue. The skin may tan, either temporarily or permanently. The irradiated breast may appear smaller due to both surgical and radiotherapy. In patients receiving WBRT, a small portion of the lung and ribs receive radiation, which can induce lung scarring and slightly increase the risk of rib fracture. Furthermore, the heart is incidentally exposed to small doses of radiation when treating left sided breast cancers, which may increase the risk of ischaemic heart disease.[91] Risk of ischaemic heart disease may increase with increasing doses of radiation to the heart.[91]

following mastectomy

1st **re-excision ± adjuvant radiotherapy**

» Patients with local recurrence of DCIS following mastectomy may undergo re-excision (if clear margins and acceptable cosmesis can

Ongoing

be obtained) followed by adjuvant radiotherapy (if not previously given).[33]

» Radiotherapy delivers local or local and regional therapy, and adverse effects are localised to the area(s) through which the radiation passes. The most common acute adverse effects are skin changes (similar to sunburn) and fatigue. The skin may tan, either temporarily or permanently. The irradiated breast may appear smaller due to both surgical and radiotherapy. In patients receiving WBRT, a small portion of the lung and ribs receive radiation, which can induce lung scarring and slightly increase the risk of rib fracture. Furthermore, the heart is incidentally exposed to small doses of radiation when treating left sided breast cancers, which may increase the risk of ischaemic heart disease.[91] Risk of ischaemic heart disease may increase with increasing doses of radiation to the heart.[91]

Emerging

Trastuzumab as adjuvant therapy for DCIS

The National Surgical Adjuvant Breast and Bowel Project (NSABP) has initiated a phase III randomised trial of trastuzumab for patients with DCIS overexpressing HER2, previously treated with breast-conserving surgery yielding negative margins.[105] Patients will be randomised to receive 6 weeks of whole breast irradiation with or without concurrent trastuzumab. Two doses of trastuzumab will be given: a loading dose during week 1 of radiation and a final dose during week 3. The primary endpoint for the trial is any cancer event, and the secondary endpoints include ipsilateral breast cancer recurrence or development of contralateral breast cancer.

Primary prevention

Chemoprevention with tamoxifen, raloxifene, or an aromatase inhibitor (e.g., anastrozole or exemestane) is recommended for women at high risk of developing breast cancer, although it should be noted that this is an off-label indication for aromatase inhibitors.[33] [34] [35] [36] Tamoxifen is indicated for chemoprevention in pre and postmenopausal women, whereas raloxifene and aromatase inhibitors are recommended for use in postmenopausal women only.[33] [34] [35] [36] Some high-risk patients may may choose to undergo prophylactic bilateral total mastectomy for breast cancer risk-reduction.[33] [37]

High-risk candidates can be evaluated using the Gail model, which determines risk based on current age, age at first menstrual period, number of breast biopsies and whether atypical hyperplasia was found, age at first live birth, and number of first-degree relatives with breast cancer.[38] [National Cancer Institute: breast cancer risk assessment tool] (http://www.cancer.gov/bcrisktool) Other risk assessment tools are available for women with certain genetic mutations (e.g., BRCA) or medical conditions.[39]

Healthy lifestyle including physical activity and a balanced diet may prevent breast cancer.[40] In the Women's Health Initiative randomised controlled study, those who consumed a low-fat diet had a reduced risk of death after a diagnosis of breast cancer compared with those who consumed a usual diet.[41] The positive association between alcohol consumption and breast cancer risk is well established.[42] A study among patients attending breast clinics or screening found low levels of alcohol health literacy in this group. These appointments could provide an opportunity for discussing alcohol use as a modifiable risk factor.[43]

Secondary prevention

Avoiding hormone replacement therapy could reduce recurrence, new breast cancer, or progression of ductal carcinoma in situ (DCIS) to invasive breast cancer.[9] History of DCIS is a risk factor for future cancer in the same breast. Hormone replacement therapy (HRT) is not advised for this population. If DCIS develops in a woman on HRT, alternatives should be sought to treat menopausal symptoms.

Selective oestrogen receptor modulators such as tamoxifen can be used to prevent recurrence or new breast cancer. Tamoxifen can be taken for up to 5 years. In women at increased breast cancer risk, raloxifene has been shown to decrease the risk of new invasive breast cancer, but the benefit in reducing DCIS risk is less.[9] Thus, raloxifene has been FDA-approved in high-risk postmenopausal women and in women at risk for osteoporosis to prevent invasive breast cancer. Treatment with raloxifene for more than 4 years has been tested, and prolonged use does not appear to be harmful in the context of osteoporosis.[115] Aromatase inhibitors have also been shown to decrease risk of recurrence after DCIS. Women with lobular carcinoma in situ (LCIS) are considered high-risk (based on the Gail model) and also should be offered chemoprevention of invasive cancer, discussing the benefits and risks of the intervention.

Patient discussions

Patients should see their consultant every 6 months for 5 years (ductal carcinoma in situ [DCIS]) or every 6 to 12 months (lobular carcinoma in situ [LCIS]) for 5 years, and have annual mammography. Women

taking tamoxifen should have an annual pelvic examination. Women who have undergone mastectomy can have immediate or delayed reconstruction. Diet and lifestyle should be such as to maintain weight, without large fluctuations of weight gain or loss, unless the patient is overweight or underweight.

FOLLOW UP

Monitoring

Monitoring

The National Comprehensive Cancer Network recommends:[58]

- History and physical examination every 6-12 months for LCIS. For ductal carcinoma in situ (DCIS), history and physical examination every 6-12 months for 5 years, then yearly
- Annual mammography (initial mammogram 6-12 months post-radiation for DCIS if breast conserved, then yearly)
- Breast awareness (women should be encouraged to be familiar with their breasts and report changes to their healthcare provider).

Complications

Complications	Timeframe	Likelihood
tamoxifen-related endometrial cancer	**long term**	**medium**
After 5 years of treatment with tamoxifen, relative risk of tamoxifen-related endometrial cancer is 2.5 compared with no treatment.[110] The risk of endometrial cancer is less with raloxifene than with tamoxifen.[111]		
invasive breast cancer	**variable**	**medium**
Lobular carcinoma in situ (LCIS) is a risk factor for cancer in either breast, whereas ductal carcinoma in situ (DCIS) confers an increased risk of cancer in either breast although it is more likely that the disease will develop in the ipsilateral breast. This is especially true if DCIS is under-treated, either due to lack of removal of the entire tumour or due to lack of radiation in those with more aggressive (higher Van Nuys score) DCIS. LCIS: 10-year risk of breast cancer is 7%. DCIS: 10-year risk is 10% to 25%.		
tamoxifen-related pulmonary embolus	**variable**	**medium**
The relative risk of hospitalisation or death from a pulmonary embolus after taking tamoxifen for 10 years compared to stopping after 5 years was 1.87 (95% CI 1.13 to 3.07, P=0.01), with a 0.2% risk of death in both groups.[112] In the shorter term, the thromboembolic effects of tamoxifen increase the risk of skin flap necrosis during breast reconstruction performed as a delayed procedure after mastectomy.[113]		
aromatase inhibitor-related cardiovascular events	**variable**	**medium**
The use of aromatase inhibitors in women with breast cancer is associated with a greater cardiovascular risk than tamoxifen.[114]		
radiotherapy-related adverse events	**variable**	**medium**
In patients receiving whole breast radiotherapy, a small portion of the lung and ribs receive radiation, which can induce lung scarring and slightly increase the risk of rib fracture. Furthermore, the heart is incidentally exposed to small doses of radiation when treating left-sided breast cancers, which may increase the risk of ischaemic heart disease.[91] Risk of ischaemic heart disease may increase with increasing doses of radiation to the heart.[91]		

Prognosis

Recurrence

Ductal carcinoma in situ (DCIS) can recur if inadequately treated or if unknown disease is present in the area treated or in other areas of the breast. Mastectomy carries the lowest risk of disease recurrence, approximately 2%. Large tumour size, high histologic grade, also suggested by the presence of comedo-necrosis, and high expression of nuclear protein p16 are associated with increased recurrence risk.[106] Positive or close resection margin and lack of radiotherapy also increase risk of recurrence. Oestrogen and

progesterone status do not affect recurrence risk, while HER2/neu expression is predictive of recurrence. Other factors that are associated with a higher risk of invasive disease after a diagnosis of DCIS include age under 60 years, pre-menopausal status, African-American race, and detection by palpation.[106] Lobular carcinoma in situ (LCIS) is not cancer so much as an indicator of increased risk, so survival rates are not pertinent. The 5-year survival from DCIS is 98%.[107]

Despite competing causes of death, breast cancer is the cause of death in many older women, with up to 40% of women over 80 years old dying from breast cancer.[108]

Recurrence of DCIS in males is unacceptably high after breast conservation therapy without postoperative radiation. Breast conservation with radiation also is not generally recommended.[109]

One study looked at 10- and 20-year mortality from breast cancer following a diagnosis of DCIS. It found that treatments that reduced 10-year breast cancer recurrences (lumpectomy with radiation or mastectomy) did not reduce breast-cancer specific mortality. This suggested that there may be subsets of people with DCIS who might be treated more or less aggressively. Some risk factors for breast-cancer related mortality included age <35 at diagnosis and black ancestry.[73]

Diagnostic guidelines

United Kingdom

Suspected cancer: recognition and referral (https://www.nice.org.uk/guidance/ng12)

Published by: National Institute for Health and Care Excellence **Last published:** 2021

Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer (https://www.nice.org.uk/guidance/cg164)

Published by: National Institute for Health and Care Excellence **Last published:** 2019

Early and locally advanced breast cancer: diagnosis and management (https://www.nice.org.uk/guidance/ng101)

Published by: National Institute for Health and Care Excellence **Last published:** 2018

Europe

Early breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up (https://www.esmo.org/Guidelines/Breast-Cancer)

Published by: European Society for Medical Oncology **Last published:** 2019

North America

ACR appropriateness criteria: supplemental breast cancer screening based on breast density (https://www.acr.org/Clinical-Resources/ACR-Appropriateness-Criteria)

Published by: American College of Radiology **Last published:** 2021

ACR appropriateness criteria: transgender breast cancer screening (https://www.acr.org/Clinical-Resources/ACR-Appropriateness-Criteria)

Published by: American College of Radiology **Last published:** 2021

NCCN clinical practice guidelines in oncology: breast cancer (https://www.nccn.org)

Published by: National Comprehensive Cancer Network **Last published:** 2020

NCCN clinical practice guidelines in oncology: genetic/familial high-risk assessment - breast, ovarian, and pancreatic (https://www.nccn.org)

Published by: National Comprehensive Cancer Network **Last published:** 2019

NCCN clinical practice guidelines in oncology: breast cancer screening and diagnosis (https://www.nccn.org)

Published by: National Comprehensive Cancer Network **Last published:** 2019

ACOG practice bulletin: breast cancer risk assessment and screening in average-risk women (https://www.acog.org/Clinical-Guidance-and-Publications/Practice-Bulletins-List)

Published by: American College of Obstetricians and Gynecologists **Last published:** 2017 (re-affirmed 2019)

ACR appropriateness criteria: palpable breast masses (https://www.acr.org/Clinical-Resources/ACR-Appropriateness-Criteria)

Published by: American College of Radiology **Last published:** 2016

Breast cancer screening for women at average risk (https://www.cancer.org/health-care-professionals/american-cancer-society-prevention-early-detection-guidelines/breast-cancer-screening-guidelines.html)

Published by: American Cancer Society **Last published:** 2015

Treatment guidelines

United Kingdom

Early and locally advanced breast cancer: diagnosis and management (https://www.nice.org.uk/guidance/ng101)

Published by: National Institute for Health and Care Excellence **Last published:** 2018

Treatment of primary breast cancer (https://www.sign.ac.uk/our-guidelines)

Published by: Scottish Intercollegiate Guidelines Network **Last published:** 2013

Brachytherapy as the sole method of adjuvant radiotherapy for breast cancer after local excision (https://www.nice.org.uk/guidance/IPG268)

Published by: National Institute for Health and Care Excellence **Last published:** 2008

Europe

Early breast cancer (https://www.esmo.org/guidelines/breast-cancer)

Published by: European Society for Medical Oncology **Last published:** 2019

GUIDELINES

North America

NCCN clinical practice guidelines in oncology: breast cancer (https://www.nccn.org)

Published by: National Comprehensive Cancer Network **Last published:** 2020

NCCN clinical practice guidelines in oncology: breast cancer risk reduction (https://www.nccn.org)

Published by: National Comprehensive Cancer Network **Last published:** 2019

Use of endocrine therapy for breast cancer risk reduction (https://www.asco.org/research-guidelines/quality-guidelines/guidelines/breast-cancer)

Published by: American Society of Clinical Oncology **Last published:** 2019

Management of ductal carcinoma in situ of the breast (https://www.cancercareontario.ca/en/guidelines-advice)

Published by: Cancer Care Ontario **Last published:** 2018

Breast cancer follow-up and management after primary treatment (https://www.asco.org/research-guidelines/quality-guidelines/guidelines/breast-cancer)

Published by: American Society of Clinical Oncology **Last published:** 2013

Nutrition and physical activity guidelines for cancer survivors (http://www.cancer.org/healthy/informationforhealthcareprofessionals/acsguidelines/nupaguidelinesforcancersurvivors/index.htm)

Published by: American Cancer Society **Last published:** 2012

Online resources

1. National Cancer Institute: breast cancer risk assessment tool (http://www.cancer.gov/bcrisktool) *(external link)*

2. Public Health England: NHS breast screening (BSP) programme (https://www.gov.uk/topic/population-screening-programmes/breast) *(external link)*

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Images

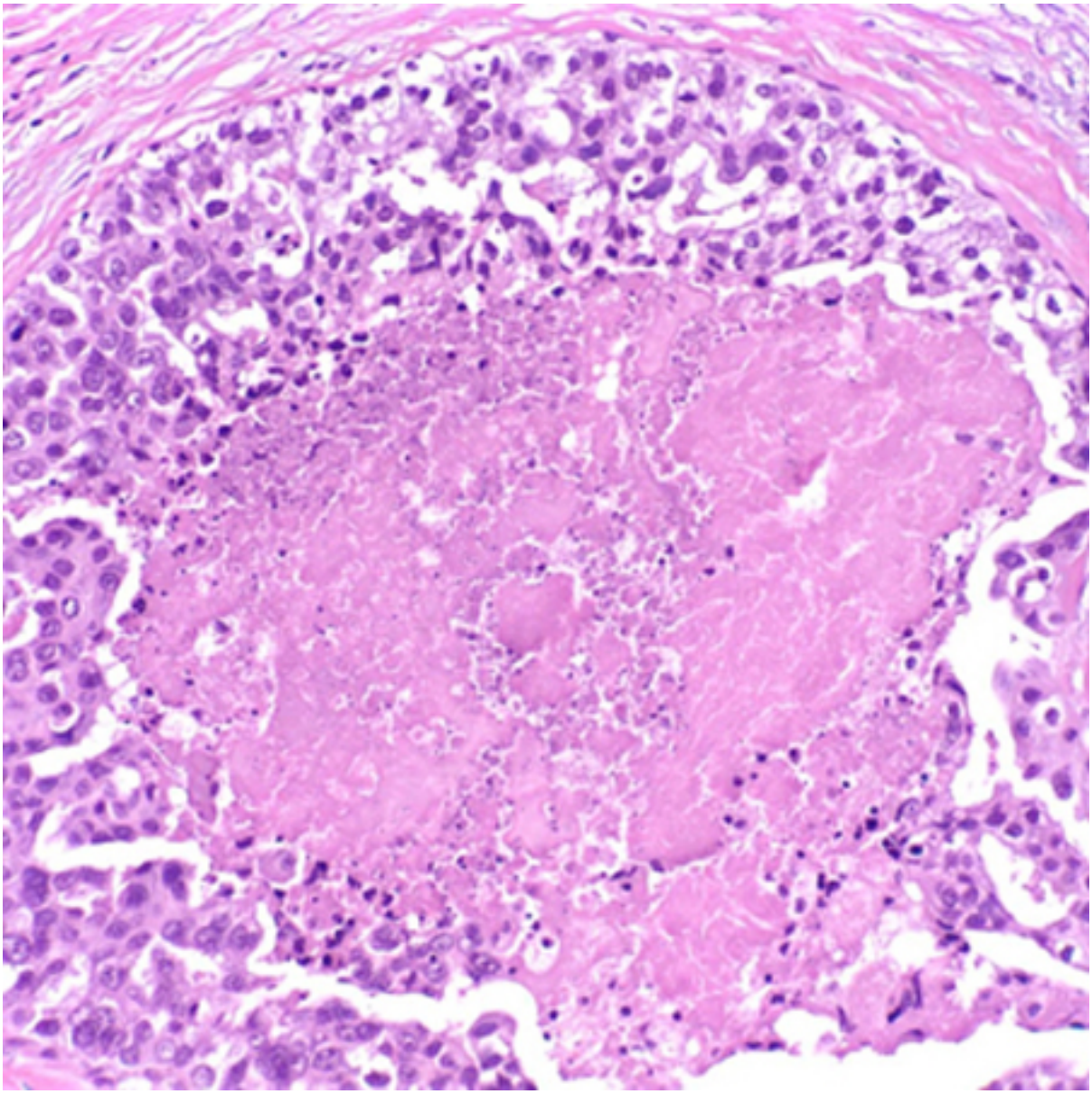

Figure 1: Ductal carcinoma in situ

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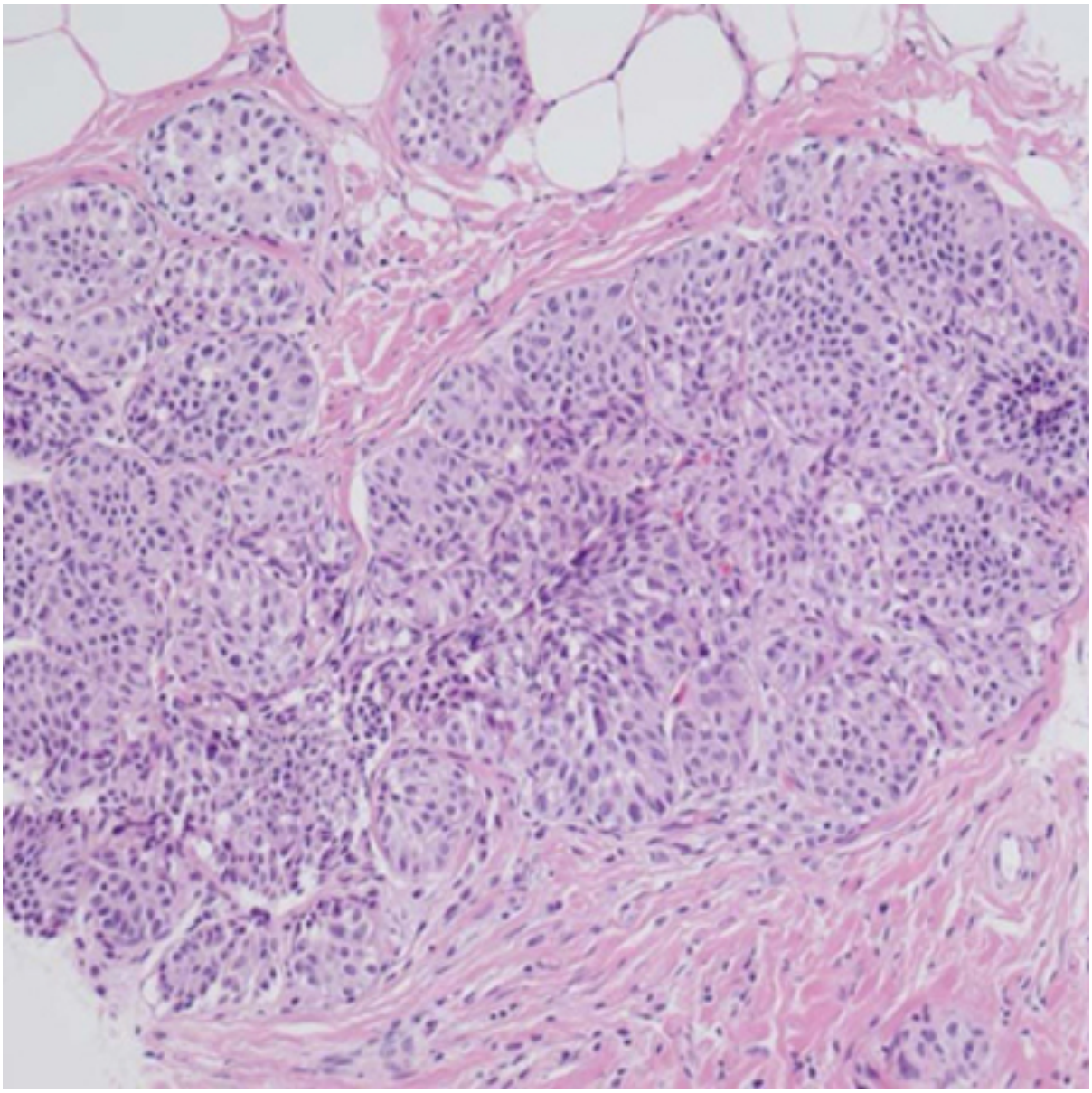

Figure 2: Lobular carcinoma in situ

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Figure 1 – BMJ Best Practice Numeral Style

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